PRODUCT SAFETY DIRECTORATE
ETHIOPIAN FOOD AND DRUG AUTHORITY

ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI) TRAINING FOR HEALTHCARE PROFESSIONALS

PARTICIPANT MANUAL

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Adverse Events Following Immunization (AEFI) Training for Healthcare Professionals

Participant Manual

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Addis Ababa, Ethiopia

Foreword

Concerted global and national efforts have been exerted to stop the spread of COVID19 and address the human and economic impacts of COVID19 on the society. It is widely understood that COVID19 has posed considerable challenges to health systems all over the world. Countries were forced to strike a balance between maintaining basic health services and coping with the health impacts of the pandemic. Ethiopia has successfully managed to lead a well-coordinated response plan that included distribution of essential medical supplies, prevention, diagnosis, and care of COVID19 patients.

On a global scale, efforts have been undergoing to develop effective vaccines. Like any other medicine, vaccines pass through a number of stringent preclinical and clinical trials to investigate their safety and efficacy. These trials happen in controlled set of conditions. Accordingly, medicines including vaccines can exhibit other benefits and adverse events when they are used at a wider scale within the population. Hence, health systems should be able to monitor these events so as to protect the safety of their citizens.

EFDA has been working to ensure the availability of quality assured COVID-19 vaccine through providing emergency use authorization (EUA) and monitoring of safety and conducting AEFI surveillance. EFDA has established COVID19 vaccine safety monitoring taskforce at national level and AEFI investigation taskforces were established at nine RHBs; and implemented interventions to strengthen the five regional PV centers for this purpose. Orientations were given to more than 4500 health professionals from health facilities and regional regulators on AEFIs monitoring and reporting. Manual and electronic reporting tools were prepared and distributed to health professionals. Moreover, weekly update of AEFIs of COVID19 vaccine was compiled and disseminated at national level.

It is believed that this training manual will strengthen the national effort to strengthen monitoring of vaccine safety and conducting AEFI surveillance. It will undoubtedly standardize capacity building efforts and contribute to better identification, reporting, investigation, and causality assessment of AEFIs following.

I would like to take this opportunity to express the authority's appreciation to all individuals and their respective organizations for the successful development of this training manual. I would also like to encourage users of this document to send their comments to EFDA at: contactefda@efda.gov.et or P. O. Box 5681, Addis Ababa, Ethiopia.

Heran Gerba,

Director General, Ethiopian Food and Drug Authority

Acknowledgement

The Ethiopian Food and Drug Authority would like to express its heart felt appreciations to the experts and their respective institutions who were involved in the development of this training manual. *Adverse Events Following Immunization (AEFI) for Healthcare Professionals training* will contribute to the national effort to protect the safety of our population from the adverse effects of vaccines. Accordingly, our gratitude is extended to the following individuals and their organizations whose role was critical in the development of this training manual.

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Acronyms

AE	adverse event
AEFI	adverse event following immunization
AESI	adverse events of special interest
COVID-19	coronavirus disease 2019
DNA	deoxyribonucleic acid
EFDA	Ethiopian Food and Drug Authority
EPHI	Ethiopian Public Health Institute
EPI	expanded program on immunization
EPSA	Ethiopian Pharmaceutical Supply Agency
EUA	emergency use authorization
MERS	Middle East respiratory syndrome
MOH	Ministry of Health
mRNA	messenger ribonucleic acid
RNA	ribonucleic acid
SARS-CoV-2	Severe Acute Respiratory Syndrome Corona Virus 2
WEO	Woreda EPI Officer
WHO	World Health Organization

Table of Content

Introduction to the training

The Government of Ethiopia developed strategic response plan for effective and efficient utilization of available resources and to seamlessly integrate different partner's roles in the health system in response to the COVID-19 pandemic. The MOH has been working with partners and different stakeholders in the control and prevention of the pandemic since the first case of COVID-19 was reported in Ethiopia. The MOH, Ethiopia Pharmaceutical Supply Agency (EPSA), Ethiopia Public Health Institute (EPHI), and Ethiopia Food and Ethiopia Food and Drug Authority (EFDA) have been working to ensure availability and quality of COVID-19 vaccine. Accordingly, Ethiopia has, so far, vaccinated more than 54 million people (1st dose= >44, million, 2nd dose > 37 million)

EFDA, in collaboration with the Ministry and EPSA, has been working to ensure the availability of quality assured COVID-19 vaccine through providing emergency use authorization (EUA). EFDA has provided EUA to four COVID-19 vaccines, namely, Johnson & Johnson's, AstraZeneca (Covidshild, Oxford University UK and South Korea), Sinopharma and Moderna. Remdesivir drug special import permit was also issued. In addition, Sinovac of China and Sputnik V of Russia are vaccines under evaluation process for EUA.

EFDA has also been leading efforts for monitoring of safety and conducting AEFI surveillance. Owing to their faster development, pre-clinical, and clinical trial stages, COVID19 vaccines are expected to show adverse drug events after marketing. Accordingly, EFDA has established COVID19 vaccine safety monitoring taskforce at national level and AEFI investigation taskforces were at nine RHBs; and strengthened the five regional PV centers for this purpose. Trainings were given to more than 4500 health professionals from health facilities and regional regulators on AEFIs monitoring and reporting. Active surveillance of AEFI was conducted by EFDA in AA and five regions. Moreover, weekly update of AEFIs of COVID19 vaccine was compiled and disseminated at national level.

So far, more than 35,000 safety data were collected for active Surveillance and AEFI reports coming from spontaneous surveillance is increasing significantly, most of the AEFIs received were minor.

All professionals involved in the vaccination process should be involved in safety monitoring of vaccines. Accordingly, the professionals need to understand and apply best practices in monitoring, managing, prevention, reporting, investigation, and causality assessment of AEFIs.

This training manual is developed to contribute to the creation of a competent workforce that will strengthen the pharmacovigilance of vaccines.

The training package contains a training manual and associated PowerPoint presentation slides. The content of the training is expected to be delivered in two days.

The outline of the training manual is as follows:

Chapter 1: National EPI

Chapter 2: Overview of National PV system

Chapter 3: Basic Concepts of Vaccines and AEFI

Chapter 4: Prevention and Management of AEFI

Chapter 5: AEFI Surveillance System

Chapter 6: AEFI detection and reporting

Chapter 7: AEFI Investigation and Causality Assessment

Chapter 8: Action, Follow-up, and Communication to AEFI

Chapter 9: AEFI for COVID-19 Vaccines

Chapter 10: Monitoring and evaluation of AEFI activities

Training goals and learning objectives

Training Goal:

This Adverse Events Following Immunization (AEFI) for COVID-19 Vaccines: Orientation Training for Health Professionals working in Vaccination Centers is developed with the goal of equipping relevant health professionals involved in COVID-19 vaccination, passive, or active surveillance, and health administrators at all levels of the health system with the necessary knowledge and skills in AEFI identification, reporting, investigation, and causality assessment.

Learning Objectives:

By the end of the orientation training, participants will be expected to:

- Describe etiology, transmission route, epidemiology and impacts of COVID-19
- Discuss about the COVID-19 vaccines
- Explain COVID-19 related AEFIs
- Discuss how to prevent and manage AEFIs
- Describe AEFI detection and reporting mechanisms
- Explain AEFI investigation and causality assessment
- Discuss communication about safety of COVID-19 vaccines

Training Schedule/Program

Adverse Events Following Immunization (AEFI) Training for Healthcare Professionals Date: _____; Venue: _____		
Time	**Session/Topic**	**Responsible**
Day One		
8:30-9:00	Registration of participants	Organizers
9:00-9:15	Welcoming/Opening speech	
9:15-9:45	Introduction to the course	
9:45-10:30	Pretest	
10:30-10:45	Health break	Organizers
10:45-11:30	Session 1: Overview of the national immunization program	MOH
11:30-12:15	Session 2: Overview of the national pharmacovigilance system	EFDA
12:15-12:30	Discussion	Participants
12:30-2:00	Lunch break	
2:00-3:30	Session 3: Basic concepts of vaccines and AEFI	EFDA
3:30-3:45	Health break	Organizers
3:45-4:30	Session 4: Prevention and Management of AEFI	
4:30-5:15	Session 5: AEFI surveillance system	
5:15-5:30	Daily evaluation	
Day Two		
8:30-9:00	Recap of Day One	Participants
9:00-10:00	Session 6: AEFI investigation and causality assessment	
10:00-10:30	Session 7: Action, follow-up, and communication of AEFI	
10:30-10:45	Health break	Organizers
10:45-12:00	Session 8: AEFI detection and reporting	
12:30-2:00	Lunch break	Private
2:00-3:30	Session 9: AEFI for COVID-19 vaccines	
3:30-3:45	Health break	Organizers
3:45-5:00	Certifications, closing speech and administrative issues	Organizers

Chapter 1: Overview of National Immunization program

Allocated time: 55 minutes

Session Description

The session provides participants with the fundamental concept and an update on the National Expanded Program on Immunization. The session describes the changing scope of immunization and its system. This is followed by rationale for revision of implementation guideline and implementation strategies and modalities. Besides, the session enumerates conditions and contraindications for vaccination.

Primary Objective: To provide participants an update on the National Program on Immunization.

Enabling objectives:

- To describe the scope of the National Immunization Program
- To discuss the national strategies for implementation of EPI
- To identify the conditions and contraindications for vaccinations
- To explain the National Immunization Schedule

Session Outline:

- Scope of National Immunization Program
- Revision of Implementation Guideline and Strategies
- Conditions and contraindications for vaccinations
- National Immunization Schedule

1.1 Introduction

Brainstorming: Discuss in groups, the target groups and vaccines included in the national EPI (5 minutes)

Immunization program is one of the most cost-effective health interventions, with proven strategies to reach the most hard-to-reach and vulnerable populations. Accordingly, the Ethiopian National Expanded Program on Immunization (EPI) was launched in 1980 with the aim of reducing mortality, morbidity and disability of children and mothers from vaccine-preventable diseases (VPDs). Children under age of two were the target group when the program was started. In 1986, in line with the global immunization target, EPI changed its target to infants and mothers. Since 2019, children of the under-one year of age, the second year of life, adolescent girls (9- 14 years) and women of reproductive age group (15- 49 years) become the targets for the currently available vaccines in the immunization program of Ethiopia.

About 80% of morbidities in mothers and children are attributable to communicable diseases including vaccine-preventable diseases and sickness associated with nutritional disorders. With progressive introduction of new and under used vaccines, there has been remarkable achievements in reducing morbidity and mortality from vaccine preventable diseases.

The MOH/MCH directorate is the overall coordinating body for the EPI activities at all administrative structural levels and coordinates EPI interagency coordinating committee (ICC) efforts towards common national goals and targets. MOH/MCH Directorate also provides technical and financial support to the regions and ensures updating EPI implementation guideline, standardization of training manuals, job aids, IEC materials and any related supplies. Monitoring, supervision and program reviews will be coordinated through the Directorate. Regional Health Bureaus (RHB) will also provide similar supports to the lower administration levels and health facilities.

1.2 Scope of Routine Immunizations

National EPI program is rapidly changing and expanding in its scope and type of antigens. At the launch of EPI in Ethiopia in 1980, six antigens (BCG, DPT, OPV, and Measles) have been given in both public health facilities and few private health facilities. The country later introduced Hep-B and Hib (as Pentavalent vaccine), PCV, Rotavirus, IPV, HPV and measles

second dose (MCV2) vaccines into the routine immunization program in 2007, 2011, 2013, 2015, 2018 and 2019, respectively.

The total number of antigens in the national schedule reached twelve, including TT for women of reproductive age (**Table 1.1**). In 2020, the country switched from TT to Td. In the near future, the country is planning to introduce Meningitis A, Yellow Fever, Hepatitis B birth dose, Typhoid, and school Td vaccines to replace the TT vaccine for women of reproductive age (and/or pregnant women as per the national immunization target), older children and adolescents.

Table 1.1: National EPI schedule and route of administration for antigens

No.	Vaccines	Targets diseases to be prevented	Age	Route/site of administration
1	**Hep B vaccine birth dose**	Hepatitis B Virus Infection	At birth or within 24 hours of birth. If child is born out of HFs or at home, track baby and vaccinate until the age of 14 days.	IM, left anterolateral thigh
2	**BCG**	Severe form of TB	At Birth or as soon as possible after birth	Intradermal (ID), right deltoid
3	**PCV**	Meningitis and pneumonia associated with Streptococcus pneumonia bacteria	Weeks 6, 10 and 14	Intramuscular (IM), Right anterolateral thigh
4	**OPV**	Poliomyelitis	Birth (OPV0), weeks 6, 10 and 14	Oral drops
5	**IPV**	Poliomyelitis	Week 14	IM, right anterolateral thigh 2.5 cm apart from the injection site of PCV
6	**DPT-Hib-Hep B**	Diphtheria, Pertussis, Meningitis and pneumonia associated	Weeks 6,10 and 14	IM, left anterolateral thigh

		with Hemophilus influenzae bacteria and Liver disease due to Hepatitis B virus		
7	**Measles containing vaccine**	MCV	9 and 15 months	Subcutaneous, left deltoid
8	**Rotavirus vaccine**	Rotavirus associated gastroenteritis	Week 6 and 10	Oral only
9	**Td**	Maternal and neonatal tetanus and diphtheria	Td1 at first contact, Td2 4 weeks later, Td3 6 months after Td2, Td4 1 year after Td3, Td5 1 Year after Td4	IM, right deltoid muscle

1.3 Components of Immunization System

The immunization system comprises of five key operational components namely service delivery, cold chain and logistics, vaccine supply and quality, VPD surveillance and response as well as Advocacy, social Mobilization and Communication (**Figure 1.1**). It also consists of three supportive components: management, financing and capacity strengthening.

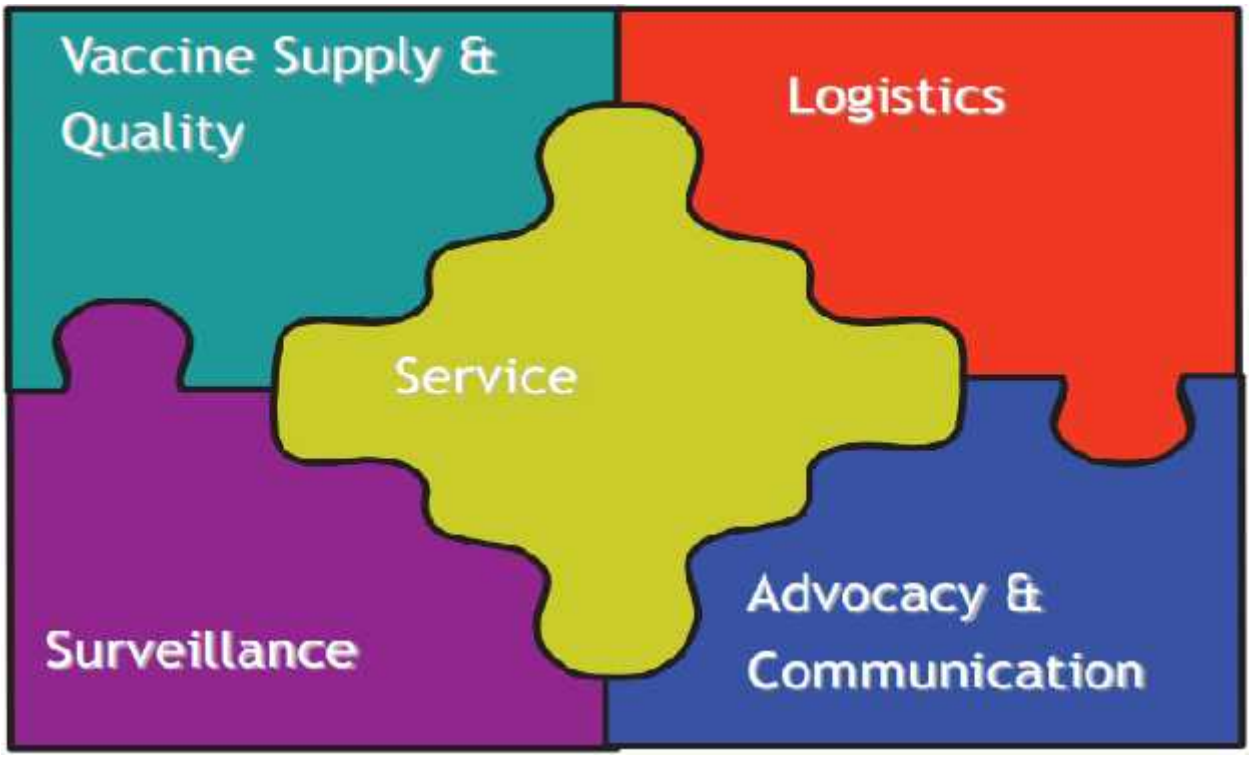


Figure 1.1: Components of Immunization System

Service Delivery

EPI program endeavors to sustain and improve on the gains made over the years by providing quality immunization services. In Ethiopia, primarily most of immunizations take place in fixed posts. EPI uses different strategies to reach eligible clients. In addition to routine fixed strategy, outreaches and supplementary immunization activities play a key role in improving service delivery.

Vaccine Supply and Quality

EPI ensures timely request and collection of required supplies/logistics to maintain minimum stocks availability and prevents intermittent supply stock out as per EPI implementation guideline. EPI's internal quality assurance mechanisms ascertain vaccine quality is maintained up to the point of utilization.

Cold-chain and Logistics

All health facilities and stores handling the vaccines need to monitor and record the temperature of the vaccines in the cold chain at least twice daily including weekend and holidays for timely action (**Box 1.1**). These health facilities should have adequate cold chain equipment, injection materials, vaccines, and other necessary supplies.

Box 1.1 Vaccine and cold chain monitoring:
Administration of potent vaccines relies on the thermoregulation of the vaccines by keeping the cold chain system is well functioning. All vaccines are heat sensitive and most are freeze sensitive. Utilizing the new technologies or tools for the cold chain monitoring such as fridge tag, thermometers and others are crucial. Health facilities and storage sites should measure the temperature of the cold rooms, refrigerators, and other storages twice per day and keep track of the record and report accordingly to the higher level. Immediate responses need to be taken for the timely identification of any abnormal temperature ranges.

VPD surveillance and response

In Ethiopia, VPD surveillance is implemented within the framework for the Integrated Disease Surveillance and Response (IDSR) strategy; the strategy was adopted by the FMOH in 2001. After the restructuring of the FMOH in 2009, the country adopted IDSR as part of Public Health Emergency Management (PHEM) and VPD surveillance became a component of the PHEM

core process at the federal level within the Ethiopian Public Health Institute (EPHI). The VPD surveillance infrastructure (human and logistics) have provided the platform on which IDSR implementation was rolled out nationwide.

Currently, diseases targeted for eradication and elimination are included in the national list of priority diseases for surveillance such as poliomyelitis, measles and neonatal tetanus. These target diseases should be immediately reported to EPHI and investigated accordingly as per the National Surveillance Guidelines. Community-based surveillance for active case searching is already instituted. MOH EPI program will continuously utilize the National and Subnational VPD Surveillance data for data triangulation to guide strengthening RI and conducting campaigns as needed.

Advocacy, Social Mobilization and Communication

Advocacy, social mobilization and communication are very crucial in EPI services. To this end, MOH EPI should ensure a high-level EPI advocacy both at national and regional levels to ensure political commitment and financial sustainability towards achieving high immunization coverage and diseases reduction goals. It is important to develop IEC materials in different local languages to promote the public understanding on the benefit of vaccines and immunization services and schedules. Moreover, EPI should promote public demand for vaccination through multi-channel interventions such as IEC (electronic/print media), social and behavioral change communication, public meetings, health education in health institutions, dissemination of information through schools and other events.

1.4 National EPI Implementation Guideline

A life-course approach to immunization has been widely utilized by vaccination beyond childhood to adolescence and adulthood for combating VPD. Hence, EPI is one of the best and cost effective preventive public health interventions. The rationale for revision is indicated in Box 1.2.

The currently updated guideline aims to provide updated guidance and direction on implementation of immunization for health managers, health service providers in government and private health facilities, administrators at different levels as well as different partners and actors in Ethiopia to enable the delivery of quality and equitable immunization services to every target population against VPD across the country.

Box 1.2 Rationale for revised implementation guideline:
EPI implementation guideline is revised due to several factors including: Requirements for updated accurate data and information, revised guideline will be an input for strengthening the EPI program, Introduction of the new vaccines (IPV, MCV2, HPV) since 2015, Engagement of private health facilities, consideration of the COVID-19 circumstances, to sustain the progress of global, regional, and national VPD control, elimination and eradication goals and Mitigate re-emerging VPD transmission.

1.4.1 EPI Implementation Strategies and Modalities

Effective integration of between immunization and other health programs can contribute to improving immunization coverage by reducing missed opportunities for vaccination and zero-dosed children. EPI implementation relies on three basic implementation strategies. These strategies outlined below are applicable in all EPI plus (Vitamin A supplementation, ECD & GMT, Deworming, etc.) programs.

- Strategies for increasing immunization access and coverage
- Strategies to reduce dropout/ Defaulter tracing
- Increasing the quality of immunization services

N.B. The common immunization service delivery modalities in EPI s are static (less than 5 km), outreach (5-10 km) and mobile strategies (greater than 10 km or a day).

1.4.2 Immunization Guidance Specific to Private Health Facilities

Immunization services should be regularly available on daily basis in all health facilities, government, NGOs or private facilities with functional vaccine refrigerator and trained health care workers. To optimize effective vaccination services, engagement of private sector, is a means to improve the program and increase access and quality coverage for immunization services, but only if the role and responsibility (Box 1.3) are clearly defined and the services are collaborative with the existing public health system and standards.

The national EPI guideline serves as tool to govern both public and private health facilities providing immunization services. However, some distinct issues need to be separately addressed for the private sector such providing immunization on voluntary basis, expected to charge the minimum amount of service fee based on an agreed estimated cost. Private health facilities should submit their vaccination data to respective government health institutions on a

regular basis by applying the standard templates and timeframes developed by the government (Box 1.3).

Box 1.3 Roles and responsibilities of private health facilities delivering RI

- *Submit a formal request and obtain the permission from respective RHB to provide immunization services*
- *Collaborate with the public sector at all levels in all issues related to EPI services through Public-Private Partnership health policy*
- *Maintain the minimum infrastructure and human resource requirements for the delivery of immunization services*
- *Provide the service as per the national EPI implementation guideline*

1.5 Conditions and Contraindications for Vaccinations

Group reflection:
Discuss on condition that are contraindicated for immunization and other related misperceived believes in our community related to immunization conditions/contraindications (5 minutes)

It is recommended that health workers should use every opportunity to vaccinate eligible children and avoid unnecessary contraindications. Based on numerous studies on this issue WHO confirms that only a few absolute or true contraindications to the vaccines.

Contraindications 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.

- ❑ Persons with a history of anaphylactic reactions
- ❑ Children with symptomatic HIV infection/AIDS should not be immunized with yellow fever vaccine.
- ❑ Children who are known to be HIV infected, even if asymptomatic, should no longer be immunized with BCG vaccine.
- ❑ A severe adverse event following a dose of vaccine (anaphylactic reaction)

Conditions that are NOT Contraindications to Immunization

- ❑ Minor illnesses, such as upper respiratory infections or diarrhea with fever < 38.5ºC
- ❑ Allergy, asthma, hay fever, or snuffles
- ❑ Prematurity; low-birth-weight infants

- ❑ Malnutrition
- ❑ Child being breastfed
- ❑ Family history of convulsions
- ❑ Treatment with antibiotics, low-dose corticosteroids, or locally-acting steroids
- ❑ Dermatoses, eczema, or localized skin infections
- ❑ Chronic diseases of the heart, lung, kidney, and liver

Chapter summary

- ✓ Immunization program is one of the most cost-effective health interventions,
- ✓ National EPI program is rapidly changing and expanding
- ✓ The immunization system comprises of the five key operational components
- ✓ EPI implementation relies on three basic implementation strategies.
- ✓ Existence of anaphylactic reactions, HIV infection and severe AEFI are some of contraindications in vaccine
- ✓ LBW, asthma, and family history of convulsion are not contraindicated in immunization
- ✓ Engagement of private sector improves EPI program coverage and accessibility

Chapter 2: Basic Concepts of Vaccines & Adverse Events Following Immunization

Allocated time: 70 minutes

Chapter description:

This chapter will explain the different types of vaccine and main components of a vaccine. The chapter will also describe about the main types of vaccine reactions and categories of adverse events following immunization (AEFI) based on frequency and severity.

Primary Objective: To equip participants with basic concepts on vaccines and AEFI

Enabling objectives:

By the end of this session, the participant should be able to:

- Define vaccine
- Explain common types of vaccines,
- List types of vaccine components and explain their functions,
- Explain the different types of AEFI

Session outline

- ✓ Introduction
- ✓ Definition and types of vaccines
- ✓ Components of vaccine
- ✓ Adverse events following immunization

2.1 Introduction

Brainstorming:
Discuss on the difference between vaccines and conventional drugs (5 minutes).

Vaccination is one of the great public health achievements of human history. Vaccines used in national immunization programmes (NIPs) are considered safe and effective when used correctly. Public trust in vaccine safety is key to the success of vaccination programmes. Vaccines are; however, not risk-free and adverse events will occasionally occur following vaccination. There are many types of vaccines. Different types or formulations affect how they are used, how they are stored, how they are administered and in occurrence of adverse events. If they are to be safe and effective, it is vital to be familiar with the different types and to know how to handle them.

2.2 Definition and Types of Vaccines

Brainstorming:

List the types and components of a vaccine (5 minutes).

The term 'vaccine' applies to all biological preparations, produced from living organisms or their components, that enhance immunity against disease and either prevent (prophylactic vaccines) on subsequent exposure to pathogens or, in some cases, treat disease (therapeutic vaccines). Based on the antigen used in their preparation, vaccines are classified into different categories (Table 2.1).

Table 2.1: Types of vaccine platforms

Vaccine platforms	Examples
Live attenuated	BCG; OPV; Measles; Mumps; Rubella; Varicella zoster; Yellow fever
Inactivated	Whole-cell pertussis (wP); Inactivated polio vaccine; Hepatitis A
Subunit purified antigen	Hepatitis B (HepB); Haemophilus influenza type b (Hib); Acellular pertussis; Pneumococcal (PCV-7, PCV-10, PCV-13)
Toxoid inactivated toxin	Tetanus toxoid (TT); Diphtheria toxoid
Viral vector	Ebola vaccine; Zika vaccine; some COVID-19 vaccines
Messenger RNA	Some COVID-19 vaccines

Live attenuated vaccines (LAV): derived from disease causing pathogens that have been weakened under laboratory conditions. LAVs stimulate excellent immune response that is nearly as good as an infection with the wild-type pathogen. Since they contain living organisms, there is a degree of unpredictability, raising some safety and stability concerns. LAVs can have increased potential for immunization errors as some come in powder form that must be reconstituted.

Inactivated or killed vaccines: made from microorganisms that are killed through physical or chemical processes. Inactivated whole-cell vaccines may not always induce an immune response and the response may not be long-lived. Several doses of vaccines may be required to evoke a sufficient immune response. They are considered more stable than LAV vaccines.

Subunit vaccines: They differ from inactivated whole-cell vaccines, by containing only the antigenic parts of the pathogen. The sub-units can be proteins, sugars, nucleic acids or conjugated forms. Protein based subunit vaccines present an antigen to the immune system without viral particles, using a specific, isolated protein. Polysaccharide vaccines are small, and often not very immunogenic. Consequently, they tend to be not effective in infants and young children and induce only short-term immunity. Nucleic acid-based vaccines, including DNA (as plasmids) and RNA (as mRNA) vaccines, exhibit promising potential in targeting various indications and diseases. They have the potential to be safe, effective, and cost-effective.

Toxoid vaccines: are based on the toxins produced by certain bacteria (tetanus or diphtheria). The toxin invades the bloodstream and is largely responsible for the symptoms of the disease. The vaccine antigens are not actively multiplying and do not spread to unimmunized individuals. They are stable, as they are less susceptible to changes in temperature, humidity and light.

Viral vector-based vaccines: viral vector-based vaccines differ from most conventional vaccines in that they don't actually contain antigens, but rather use the body's own cells to produce them. They do this by using a modified virus (the vector) to deliver genetic code for antigen, in the case of COVID-19 spike proteins found on the surface of the virus, into human cells. By infecting cells and instructing them to make large amounts of antigen, which then trigger an immune response, the vaccine mimics what happens during natural infection with certain pathogens - especially viruses. This has the advantage of triggering a strong cellular immune response by T cells as well the production of antibodies by B cells.

2.3 Components of a vaccine

In addition to the bulk antigen, vaccines include a variety of ingredients: stabilizers, adjuvants, antibiotics, and preservatives. These ensure the quality and potency of the vaccine over its shelf-life. They may also contain residual by-products from the production process. Knowing precisely what is in each vaccine can be helpful when investigating AEFIs and for choosing alternative products for those who have allergies or known/suspected adverse events. Regulatory authorities must ensure that all components, singly and in combination, do not compromise vaccine's safety.

Antigens: are derived from the structure of disease-causing organisms, which are recognized as 'foreign' by the immune system and trigger a protective immune response to the vaccine.

Stabilizers: are used to help the vaccine maintain its effectiveness during storage. Vaccine stability is essential, particularly where the cold chain is unreliable. Instability, due to factors like temperature, can cause loss of antigenicity and decreased infectivity of LAV. Stabilizing agents include $MgCl_2$ (for OPV), $MgSO_4$ (for measles), lactose-sorbitol and sorbitol-gelatin.

Adjuvants: stimulate the production of antibodies against the vaccine to make it more effective, but do not act as antigens by themselves. Adding adjuvants into conventional vaccine formulations is aimed at enhancing, accelerating and prolonging the specific immune response to vaccine antigens. Newly developed purified subunit or synthetic vaccines are poor vaccine antigens and require adjuvants to provoke the desired immune response. Aluminum salts are the most commonly used adjuvant for vaccines. However, adjuvanted vaccines may have a slightly higher rate of adverse reactions, including pain at the injection site, malaise and fever.

Box 2.1: Aluminium salts
Aluminium salts slow the escape of the antigen from the site of injection thereby lengthening the duration of contact between the antigen and the immune system. They are generally recognized as safe, however, they can cause sterile abscesses and nodules at the site of injection. The formation of a small granuloma is inevitable with alum-precipitated vaccines. To ensure safe vaccination it is important to administered IM and not SC, which can result in necrotic breakdown and cyst and abscess formation. To ensure the proper handling of IM injections, it is critical to ensure that vaccination staff has been well trained.

Antibiotics: are used during the manufacturing phase to prevent bacterial contamination of the tissue culture cells. Usually, only trace amounts appear in vaccines, for example, MMR vaccine and IPV each contain less than 25 micrograms of neomycin per dose. Persons who are known to be allergic to neomycin should be closely observed after vaccination so that any allergic reaction can treated at once.

Preservatives: are added to ensure the sterility of the vaccine over the period of its shelf-life. They may be used to prevent contamination of multi-dose containers: when a first dose of vaccine is extracted, a preservative will protect the remaining product from any bacteria that may be introduced into the container. Or, in some cases, preservatives may be added during manufacture to prevent microbial contamination. Common preservatives (table 2.2) are non-toxic in the amounts used and do not diminish the potency of vaccines. But not all preservatives can be used in all vaccines. Some preservatives will alter the nature of some vaccine antigens.

Table 2.2: examples of vaccines with preservatives

Preservative	Vaccines
Phenol	Typhoid, pneumococcal polysaccharide
Benzethonium chloride	Anthrax
2-phenoxyethanol	Inactivated polio
Thimerosal	Multidose influenza

Discuss and reflect

Discuss on how do the vaccines work and impact they have on diseases? (5 minutes)

2.4 Adverse events following immunization

Brainstorming:

Discuss on the safety of vaccines (5 minutes).

Under recommended conditions, all vaccines used in national immunization programmes are safe and effective if used correctly. Rigorous procedures are followed before registration and sale but there is no such thing as a “perfect” vaccine which has no adverse events. Vaccination Programmes are usually complex in nature and in spite of all precautions taken, some people may be affected by adverse events (minor to more severe reactions). Due to its peculiarities form conventional drugs, pharmacovigilance activities in PV is imperative (Box 2.2). Adverse events can range from minor side-effects to more severe reactions. They can be a cause of public concerns about vaccine safety. To understand a specific event and to be able to respond appropriately, there are several questions that you need to answer:

- What caused the reaction?
- Was it related to the vaccine, or the way it was administered, or was it unrelated?
- Are the reactions minor or severe?

Box 2.2: Pharmacovigilance of these vaccines is imperative for a number of reasons:

- Vaccines as opposed to medicines are for prevention in healthy, larger population. Therefore, there is lower tolerance to risk
- Vaccines are biological products, therefore are more prone to lot/batch variation and instability
- For vaccines unlike medicines, there are relatively limited number of products
- With single dose, there is a greater potential for temporal "coincidence" adverse events
- Vaccines are prone to "programme error"
- Vaccines are mostly injectables and are more likely to have injection "reaction"
- Cold chain is often critical in Immunization
- Vaccines are commonly administered in mass campaigns
- Vaccines are associated with politics of access/safety

2.4.1 Definition of AEFI

AEFI is any untoward medical occurrence following immunization and does not necessarily have a causal relationship with the usage of the vaccine. It may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

2.4.2 Classification of AEFIs

AEFIs can classified based on the 1) cause, and on 2) severity, and frequency. Vaccine reactions may be grouped into two broad categories:

A) Cause-specific reactions

i. Vaccine product-related reaction
ii. Vaccine quality defect-related reaction
iii. Immunization error related reaction
iv. Immunization anxiety-related reaction
v. Coincidental event

B) Vaccine reactions by severity and frequency

i. Common or minor reactions
ii. Rare or serious reactions

A) Cause-specific reactions

Vaccine product-related reaction: It is caused/precipitated by a vaccine product due to one or more of its inherent properties (table 2.3 and 2.4). Distinguishing genuine vaccine product-related events from coincidental or concomitant medication-related AEFI's will be a challenge.

Table 2.3: Common, minor vaccine reactions

Vaccine	Local reactions	Systemic reactions	
	(Pain, swelling, redness)	Fever > 38 C	Irritability, malaise and systemic symptoms
BCG	90% - 95%	-	-
Hepatitis B	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%
Pertussis C (DTwP)	up to 50%	up to 50%	up to 55%
Pneumococcal conjugate	20%	20%	20%
Tetanus/ DT/aTd	10%	10%	25%

Table2.4: Selected childhood vaccines and associated severe reaction

Vaccine	**Reaction**	**Onset interval**	**Frequency/dose given**
BCG	Fatal dissemination of BCG infection	1-12 months	0.2-1.6/1,000,000
	BCG osteitis	-	Very rare
OPV	VAPP	4-30 days	2-4/1,000,000
DTwP	Prolonged crying and seizures	0-24 hours	<1/100
	HHE	0-24 hours	<1/1000-2/1000
Hib	None known	-	-
Measles	Febrile seizures	6-12 days	1/3,000
	Thrombocytopenia	15-35 days	1/30,000
	Anaphylaxis (Hypersensitivity)	0-few hours	1/100,000
	Encephalitis	4-9 months	1/3,000,000
Rotavirus	None reported to WHO	-	-
PCV-13	Not known yet	-	-
Yellow fever	Anaphylaxis (Hypersensitivity)	0-few hours	Very rare
	Acute Neurotropic Disease (YEL - AND)	Up to 30 days	Very rare

	Acute Viscerotropic Disease (YEL - AVD)	Up to 10 days	1-40/100,000
Hep B	Anaphylaxis (Hypersensitivity)	0-few hours	Very rare

Frequency: Very common ≥10%; Common ≥1% &< 10%; Uncommon ≥ 0.1%&<1%; Rare ≥0.01%<0.1%; Very rare <0.01

Adapted from: World Health Organization. Vaccine Safety Basics: Learning Manual. WHO, Geneva 2013

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 vaccine manufacturer. Potential vaccine quality defects might not be known at the time of authorization. Hence, vaccine safety pharmacovigilance surveillance must be strengthened to be able to gather this knowledge (Example: failure to inactivate polio virus in some Salk vaccine lots prepared by Cutter laboratories in 1955 resulting in poliovirus infection among some vaccines).

Immunization error-related reaction: An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and so is preventable. Staff who are not familiar with immunization, may be asked to perform immunization duties. Multiple vaccines with different specifications for storage, administration, dose etc, may be in use in a country simultaneously (Example: inappropriate administration of live measles vaccine to immunocompromised persons resulting in measles encephalitis or pneumonia).

Immunization anxiety-related reaction: AEFI arising from anxiety about the immunization and is unrelated to the content of the vaccine but to fear of the injection. Individuals can react in anticipation to and as a result of an injection of any kind. A larger number such AEFI reactions are anticipated due to: older age groups, the different vaccination environments, the novelty of the vaccines and their administration modalities (examples include syncope or hyperventilation).

Coincidental event: An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety. They mostly occur after a vaccination has been given but are not caused by the vaccine or its administration. Because of real and potential underlying comorbidities in a large number of the potential vaccinees, it will be challenging to differentiate true coincidental events from vaccine product related reactions or drug reactions or interactions (Example: meningitis that occurs within days of MMR vaccination that upon investigation is shown to be caused by *Streptococcus pneumoniae*).

CASE STUDY-1	What type of AEFI is the following incident?
	In 1955, after administration of inactivated polio vaccine manufactured by Cutter Laboratories in the USA, 40 000 people developed abortive polio, 200 were permanently paralyzed and 10 died. Investigations revealed that two production pools of 12 000 doses contained live virus.

B) Vaccine reactions by severity and frequency

Most vaccine reactions are minor and subside on their own. Serious reactions are very rare and, in general, do not result in death and long-term disability. Categorization of vaccine reactions by frequency of occurrence is given in Table 2.3.

Table 2.3: Frequency of occurrence of reported adverse reactions

Frequency category	Frequency in rate	Frequency in %
Very common	≥ 1/10	≥ 10%
Common (frequent)	≥ 1/100 and < 1/10	≥ 1% and < 10%
Uncommon (infrequent)	≥ 1/1000 and <1/100	≥ 0.1% and < 1%
Rare	≥ 1/10000 and< 1/1000	≥ 0.01% and <0. 1%
Very rare	< 1/10 000	< 0.01%

Vaccine reactions can be classified into two groups: minor and severe reactions (**table 2.5**). Ideally, vaccines will cause no, or only minor (i.e., non-severe) adverse reactions. Local and systemic reactions such as pain or fever that usually occurs as part of the immune response are typical examples of minor reactions. Severe is used to describe the intensity of a specific event (as in mild, moderate or severe). Severe vaccine reactions include among others seizures, thrombocytopenia, hypotonic hyporesponsive episodes (HHE) and prolonged crying, which all need to be reported. Most severe vaccine reactions do not lead to long-term problems. Anaphylaxis, while potentially fatal, is treatable without leaving any long-term effects.

Table 2.5: Comparisons of minor and severe vaccine reactions

Minor reactions	Severe reactions
Usually occur within a few hours of injection.	Usually do not result in long-term problems
Resolve after short period of time and pose little danger.	Can be disabling
Local (includes pain, swelling or redness at the site of injection).	Are rarely life threatening.

Systemic (includes fever, malaise, muscle pain, headache or loss of appetite).	Include seizures and allergic reactions caused by the body's reaction to a particular component in a vaccine

It is important to note that there is a difference between the terms “serious” and “severe” adverse events or reactions. A serious adverse event or reaction is a regulatory term, which, as defined by the Uppsala Monitoring Centre (UMC), is any untoward medical occurrence that at any dose results in death, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is life-threatening.

A severe reaction is a broader term, which includes severe reactions, but also other reactions that are severe but do not necessarily lead to long term problems (**figure 2.1**).

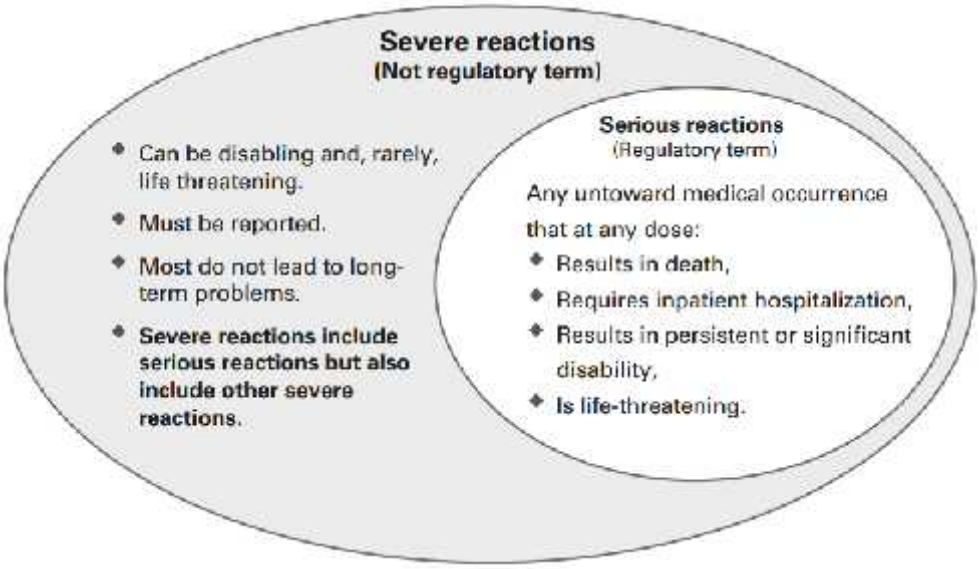


Figure 2.1: Serious versus severe vaccine reactions

Chapter summary

- Vaccines are biological preparations produced from living organisms or their components to boost immunity against disease
- Based on the antigen used in their preparation vaccines are categorized into different platforms
- Vaccines include a variety of ingredients including stabilizers, adjuvants, antibiotics, and preservatives.
- AEFIs can classified based on the cause and on severity/frequency

- Vaccine product-related AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
- Severe vaccine reactions include among others seizures, thrombocytopenia, hypotonic hyporesponsive episodes (HHE) and prolonged crying
- Serious reaction is a regulatory term

Chapter 3: Prevention and Management of AEFI

Allocated time: 140 minutes

Chapter description: The focus of this course is to develop an understanding on prevention and management of AEFI. Health professionals need to have the knowledge and skills to prevent adverse events from occurring, identify adverse events early, and clinically manage.

Primary Objective: The primary objective of this chapter is to equip programme managers at local, regional and national level and health care professionals with the technical knowledge to prevent and manage AEFI.

Enabling objectives:

Upon the completion of this chapter, trainees are expected to

- Explain Prevention and Management of vaccine reactions
- Explain Prevention and Management of anaphylaxis
- Discuss Prevention and Management of Immunization Error-Related Reactions
- Discuss Prevention and Management of Immunization Anxiety-Related Reactions
- Explain general preventive and management approaches of coincidental events

Background

Vaccines used in national immunization programmes are extremely safe and effective. However, no vaccine is perfectly safe and adverse events can occur following immunization. In addition to the vaccines themselves, the process of immunization is a potential source of adverse events. An adverse event following immunization (AEFI) is any adverse event that follows immunization that is believed to be caused by the immunization. Reported adverse events can either be true adverse events, i.e. really a result of the vaccine or immunization process, or coincidental events that are not due to the vaccine or immunization process but are temporally associated with immunization. Immunization can cause adverse events from the inherent properties of the vaccine (vaccine reaction), or some error in the immunization process (programme error). The event may be unrelated to the immunization, but have a temporal association (coincidental event). Anxiety-related reactions can arise from the fear or pain of the injection rather than the vaccine. In some cases, the cause of the AEFI remains unknown.

Vaccine reactions may be classified into common, minor reactions or rare, more serious reactions. Most vaccine reactions are minor and settle on their own. More serious reactions are very rare and in general do not result in long-term problems. Vaccines are very rarely contraindicated. However, it is important to check for contraindications to avoid serious reactions.

Programme errors result from errors and accidents in vaccine preparation, handling, or administration. They are preventable and detract from the overall benefit of the immunization programme. The identification and correction of these errors are of great importance. In addition, an event may occur coincidentally with immunization and at times may be falsely attributed to be a result of the vaccine. In other words, a chance temporal association (i.e., event happens after immunization) is falsely considered to be caused by immunization. These purely temporal associations are inevitable given the large number of vaccine doses administered, especially in a mass campaign.

3.1 Prevention and Management of Vaccine Reactions

	**Activity 2:** Brainstorming (5 minutes) What kind of vaccine reactions have you been encountered with and how did you manage it?

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.

For parents, advice should be given on managing the common minor reactions, in addition to instructions on seeking proper medical care if there are more serious symptoms. Such action will help to reassure parents about immunization and prepare them for common reactions. 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 the 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.

Table 3.1: Adverse events and their treatments

Adverse event	Treatment	Vaccines
Acute flaccid paralysis (Vaccine associated paralytic poliomyelitis)	No specific treatment available; supportive care	OPV
Anaphylactoid reaction (acute hypersensitivity reaction)	Self-limiting; anti-allergies may be helpful.	All
Anaphylaxis	Adrenaline injection	**Anaphylaxis**
Arthralgia	Self-limiting; analgesics	Rubella, MMR

Brachial neuritis	Symptomatic only; analgesics	Tetanus
Disseminated BCG infections	Should be treated with anti-tuberculous regimens including isoniazid and rifampicin	BCG
Encephalopathy	No specific treatment available; supportive care	Measles, Pertussis
Fever	Symptomatic; paracetamol.	All
Hypotonic, hyporesponsive episode (HHE or shock-collapse)	The episode is transient and self-limiting, and does not require specific treatment. It is **not** a contraindication to further doses of the vaccine	Mainly DTP, rarely others
Injection site abscess	Incise and drain; antibiotics if bacterial	All
Lymphadenitis (includes suppurative lymphadenitis)	Heals spontaneously (over months) and best not to treat unless lesion is sticking to skin. If so, or already draining, surgical drainage and local instillation of anti-tuberculous drug. Systemic treatment with anti-tuberculous drugs is ineffective	BCG
Osteitis/ Osteomyelitis	Should be treated with anti-tuberculous regimens including isoniazid and rifampicin.	BCG
Persistent inconsolable screaming	Settles within a day or so; analgesics may help	DTP, Pertussis
Seizures	Self-limiting; supportive care; paracetamol and cooling if febrile; rarely anticonvulsants	All, especially Pertussis, Measles
Sepsis	Critical to recognize and treat early. Urgent transfer to hospital for parenteral antibiotics and fluids	All
Severe local reaction	Settles spontaneously within a few days to a week Symptomatic treatment with analgesics. Antibiotics are inappropriate	All
Thrombocytopenia	Usually mild and self-limiting; occasionally may need steroid or platelets	MMR
Toxic shock syndrome (TSS)	Critical to recognize and treat early. Urgent transfer to hospital for parenteral antibiotics and fluids	All

3.2 Anaphylaxis

3.2.1 Recognition

 Time: 5 minutes	A 30 years old female took Janssen C-19 vaccine (First dose). Around 10:00 in the morning after 20 minutes of vaccination, she started to manifest wheezing, shortness of breath, uvular swelling along with tachycardia (PR=122) and hypotension (80/50), epigastric pain, high grade fever, headache, myalgia, chest pain, itching, cramping type of abdominal pain and rash starting from lower extremities which progressively involve all over the body. For this compliant she went to Mudula primary hospital after a day. - What should be the clinical impression from this case? - How should it be managed?

Vaccine anaphylaxis is a very rare, unexpected, and occasionally fatal allergic reaction. In addition, misdiagnosis of faints and other common causes of collapse as anaphylaxis, can lead to inappropriate use of adrenaline. Vaccinators should be able to distinguish anaphylaxis from fainting (vasovagal syncope), anxiety and breath-holding spells, which are common benign reactions. Indeed, it is recommended that preparedness to provide emergency treatment for anaphylaxis is necessary in all clinic settings.

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

Anaphylaxis develops over several minutes and usually involves multiple body systems. Unconsciousness is rarely the sole manifestation of anaphylaxis - it only occurs as a late event in severe cases. A strong central pulse (e.g., carotid) is maintained during a faint, but not in anaphylaxis.

When sudden loss of consciousness occurs > 5–10 minutes after immunization, anaphylaxis should be considered a possible diagnosis, in addition to vasovagal syncope. As anaphylaxis may be life-threatening and requires immediate medication, it should be ruled out quickly. Blood pressure, pulse, respiratory rate and peripheral circulation should be measured. The lungs should be auscultated for wheeze or stridor and the skin inspected for rash (urticaria, erythema, swelling). During this examination, the patient should remain supine, on the side, in the recovery position. Vaccinators should be able to recognize the following signs and symptoms of anaphylaxis:

Skin: A generalized red, raised and itchy rash (urticaria); swelling of the face and body (angioedema).

Respiratory: Dry persistent cough; noisy breathing (wheeze or, stridor); hoarse voice; difficulty talking or swallowing; struggling for breath (respiratory distress); blue tongue and lips (cyanosis).

Gastrointestinal: Cramps (abdominal pain); urge to pass stool.

Cardiovascular: Fast pulse (tachycardia); limb pulses not felt (hypotension).

Neurological: Collapse (loss of consciousness)

Table 3.2: Signs and symptoms of anaphylaxis based on severity

Time Scale	Signs and symptoms of anaphylaxis	Severity
Early Warning Signs	**Dizziness, perineal burning, warmth, pruritus**	Mild
	Flushing, urticaria, nasal congestion, sneezing, lacrimation, angioedema	Mild to moderate
	Hoarseness, nausea, vomiting, sub-sternal pressure	**Hoarseness, nausea, vomiting, sub-sternal pressure**
	Laryngeal oedema, dyspnea, abdominal pain	Moderate to severe
Late, life-threatening symptoms	**Bronchospasm, stridor, collapse, hypotension, dysrhythmias**	Severe

In general, the more severe the reaction, the more rapid the onset. Most life-threatening reactions begin within 10 minutes of immunization. Keep the recipient under observation for at least 20 minutes after the injection.

Symptoms limited to only one system can occur, leading to delay in diagnosis. Biphasic reactions where symptoms recur 8 to 12 hours after onset of the original attack and prolonged attacks lasting up to 48 hours have been described. The following table depicts the difference between acute stress response and anaphylaxis.

Table 3.3: Distinguishing anaphylaxis from acute stress response/Faint/Vasovagal Reaction

	Acute stress response (vasovagal syncope -VVS)	**Anaphylaxis**
At onset	**VVS and General:** Occurs suddenly, before, at time of, or soon after injection	Seconds to minutes after exposure, almost all cases within 1 hour
Skin	**VVS and General:** Pale, cold, sweaty/clammy	Red, raised itchy rash, swollen eyes, and face, generalized rash
Respiratory	**VVS:** normal to deep breaths **General:** rapid deep breathing	Noisy breathing, wheeze or stridor, persistent cough
Heart	**VVS:** slow pulse, transient hypotension **General:** normal or fast pulse or hypertension	Fast pulse, hypotension
Gastrointestinal	**VVS:** nausea, vomiting **General:** nausea	Abdominal cramps, vomiting, nausea
Neurologic	**VVS:** transient loss of consciousness reversed by supine position **General:** fearfulness, dizziness, numbness, weakness, tingling around lips, spasms in hands and feet	May develop loss of consciousness not relieved by supine position

3.2.2 Management of Suspected Anaphylaxis or Collapse after Vaccination

Each vaccinator must have an emergency kit with adrenaline, and be familiar with its dosage and administration. The expiry date of the adrenaline should be written on the outside of the emergency kit and the whole kit should be checked three- or four-times a year. Adrenaline that has a brown tinge must be discarded.

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.

Initial Management

1. Place the unconscious recipient in the recovery position and ensure the airway is clear.

2. Assess breathing and pulse (if strong carotid pulse, is not anaphylaxis).
3. If appropriate begin cardiopulmonary resuscitation.
4. Give adrenaline (see below for dosage) by deep intramuscular injection.
5. If the recipient is conscious after the adrenaline is given, place the head lower than the feet and keep the recipient warm.
6. Give oxygen by facemask, if available.
7. Send for professional assistance but never leave the recipient alone. Call an ambulance, and medical practitioner, if necessary, after the first injection of adrenaline, or sooner if there are sufficient people present.
8. If there is no improvement within 5 minutes, repeat the dose of adrenaline up to a maximum of three doses. Recovery from an anaphylactic shock is usually rapid after adrenaline.

Further management is usually provided in a medical Centre or hospital

- If there is shock (hypotension) – IV saline.
- If there is extrathoracic airway obstruction (stridor) -nebulized adrenaline/airway intervention.
- If there is intrathoracic airway obstruction (wheeze) – nebulized salbutamol and airway intervention.
- Hydrocortisone and an anti-histamine may be used as adjunctive medication.
- Nebulized salbutamol is helpful for bronchospasm and nebulized adrenaline for laryngeal oedema.

Table 3.4: Treatment of anaphylaxis (WHO recommended)

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

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

Steps to be taken after preliminary management and the patient is transferred to a medical Centre?

- A physician should conduct a complete clinical examination to confirm the diagnosis.
- Carry out case management (treatment and investigations) as recommended by clinical experts.
- Complete and submit an AEFI report form (within 24 hours).
- Document carefully all the symptoms and signs that were observed and the treatment given.
- Mark the immunization card clearly to indicate that further doses of that vaccine are contraindicated so that the patient never receives a repeat dose.
- List the event in the permanent health records of the vaccine recipient if possible.

Table 3.5: AEFI treatment kit

Contents of an AEFI treatment kit	
Injection adrenaline (1:1000) solution – 2 ampoules Disposable syringe (insulin type) having mL graduations and IM needle (gauges and length adjusted to targeted recipients) – sets Scalp vein set – 2 sets with medium-bore needles (gauges and length to be adjusted to targeted recipients)	IV fluid therapy – 1 unit in plastic bottle IV drip set – 1 set Cotton wool + adhesive tape – 1 each AEFI reporting forms Label showing: date of inspection, expiry date of injectable adrenaline and shortest expiry date of any of the components

) IV canula (various sizes, adjusted to targeted recipients)) Paracetamol (500 mg) – 10 tabs) IV fluids (Ringer's lactate or normal saline) - 1 unit in plastic bottle	) Drug dosage tables for injecting adrenaline) At hospital, oxygen support and airway) intubation facility should be available.

3.3. Prevention and Management of Immunization Error-Related Reactions

A full-term baby boy, birth weight 3.4 kg received intradermal injection of BCG on his left arm, Hepatitis B vaccine intramuscularly on right thigh and oral Polio vaccine 8 hours after birth. The baby received Hepatitis B vaccine (each dose of 0.5 ml contains purified HBsAg>10 microgram, Aluminum hydroxide gel equivalent to AL +++ 0.25mg and Thiomersal IP 0.025mg). Subcutaneous administration of aluminum salt containing vaccines can result in cyst, necrotic breakdown and sterile abscess formation.

A month later his mother noticed a lump in the right thigh at the site of Hepatitis B injection. As the lump was asymptomatic and non-progressive, mother waited until the 6 weeks vaccination visit. The baby was given subsequent doses of Pentavalent Vaccine and Inactivated Polio Vaccine (IPV) injections on his left thigh only. Baby completed all the recommended vaccinations until the age of eight months.

The lump was left untreated until eight months and later started to show progressive enlargement and diagnosis of post-injection abscess.

- What is the diagnosis of this child?
- How do you manage the post-injection abscess?
- How do you prevent such type of immunization error?

Immunization error-related reactions are AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable. Identification and correction of these errors in a timely manner are important. The main focus in these reactions is on the nature of the error rather than on the biologic process giving rise to the specific AEFI.

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

Prior to the introduction of auto-disable (AD) syringes, the most common immunization error was an infection as a result of a non-sterile injection because of contamination of the vaccine or diluent

vial or the injecting device (syringe and/or needle). The infection could manifest as a local reaction (e.g., suppuration, abscess) or a severe systemic reaction (e.g., sepsis, toxic shock syndrome). In addition, there was the perception of a risk linking immunization with blood borne infections. Nevertheless, one needs to consider infection that can occur in cases of mass vaccination or in disaster situations, particularly if there is a shortage of supplies or problems with logistics.

Sterile abscesses, while rare (~1 per 100 000 doses) are local reactions from aluminum-containing vaccines, especially Diphtheria- Tetanus- Pertussis (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. Contamination of vaccine or injection equipment can also 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. Any uncertainty should be referred to a higher level - a programme manager, pediatrician or physician. However, it is equally important not to overreact to concerns of false contraindications as this may lead to missed opportunities for vaccination, reducing coverage and thereby increasing the risk of disease in both individuals and the community.

Case Study
A child is supposed to receive a rotavirus vaccine with expired date of June 20, 2021. However, vaccine recipients receive after six months expire date. To this effect, three months later the patient develops of infection and admitted to hospital with the virus the vaccine was supposed to prevent. Following this, the child treated the infection with severe vomiting and diarrhea and fully recovered from his /her illness. It cannot be excluded that the patient would not have hospitalized of the infection if he/she had received the complete series of the vaccine, but it is likely. - Why type of immunization error encountered? - What type of precaution and measure should be taken to avoid such error. - What to do after such an error:

Case Study
An immunocompromised patient dies because of a vaccine A-strain infection after immunization with live-attenuated vaccine A, whereas the patient was supposed to have received vaccine B (not live). Therefore, if vaccination had been administered according to plan, the patient would never have encountered the vaccine A-strain infection that became fatal. - What type of immunization error encountered - What type of precaution and measure should be taken to avoid such error.

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

- It is both important and necessary to maintain the cold chain at all levels.
- Vaccines must be reconstituted only with the diluents supplied by the manufacturer.
- Reconstituted vaccine should be maintained in the recommended cold chain and used within six hours after reconstitution; it must be discarded at the end of each immunization session and should never be retained.
- Other than vaccines, no other drugs or substances should be stored in the refrigerator of the immunization center.
- Immunization workers must be adequately trained and closely supervised to ensure that proper procedures are followed.
- Careful epidemiological investigation of an AEFI is needed to pinpoint the cause and to correct immunization practices.
- Prior to immunization, adequate attention must be given to contraindications.
- Follow-up and corrective actions following immunization error-related reactions should be based on the findings of the investigation. Depending on the nature of the immunization error, these actions can be both general (e.g. training and awareness) and specific (e.g. strengthening cold chain maintenance if the problem found to be related to cold chain issues). Continued monitoring and supportive supervision can help to minimize these adverse events.

3.4 Prevention and Management of Immunization Anxiety-Related Reactions

3.4.1. Identification and Recognition

AG, a 13-year-old girl, received HPV vaccine in a school programme. She had fainted 2 months previously when a blood sample was taken, and, just before receiving the vaccine, she received a message from a friend complaining about how painful the injection had been. She was the last girl in her class to be vaccinated and had been standing, watching her classmates receive the vaccine. Before being vaccinated, she complained of chest pain, but the vaccinator was in a hurry and did not follow up on this complaint. Less than 2 minutes after immunization, AG said that she felt light-headed, had blurred vision and was having difficulty in breathing. The vaccinator administered a dose of adrenaline into the left deltoid; however, the shortness of breath persisted, and severe palpitations began. An ambulance was called, and AG was admitted to the local health care facility with a diagnosis of anaphylaxis due to the HPV vaccine.

What do you understand from this case?

What kind of measures do you took if you were in place of the vaccinator?

Health care providers involved in immunization should be informed about the characteristics of Immunization Anxiety-Related Responses (IARR), including measures to prevent or minimize their occurrence and recognition of the symptoms and signs in order to address them when they occur in one or more vaccine recipients.

In some situations, clusters of IARR can be anticipated, and measures should be taken to prevent them or to identify them rapidly. For example, the frequency of syncope is higher in HPV immunization than for other vaccines. This is probably because many programs deliver HPV immunization in schools, predominately for adolescent girls. HPV vaccine teams should therefore be prepared, and health care providers involved in large or mass immunization campaigns should be re-trained or sensitized about IARR just before they deliver these services.

Prevention begins before immunization, by addressing predisposing risk factors, such as identifying potential vaccinees at high risk of an IARR in discussions with the potential recipient, parents or teachers, paying special attention to precipitating factors for the expected recipient during immunization. Once identified, it is necessary to follow up with interventions to reduce perpetuation of the risk factors. Environmental factors such as an overheated, crowded waiting area, lack of privacy for immunization and access to negative social media and communications during school and mass immunization campaigns should also be addressed to decrease the risk of IARR.

Screening For High Levels of Needle Fear

- For children > 8 years and adults:
  - How afraid of needles are you? Not afraid; a little bit; medium or moderate amount; a lot; or the most afraid possible?
    - Do you think this level is higher than it should be (or higher than that of most of your friends)?
    - Do you avoid getting needles because you are afraid?
  - Parents can be asked similar questions about their children.
- Children aged 5–8 years could be asked:
  - How afraid of needles are you? Not all; a little bit; a medium amount; a lot; very, very much/ most possible?
  - Do you try hard to miss having a needle because you are so scared?

Identification of individuals with predisposing risk factors for an IARR

A rapid, targeted history before immunization can help to identify individuals with predisposing risk factors for an IARR. The risk factors relevant to immunization include:

- Age 10–19 years (but can occur outside this age group);
- history of vasovagal syncope
- a previous negative experience (e.g., from pain or vasovagal syncope) and an expressed fear of injections, including blood–injection–injury phobia; and
- pre-existing conditions such as anxiety disorders and developmental disorders (particularly autism spectrum disorder)

In some circumstances, targeted questions can be posed to identify strong needle fear. Such questions could be included on written consent forms or checklists, when these are used.

- If the responses to questions that suggest very strong needle fear (without avoidance), consideration should be given to treating the fear before future immunizations or at least taking time to manage the special needs of these individuals.
- If the fear leads to refusal (i.e., avoidance), additional measures may be required before immunization, such as counselling or behavioral interventions with appropriate health professionals.
- In selected circumstances of extreme fear and when the expertise is available, a patient might be referred for pharmacological anxiolytics and sedation. In some very rare instances, immunization could be done concurrently with a procedure that requires anesthesia.

Immunization environment and procedure

The immunization environment is important. When possible, vaccines should be administered in a calm, private, planned environment. This may be difficult when vaccines are provided during a short period for large groups of individuals, such as in mass campaigns or a school programme.

Attitude of health care providers and parents

A vaccinator who adopts a friendly, confident, relaxed approach is more likely to allay fear and anxiety. A trusting relationship should be formed, if possible, within the time constraints, supported by demonstration of competence and compassion. In some instances, parents may instill fear of needles and of health care professionals in their children, which can aggravate the children's fear. Such interactions should be discouraged.

Communication

Communication can help to mitigate anxiety and fear about immunization. Communication should be directed to both vaccine recipients and any accompanying parent or guardian. Age-appropriate language should be used, and words and phrases that might arouse fear should be avoided. Prior to mass immunization campaigns including school programs, targeted messages and awareness sessions, especially for adolescents, can help alleviate some concerns and with other interventions improve the immunization experience.

Pain and measures to reduce pain associated with injectable vaccines

As most vaccines are given by injection, people may receive many injections between infancy and adolescence and experience pain. Pain may play an important part in the stress response to immunization because it may be associated with mild to severe psychological distress. Pain

management is important as many children and some adolescents and adults experience significant pain and fear during needle procedures. Unmanaged pain from such procedures can have negative consequences, including longer procedures, syncope, greater distress, exaggerated negative memories, fear of needles and potential future avoidance of health care. General measures to reduce pain and fear are advisable in preparation for injection of a vaccine, which include physical, psychological and pharmacological strategies.

Additional Measures to Reduce the Risk of An Acute Immunization Anxiety Response in People Identified as At Risk

- The presence of a familiar person, such as a trusted family member or friend can be helpful. If this trusted person is anxious or fearful, however, their presence may exacerbate the potential for a stress response.
- When possible, people who are particularly anxious or fearful of injections should not have to wait with others prior to immunization.
- Immunize at the beginning of a clinic, if possible, separately from the group
- Immunization in private will also prevent their peers from observing any negative reaction, which could in turn make others more fearful.

Interventions for people at risk of syncope and vasovagal reaction

Once an individual has been identified as at risk for IARR, additional measures should be taken. This will depend on the available expertise and resources, with wide variation both among regions and situations (e.g., urban or rural, clinic or school programme). Nevertheless, some simple, inexpensive measures can be applied anywhere, such as immunizing a person who is at risk of a vasovagal reaction in a supine position. The risk of syncope can be decreased by use of a strategy called “muscle tension”, designed to maintain the blood pressure to avoid syncope. Reviewing the steps listed below with potential vaccine recipients can also give them a sense of control and distract them from the procedure.

Additional measures for people at risk of a vasovagal reaction

- Immunize in a seated or supine position.
- Consider using muscle tension
- After immunization, allow them to remain seated for at least 15–30 min

- People who are immunized in the supine position should adopt an upright position only if they have no vasovagal symptoms.
- Ideally, the vaccinator should remain with the vaccine recipient during this period and be alert for early signs or symptoms of a vasovagal reaction.

Muscle Tension

- Ask the vaccine recipient to tense his or her large muscle groups, such as by clutching a ball in the hand of the arm not used for immunization or tensing the leg and abdominal muscles.
- Ask him or her to maintain the tension for 15–30 seconds, until he or she feels warm or flushed in the face.
- Ask the vaccine recipient to release the tension to the starting point for 15–30 seconds.
- Repeat the tension and releasing cycles before, during and after the vaccination procedure.

3.4.2. Management

The general principle of managing an acute stress response such as a vasovagal reaction is calm, reassuring, positive communication with the vaccine recipient and family until the symptoms resolve.

- The immediate steps should include the following.
  - Reassure the affected person, others in the vicinity and the parent or caregiver where applicable that short-term anxiety and fears about insects, storms, heights, water, blood and needles are normal, as are similar worries about immunization.
  - In a clinic or school programme, segregate the affected person, assist him or her in lying down in a calm, well-ventilated place, manage crowd flow and minimize the presence of unnecessary staff, services and noise.
  - Keep calm and confident to comfort the patient, help him or her to breathe slowly and advise use of the muscle tension technique **(see section 4.1.7)** if necessary.
  - Once the patient's questions have been answered and if he or she is relatively calm, distraction e.g., listening to music, talking about something else, drawing etc.) may help to further decrease stress.
  - Encourage a return to "normal activity". Continue the session as planned, making sure that groups waiting for immunization are not in contact with the affected person.

The important aspects of management and communication include the following.

- The key is to differentiate an immunization stress-related response from anaphylaxis and other diagnoses (Refer table 3.1).
- If a vasovagal reaction has occurred, the individual should be maintained in the supine position and practice muscle tension if appropriate for their age.
- Once an immunization stress response has been identified, the vaccinator should clearly explain that it was not related to the vaccine product or to an immunization program or procedure error.
- The nature of the symptoms and the fact that they were to be expected, are not harmful and will resolve spontaneously without medication should be explained.
- Medication and hospitalization should be avoided, if possible, as they may aggravate the situation and result in additional cases.

Management of complex presentations

- They should be differentiated from other conditions
- Management of complex interventions consists of a multi-disciplinary approach, including
  - medical and psychological assessments and interventions to reduce any functional disability.
  - the patient should be referred to a health practitioner or a health center with the necessary expertise.
  - treatment should be tailored to the symptom constellation and may include physiotherapy, cognitive behavioral therapy or pharmacological interventions.

3.5. Coincidental events

Case study

In response to a severe diphtheria outbreak, DT was delivered to children in a mass campaign. The death of a seven-year-old girl, two to three days following immunization was reported. The symptoms reported included convulsions that might have been attributable to a vaccine reaction. Upon investigation, it was found that the girl had a history of convulsions and neurological symptoms unrelated to immunization.

- What type of AEFI was experienced
- What kind of precaution is needed to identify the real AEFI cases

In general, coincidental events are clearly unrelated and do not require any investigation (e.g., pneumonia). However, certain serious events may be blamed on the vaccine by the parents or community because of the close temporal association with immunization, especially if the child was previously healthy. Such cases need to be investigated, to allay public fear and maintain credibility. Responding to a community's concerns about immunization safety is important in maintaining confidence in the immunization programme. Calculation of the expected coincidental rate of that event may be helpful in the investigation of an AEFI.

If the same or similar event also affected others in the same age group around the same time, but they did not receive the suspect vaccine(s), then a coincidental event is more likely. There may also be evidence showing that the event is not related to immunization.

Chapter Summary

- Most adverse events after immunization are minor and health care workers need to alert parents to identify and provide simple remedies
- Lives can be saved if there is-
  - A clear plan for emergency response
  - Health care workers are trained to identify serious AEFI and respond to them quickly
  - Adequate preparation to identify and respond to serious AEFI exist in every vaccination site
  - Emergency equipment and drugs particularly adrenaline are essential

Chapter 4: Overview of the National Pharmacovigilance system

Allocated time: 65 minutes

Session Description

This session describes the importance of Medicines Safety Monitoring/Pharmacovigilance as one of the major regulatory functions mandated to the Ethiopian Food and Drug Authority (EFDA) for ensuring Safety, Efficacy and Quality of Medicines after they are made available for use in the market. Moreover, it also describes the National Pharmacovigilance System and Role of healthcare professionals (HCPs) in medicines/vaccines safety monitoring.

Primary objective: To enable participants understand the overall system of pharmacovigilance in Ethiopia

Enabling Objectives

After completion of this session, the participant is expected to:

- Define pharmacovigilance and related terminologies
- Explain the importance of pharmacovigilance
- Describe the national pharmacovigilance system
- Explain the role of HCPs in medicines/vaccines safety monitoring

Session outline

- Introduction
- Brief overview of Pharmacovigilance
- Important terminologies in Pharmacovigilance
- The National pharmacovigilance system
- Roles and responsibilities of healthcare professionals in pharmacovigilance

4.1 Introduction

Brainstorming:

Discuss about drug development cycle and its limitations? (5 minutes)

Continuous availability and accessibility of medicines/vaccines with proven safety, efficacy/performance and quality as well as their appropriate use are indispensable. The safety, efficacy /performance and quality of such products shall be assured throughout their life cycle from innovation until they are used by consumers (Figure 4.1). Broadly, the life cycle of a medicine consists of the discovery stage/innovation, pre-clinical research, clinical trials, marketing authorization, post-market surveillance: pharmacovigilance and changes in the use of a medicine.

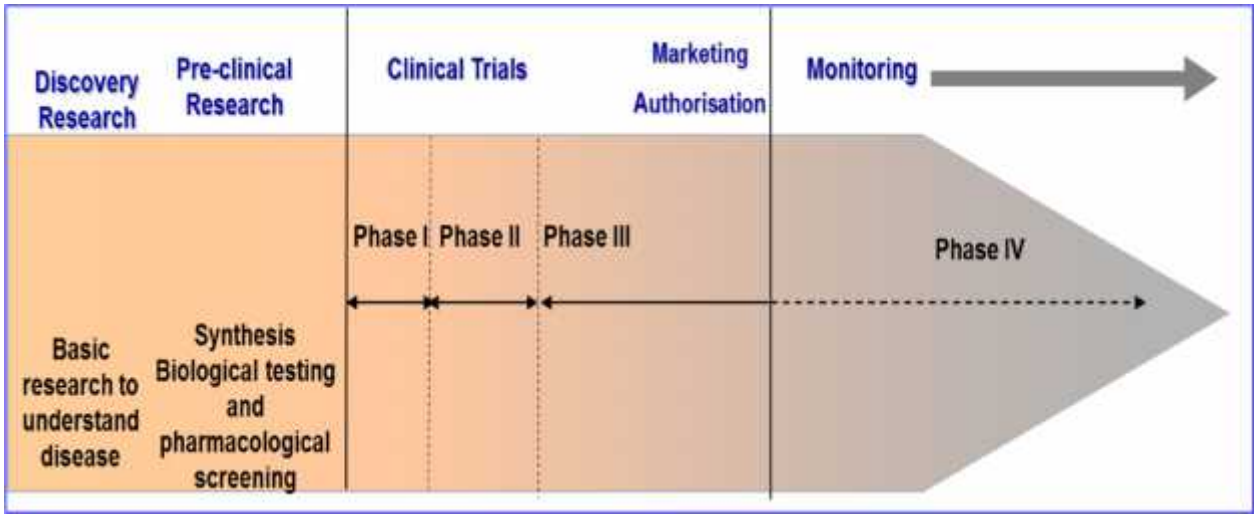


Figure 4.1: Overview of the life cycle of a typical human medicine

Thus, assuring safety, efficacy and quality of such products is the responsibility of manufacturers, importers, distributers, retail out-lets, public health programs, health institutions, health professionals and patients. However, the responsibility of assuring of safety, efficacy/ performance and quality of such medicinal products is not left only to these stakeholders. Hence, countries shall establish national medicine regulatory authorities that are legally mandated for ensuring safety, efficacy, quality, and appropriate use before and after they are made available in the market.

Accordingly, the Ethiopian Food and Drug Control Authority (EFDA), a national regulatory agency, is established and mandated as per the proclamation 1112/2019, to ensure the safety, quality and efficacy of medicines by undertaking the major regulatory functions including market authorization, quality testing, regulatory inspection, pharmacovigilance, market surveillance & control and clinical trial monitoring. No medicine obtained either from locally manufacturers or foreign sources, can be marketed and made available for use in the country without market authorization or permission from EFDA.

EFDA authorizes marketing or availability for use of medicines in the country after ensuring the safety, efficacy, and quality of medicines through dossier evaluation, good manufacturing practice inspection, and laboratory quality testing, as well as issuing pre-import approval and port clearance permit. EFDA undertakes and coordinates post-market or use surveillance including undertaking regulatory inspection, marketing surveillance & control, and pharmacovigilance to ensure safety, efficacy and quality of medicine and medical device after are made available for use in the country and safeguard the public.

It is evidenced that during the premarketing evaluations, the safety profiles of medicines are not fully identified and understood because tests in animals are insufficient to predict human safety, limited size and profile of trial participants, strict criteria of inclusion and exclusion for the trial and the duration of the clinical trial. Moreover, sometimes accelerated/emergency use approvals may be granted by regulatory bodies with limited safety profile of medicines. Hence, it is necessary to undergo post marketing safety monitoring/pharmacovigilance of medicines while they are in the market.

4.2 Brief overview of Pharmacovigilance

Pharmacovigilance started about 170 years ago, although it was not yet named as such at that time. In 1961, a big change of global Pharmacovigilance happened following the tragedy of Thalidomide, which was marketed in 1960 as a mild sleeping pill, considered safe, to alleviate morning sickness. However, by 1961, it started being associated with severe birth defects in babies delivered by mothers who had consumed it. It was discovered that the drug interfered with the babies' normal development, causing thousands of babies worldwide to be born with malformed

limbs. It was soon reported that 161 babies were adversely affected by thalidomide and this led to banning of the drug in Germany, followed by many other countries. This tragedy catalyzed the beginnings of the rigorous drug approval and safety monitoring systems seen around the world.

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems. Due to variations in drug production, distribution and use of drugs, genetics, diet, tradition of the people and pharmaceutical quality and composition, pharmacovigilance is needed in every country. The major aims of pharmacovigilance include:

- ❑ Promote safe, rational and more effective use of medicines
- ❑ Early detection of hitherto unknown adverse reactions and interactions,
- ❑ Detection of increases in frequency of (known) adverse reactions,
- ❑ Identification of risk factors and possible mechanisms underlying adverse reactions,
- ❑ Estimation of quantitative aspects of benefit/risk analysis and
- ❑ Dissemination of information needed to improve drug prescribing and regulation

Box 4.1 PV activities

- ✓ PV activities include: collecting and managing data on the safety of medicines, looking at individual case reports to detect new "signals", pro-active risk management to minimize any potential risk associated with the use of medicines, communicating and informing stakeholders and patients.

! **Key point**

Pharmacovigilance may also aid in identifying medication errors, substandard and falsified medicinal products, therapeutic failure and adverse drug reactions.

4.3 Important Terminologies in Pharmacovigilance

Terms	Definition
Drug or Medicine	Any substance or mixture of substance used in the diagnosis, treatment, mitigation or prevention of human disease, disorder, abnormal physical or mental state, or the symptoms thereof; used in restoring, correcting or beneficial modification of organic or mental functions in human.
Adverse Event	Any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment, that is an adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it.
Adverse drug reaction (ADR)	Any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.
An unexpected ADR	Any reaction, the nature or severity of which is not consistent with domestic labeling or market authorization or is unexpected from characteristics of the medicine
Serious Adverse Effect	Any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability or incapacity, or is life threatening.
Medication error	Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Medication error may be related to professional practice, healthcare products, procedures, and systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use.
Product quality defect	Quality problem of products with suspected contamination, questionable stability, defective components, poor packaging and labeling and therapeutic failure.
Passive surveillance	is a system in which regulatory authorities and pharmaceutical companies wait for healthcare professionals, patients, or consumers to make the effort to contact the authority or company to spontaneously report an encountered adverse drug event. It is also called voluntary reporting.
Active surveillance	systems or situations in which adverse events are purposely sought in the post marketing setting by a health authority's request health professionals to report an adverse drug event of a particular drug or class of drugs in the form of prompted reporting or stimulated reporting or observational studies to more closely follow, identify and investigate on a potential or weak signal.
Signal	Reported information on a possible causal relationship between an adverse event and a medicine, the relationship being previously unknown or incompletely documented. Usually more than one signal report is required to

	generate a signal, depending on the seriousness of the event and the quality of the information.
Cluster	Two or more cases of the same or similar event related in time, geography and/or vaccine administered. National program managers may decide upon a more precise definition.
Therapeutic Failure	Failure to accomplish goals of treatment due to inadequate or inappropriate drug therapy and not related to natural progression of the disease.
Substandard Medicine	A genuine, authorized medical product that fails to meet the quality specifications acceptable as per national standards. Therefore, their composition or ingredients may not meet specifications; and consequently, they may be dangerous to the patient.
Counterfeit	Medicine which is deliberately or fraudulently mislabeled with respect to source or identity. Counterfeit products may include products with the correct ingredients or those with the wrong ingredients, those with

4.4 The National Pharmacovigilance System

Brainstorming: Discuss in group and reflect on status of pharmacovigilance activities in Ethiopia (5 minutes)

EFDA is mandated by proclamation 1112/2019, to conduct medicines safety monitoring. Article 4; sub articles 9 and 10, describes that EFDA undertake/order post-marketing surveillance to ensure safety, efficacy and quality of medicines and take appropriate legal measures and ensures that evidence of existing and new adverse events and information about pharmacovigilance of globally monitored products are followed upon and, as appropriate take the necessary legal measure, respectively. Moreover, article 22 states any medicine, its raw or packaging material shall meet quality, safety and efficacy requirements prescribed in nationally accepted pharmacopeia.

Article 24 -Every health professional working for a medicine or medical device institution shall have the duty to immediately report risks of public health significance related to the quality, safety and efficacy of medicine or quality, safety and effectiveness of a medical device to the executive. Moreover, article 39: Every market authorization holder (MAH), as appropriate, shall perform periodic monitoring of the quality, safety, and efficacy of its manufactured or imported medicine and every MAH of a medicine or medical device shall, when required by the executive organ or on its own will, perform a post-marketing surveillance that enable it to continuously monitor its medicine or medical device; establish a vigilance system, and furnish adverse event information.

National Pharmacovigilance System has been established in 2002 and by the year 2008, Ethiopia became the 88th official full member of the WHO International Drug Monitoring Center at Uppsala (UMC). Currently, EFDA, is mandated to establish and coordinate a pharmacovigilance system to make follow up of adverse drug events both from global and local evidences and then undertake appropriate regulatory measures. Many efforts have been under taken since its establishment and the major ones include:

- Establishing organizational structure for pharmacovigilance: at national and sub-national pharmacovigilance centers:
- Pharmacovigilance roadmap development
- Developing national directive, guideline and SOPs for pharmacovigilance functions;
- Implementing various Adverse Drug Reaction Reporting tools
- Developing and implementing various AEFI Reporting Tools
- Establishing national pharmacovigilance advisory committee,
- Conducting active PV on HIV, MDR-TB medicines, and COVID-19 vaccines;
- Reporting ADR/AEFI to the WHO drug monitoring center (UMC)
- Undertaking investigation and causality assessment for eligible cases
- Undertaking risk – benefit analysis and taking regulatory measures
- Developing standardized training materials on pharmacovigilance (Basic pharmacovigilance, COVID-19 AEFI) and build the capacity of healthcare professionals

4.4 Roles and responsibilities of healthcare professionals in pharmacovigilance

Brainstorming: What do you think are the roles and responsibilities of HCPs in pharmacovigilance? (5 minutes)

All healthcare professionals in the nation have a very important role of identifying and notifying problems occurring when marketed medicinal product/vaccines are used. They need to alert EFDA about suspected ADRs/AEFIs, medication errors and product quality problems in order for the authority to take action in preventing or minimizing the occurrence of medicine-related injuries in the future. The activities that healthcare professional need to perform when encountering an adverse drug event should include:

a. Being vigilant and detect adverse drug events

It is important that healthcare professionals are vigilant and perceptive towards any unexpected sign, symptom or complaint voiced by patients/consumers taking medicines/vaccines, particularly in the early phases of treatment. Even if distinguishing between the natural progression of a disease and an adverse effect by a medicine/vaccine can be difficult, when an unexpected event, for which there is no obvious cause, occurs in a patient taking a medicine/vaccine, the possibility that it is caused by the medicine/vaccine or its use must always be considered. Thus, healthcare professionals should monitor for medication errors whilst prescribing, transcribing, dispensing and administering medicines to patients.

Health professionals should make physical inspections of the pharmaceutical product to be dispensed or administered and report any quality defect. Pharmacy professionals have an important role in the work of detecting product quality defects such as color changes, separating components, powdering, crumbling, caking, molding, change of odor, incomplete pack, suspected contamination, poor packaging/poor labeling.

b. Have knowledge on the common AEFIs

Healthcare professionals shall have adequate knowledge of common AEFIs and they need to be vigilant and detect them when the events occur. They should also be able to report whenever they are encountered.

c. **Assessing the patient**

When a vaccine-related problem is suspected, the clinician should carry out a thorough physical examination with appropriate laboratory tests and consider:

- The patient's medical history, including history of a similar reaction or allergy,
- The existence of any potential risk factors, such as hepatic or kidney insufficiency,
- The existence of risk groups such as pediatric, elderly, pregnant and lactating patients.

d. **Managing the encountered AEFIs**

If an AEFI is suspected, the health care professional should treat the patient and consider adjusting the dose or replace the vaccine or withdraw the vaccine. The patient should be informed about the suspicion of the AEFI and what actions are planned. Careful documentation of the AEFI in the patient's medical records should take place. Documenting and informing the patient is important to avoid future problems. Moreover, the health care professionals should also fill and provide

allergic card to patient/consumers that have shown allergic reaction to medicine. If a vaccine has caused an allergy, the EFDA "Allergy card" is recommended to be used (Fig. 4.2).

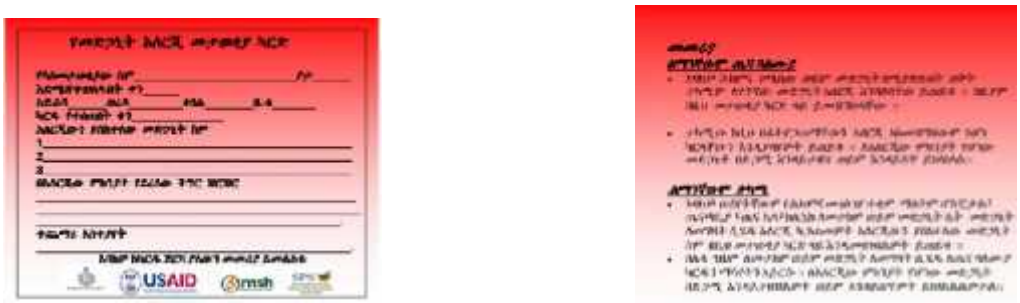


Figure 4.2. EFDA Allergy card format.

The purpose of the allergy card is to prevent patients from being prescribed again the medicines/vaccine for which they are allergic in the first encounter. Patients should then carry the card with them and present it to any health facility at upcoming visits.

If the event is believed to be caused by a medication error, action should be taken according to the hospital or healthcare facility's routines in order to avoid similar problems in the future. Accordingly, the AEFIs, medication error or product quality defects encountered should be reported to EFDA immediately.

e. Reporting AEFIs

Healthcare professionals should report any suspected AEFI to the pharmacovigilance center at EFDA.

Chapter summary

- ✓ Safety, efficacy /performance and quality of medicines/vaccines shall be assured throughout their life cycle.
- ✓ Regulatory authorities are legally mandated for ensuring safety, efficacy, quality, and appropriate use before and after they are made available in the market.
- ✓ EFDA is established and mandated as per the proclamation 1112/2019, to ensure the safety, quality and efficacy of medicines.
- ✓ Accelerated/emergency use approvals may be granted by regulatory bodies with limited safety profile of medicines.
- ✓ PV is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems.
- ✓ HCPs need to alert EFDA about suspected ADRs/AEFIs, medication errors and product quality problems

Chapter 5: AEFI surveillance system in Ethiopia

Allocated time: 60 Minutes

Chapter Description:

The chapter introduces the AEFI surveillance system of Ethiopia with particular emphasis on what, how, and when AEFI should be detected, recorded reported, investigated analyzed with the involvement of all relevant stakeholders with respective roles and responsibilities. Hence, appropriate information will be obtained on a given AEFI, and a timely response is provided to prevent vaccine-related harms and ensure the public trust of immunization.

Chapter Objective:

At the end of this chapter, participants will be able to understand and describe the rationale behind conducting vaccine safety surveillance, the different components of AEFI surveillance system and the roles and responsibilities of stakeholders of the AEFI surveillance system

Enabling Objective:

- Describe the rationale behind conducting AEFI surveillance
- Explain the different components of the AEFI surveillance cycle
- Understand AEFI surveillance methods
- Understand the role of different stakeholders of the AEFI surveillance system

Chapter Outline:

- Introduction to AEFI surveillance
- Objectives of AEFI Surveillance
- AEFI surveillance cycle
- Types of AEFI Surveillance system
- Roles and Responsibilities of stakeholders of national AEFI surveillance system
- Chapter Summary

5.1. Introduction to AEFI surveillance (5min)

Currently, Pharmacovigilance is an integral part of the regulation of drug and vaccine safety globally. Immunization Safety Surveillance (vaccine pharmacovigilance) is system for ensuring immunization safety through detecting, reporting, investigating and responding to AEFI. While regulatory and public health agency pharmacovigilance activities are equally robust for medicines and vaccines, AEFI surveillance which is an integral part of the National Pharmacovigilance Activities, often relies on different systems and procedures. This is because, though vaccines are considered drugs they require different "immunization safety" surveillance systems to monitor adverse events

5.2 . Objectives of AEFI surveillance (10min)

General Objective of AEFI surveillance

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

Specific Objectives of AEFI surveillance

- To rapidly detect and respond on time to occurrence AEFIs
- To trigger further clinical, epidemiologic, or laboratory investigations regarding a possible causal relationship between a vaccine and adverse event
- To provide descriptive epidemiologic data on national numbers of reported adverse events following immunization (AEFI) to identify risk factors and mechanism of actions
- To closely monitor the safety of newly licensed vaccines
- To detect previously unrecognized AEFI from both existing and newly licensed vaccines
- To detect apparent increases or decreases in previously reported events
- To detect preexisting conditions that may promote reactions and may represent contraindications or precautions to additional doses, in addition to that it prevents false blaming arising from coincidental AEFI.
- To identify vaccine lots associated with unusual numbers and types of reported events

- To detect, correct and prevent immunization error related AEFIs caused by errors in vaccine preparation, handling, storage or administration
- To effectively communicate with parents, community, the media and other stake holders to create awareness on AEFIs without jeopardizing the immunization program credibility.
- To maintain the confidence of the community and health staff in the immunization programme by appropriate and timely responses to their concerns about immunization safety
- To collaborate and share information with WHO (through post-marketing surveillance), to support generation of new and additional information on vaccine safety.
- To manage, prioritize and validate signals of vaccine safety

5.3. AEFI surveillance cycle(5min)

AEFI surveillance cycle starts with identification of AEFIs from the lower level of immunization service delivery. This will then be notified to health care workers and reported to the next level as per the standard route. Investigation, analysis and causality assessment will be performed for SAEs and other AEFIs of the concern. Based on the findings obtained, the corrective action will be taken and feedback will be communicated to the relevant stakeholders.

Fig 5.1 AEFI Surveillance cycle

5.4 Types of AEFI Surveillance System(15min)

There are mainly two types of AEFI surveillance systems: passive and active surveillance. Each are described below in detail.

5.4.1. Passive surveillance:

This encompasses all spontaneous AEFI reporting from immunization service providers/hospitals/patients to the first administrative level (district/wereda level) in the surveillance system spontaneously and voluntarily. From there, reports are sent to the next reporting sub national level(s), ending at the national-level unit and global institutions responsible for AEFI surveillance. Passive surveillance systems theoretically allow anyone in a country to report, and due to their broad coverage they can provide the first indication of an unexpected AEFI.

Advantages of Passive AEFI Surveillance

1. Enables to early detect rare and the unknown serious AEFIs.
2. Not resource intensive
3. Helps in hypothesis generation
4. Covers the whole population and all vaccines used in the national immunization system

Limitation of passive AEFI surveillance

1. Underreporting of AEFIs
2. Difficulty to determine rates of AEFIs due to the absence of denominator
3. Inability to properly characterize the strength of association between vaccine exposure and adverse events

Due to the above limitations AEFI surveillance systems should add layers of active surveillance and/or epidemiological studies to maximize the effectiveness of passive AEFI surveillance (e.g. enhanced spontaneous surveillance introduced during special immunization campaigns to encourage reporting by service providers or receivers).

5.4.2. Active surveillance:

Active (proactive) vaccine safety surveillance is an active system for the detection of adverse events. This is achieved by active follow-up after vaccination. Events can be detected by asking

patients directly or by screening patient records. It is best done prospectively. This method aims to monitor certain specific adverse events and seeks to ascertain the number of AEFI entirely through a pre-planned process. This is primarily used for characterization of the AEFI profile, rates and risk factors, but logistical and resource constraints limit its wide application. Countries may carry out active AEFI surveillance only for selected AEFI or vaccines at selected institutions (sentinel sites). Active surveillance can also be carried out in the community setting (e.g. cohort event monitoring).

Advantages and Disadvantages of active AEFI surveillance

Advantages:

1. Availability of Denominator which enables calculation of rate of AEFIs
2. Ability to produce a complete profile of AEFIs
3. Ability to identify and assess risk factors
4. Effective in early detection of signals

Disadvantages:

1. It involves the collection of AE data from only part of the total population
2. More resource intensive than passive AEFI surveillance

5.5. Roles and Responsibilities of stakeholders of national AEFI surveillance System(20min)

Activity:

Group Work	
	▪ What are national and sub national level stakeholders and their specific role and responsibilities?

AEFI surveillance systems exist to ensure effective monitoring and prompt actions in response to AEFIs. AEFI surveillance in Ethiopia is a collaborative venture between the EFDA, the National EPI programs of FMoH, EPHI, pharmacovigilance advisory committee, regional health bureaus and regulatory bodies, regional task forces of AEFI, professional associations, academic institutions,

Market Authorization Holders (MAHs) (manufacturers, importers and distributors), health institutions, clients including guardians and all concerned development partners as all are responsible for the safety of vaccines (Figure 5.1).

EFDA is responsible to ensure that all medicines, including vaccines are safe, effective and of good quality. On the other hand, the EPI program of the FMOH is responsible for preventing disease, disability and death by providing safe and effective vaccine to children and adults to prevent and control vaccine preventable diseases. The successful implementation of AEFI surveillance system requires active involvement of EFDA, immunization program of the FMOH and other stakeholders. National and sub national level AEFI surveillance stakeholders as listed below:

National stakeholders in AEFI investigation

- FMoH/EPI
- EFDA
- Pharmacovigilance advisory committee
- EPHI

Sub national Stakeholders in AEFI reporting and investigation

- Parents/ guardian
- Health workers
- Woreda EPI Office (WEO)
- Zonal EPI Office(ZEO)
- Regional EPI Office (REO)
- The EFDA branch offices
- Decentralized university hospital based pharmacovigilance centers.
- The regional AEFI Taskforce

Figure 5.1. **Stakeholders of AEFI surveillance system**

5.5.1. The National level Stakeholders

5.5.1.1. Ethiopian Food and Drug Authority (EFDA)

EFDA has the mandate of ensuring that every pharmaceutical product (including vaccines) used within the country is of good quality, effective, and safe for the purposes for which it is proposed. Therefore, EFDA is responsible for the following activities regarding AEFI surveillance. When pharmacovigilance team in EFDA receives the filled AEFI report, review will be conducted in the context of other reported AEFIs received from all parts of the country, particularly in the same period, 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 report and reviewing the data or running analyses as needed. If similar cases were reported earlier, it is essential to determine if an epidemiological linkage or other pattern can be identified if there is one. The need for technical or operational assistance for the investigation has to be assessed. Advice can be sought from the pharmacovigilance advisory committee at this point.

The EFDA pharmacovigilance center (PVC) and the pharmacovigilance advisory committee play a key role in supporting the immunization program for AEFI investigation and causality assessment. They also provide recommendations to the FMoH/EPI on vaccines based on their causality assessment findings.

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

EFDA/PVC is responsible to share the information with the global community through VigiBase®, maintained by the Uppsala Monitoring Centre under the WHO International Drug Monitoring Program. EFDA can also provide information on the vaccines and lots distributed in the country when requested by FMOH/EPI). The EFDA can also analyze and use information on AEFI from other reliable international sources. Cases shared by EFDA to EPI should be a part of the total AEFI cases documented by EPI in the WHO-UNICEF Joint Reporting Form (JRF).

In addition, the following major activities will be performed by EFDA/PVC:

- Designing, establishing, maintaining, monitoring and evaluating AEFI surveillance system in the country in collaboration with FMOH /EPI and other stakeholders
- Revising, updating and distributing AEFI surveillance reporting tools and guidelines
- Coordinate pharmacovigilance advisory committee to evaluate reports and assess causality
- Maintaining and ensuring the use of the database at the national level.
- Provision and follow-up of training of personnel involved in AEFI surveillance in collaboration with other stakeholders.
- Conducting supportive supervision of AEFI surveillance activities
- Establishing a coordination platform of stakeholders through bimonthly (once every two months) AEFI partners coordination meetings
- Sharing information with international agencies and manufacturers
- Carrying out risk- benefit analysis of vaccine used in the immunization program
- Taking the necessary corrective measures when there is a safety and quality problem of vaccines.
- Communicating AEFIs that needs public attention at the national level with FMOH.
- Supporting regions and strengthening AEFI documentation and reporting system.
- As a member of EPI taskforce, EFDA will participate in the planning, training, implementation and monitoring phases of immunization campaigns and new vaccine introductions.

5.5.2.2. National Immunization Program of FMOH

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

- Collaborating with EFDA in the continuous development, revision and distribution of tools and guidelines for AEFI surveillance
- Ensuring further distribution of tools (AEFI Reporting Form; Guidelines etc.) from the Regional Health Bureaus to lower levels
- Training of peripheral level health staff on AEFI activities and case management in collaboration with regional and zonal health bureau.
- Providing support to Region, Zone and Woreda on AEFI reporting and investigations as needed
- Submitting AEFI reports received from routine immunization and campaigns to EFDA as soon as possible.
- Strengthening AEFI documentation and reporting system through the routine immunization, supplemental immunization activities as well as during new vaccine introductions.
- Ensure participation of EFDA in the planning, training, implementation and monitoring phases of immunization campaigns and new vaccine introductions.

5.5.2.3 Ethiopian Public Health Institution

- The EPHI at all levels will collaborate with EFDA in the detection and reporting of AEFI reports in the immunization programme.

5.4.1 Roles and Responsibilities of the Sub-national Stakeholders

The parent/ guardian

At the time of immunization, it is important for health workers to sensitize the parents about expected events such as fever and pain at injection site, etc. following immunization. Parents should be advised about simple home remedies (e.g. correct positioning of the child when sleeping, increasing intake of fluids, sponging, breast feeding, antipyretics etc.).However, at the same time, they should also be instructed to detect and notify to the health worker any unexpected events (e.g.

very high fever not responding to anti pyretic) or other unusual events that occur after immunization if they occur.

The health worker

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

The Woreda EPI office

When an AEFI report is received by the WEO, s/he should review the report and determine if the reported AEFI case meets the criteria required for a detailed investigation. If necessary s/he should contact the primary reporter and visit the locality of the event and interview relevant stakeholders for additional information. The case may be considered not warranting detailed investigation if it is a minor AEFI and not serious AEFI, WEO should indicate this on the reporting form and email/ fax the same to the concerned zonal EPI Officer or directly report to EFDA.

The Zonal EPI Office

The Zonal EPI Officer will report to regional EPI Officer (REO) or to EFDA and should collaborate during investigation of SAEs or other AEFIs as necessary.

The Regional EPI Office

At the regional level, the regional EPI officer (REO) should share the reports to Branch EFDA pharmacovigilance focal person. The regional EPI officer should also participate in investigations initiated by the region, zone, woreda and at national level.

Other stakeholders of AEFI include academic and research institutions, media, and consumer associations

Chapter Summary(5min)

- Immunization Safety Surveillance (vaccine pharmacovigilance) is system for ensuring immunization safety through detecting, reporting, investigating and responding to AEFI.
- In Ethiopia vaccine safety surveillance needs to be done in collaboration of different stakeholders: national immunization program (FMoH/EPI), the national regulatory authority (EFDA), market authorization holders (MAHs), different regional regulatory bodies, academia, healthcare workers/health institutions, media, patient/parents and academia with clear role and responsibility to be undertaken.
- Mainly two types of AEFI surveillance systems are followed: passive and active surveillance and implemented based the safety concern of vaccines and immunization service delivered.
- The functional surveillance system should follow AEFI surveillance cycle encompassing identification, notification, reporting, investigation, analysis, causality assessment and feedback/corrective actions.
- The ultimate goal of establishment of vaccine safety surveillance is reporting AEFI through standardized and available tools for further surveillance related activities; such as further investigation, causality assessment and feedback/corrective actions to be taken.

Chapter 6: AEFI detection, notification, and reporting

Allocated time: 100 min

Chapter description:

The chapter introduces participants with components of AEFI reporting system and the different types of AEFI reporting tools. The chapter describes the detection/identification and notification of AEFI. It focuses on what, when, how, who and for whom to report adverse events. It is designed to improve these important functions of the country's pharmacovigilance system by encouraging participants to be more vigilant for the safety of vaccine recipients and to create awareness on the mechanisms and the different reporting tools.

Chapter objective:

At the end of this chapter, participants will be able be explain about AEFI detection, notification, components of AEFI reporting system and different types of reporting tools.

Enabling objective:

- Describe the basics of AEFI detection, notification, and reporting
- Identify components of reporting system
- Recognize various reporting tools
- Describe AEFI reporting during campaign
- Identify the barriers of AEFI reporting

Chapter outline:

- Introduction to AEFI detection, notification and reporting
- Components of AEFI reporting system
- Types of AEFI Reporting tools
- AEFI reporting during campaign
- Barriers of AEFI reporting

6.1 AEFI detection, notification, and reporting

AEFI identification/detection: when the adverse event is first identified by the vaccine recipient, caregiver, or healthcare provider.

AEFI notification: when the event is brought to the notice of the health-care system, either by the patient or by their relative.

AEFI reporting: when the first information of the event is obtained by a health-care worker (any person in the health-care system) and the information on the event is documented in an AEFI reporting form and is sent to the next level.

AEFI case detection is the first important step in AEFI reporting system. The primary reporter (i.e., the one who first reports an AEFI) may be a field health worker, clinic or hospital staff, a volunteer, parent, vaccine recipients or any other person who detects the AEFI.

Suspicion alone is sufficient for reporting, and the primary reporter is not expected to assess causality. Rapid detection and evaluation of a possible link to vaccines is essential to ensure the continued safety of vaccines. Thus, in case of a suspected AEFI, it is preferable to submit a report to a suitable health institution/health office on time rather than waiting for all aspects of an investigation to be completed. In many settings the primary reporter submits a report to the immediate reporting to health institution/health office/authority. The report is then transferred up through the intermediate level to the national level, and to the central immunization program and/or EFDA. The reporters at different levels may seek to clarify or request additional information before sending the report onward.

6.2 Components of AEFI reporting

6.2.1 What to report?

All AEFIs shall be reported regardless of seriousness/severity. The following AEFIs should be reported immediately to EFDA;

- Serious AEFIs in vaccinated patients or events that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability/incapacity, or result in a congenital anomaly or birth defect or is a medically important event or reaction.

- The occurrence of events with an unexpected high rate or unusual severity
- Signals generated as a result of individual or clustered cases
- Significant events of unexplained cause occurring within 30 days after vaccination
- Events causing significant parental, family, healthcare worker, or community concerns
- AEFI as a result of potential immunization errors
- Adverse Events of Special Interest (AESIs)

Reporting all minor AEFI such as high fever and minor local reactions is recommended. Particularly, in case of new vaccines with insufficient safety data in the population healthcare professionals should report all AEFI that are brought to their notice regardless of its seriousness.

6.2.2 When to report?

A report must be made as quickly as possible so that an immediate decision can be made on the need for action and investigation. In case of serious AEFI, vaccine administrators should inform their supervisor and/or woreda immunization officer immediately (over telephone) and complete the reporting form within 24 hours. The woreda immunization officer should review the report and send immediately to the zonal or regional immunization officer through e-mail or fax. The zonal or regional immunization officer should send the reports to EFDA (Fig. 5.1). Moreover, AEFI reports can be sent directly to EFDA. In case of minor AEFIs, individual cases has to be line listed and sent to the next higher level on at least on a monthly basis.

6.2.3. Who should report

All health care professionals are responsible for reporting AEFIs

- Physicians
- Nurse
- Pharmacy professionals
- Public health professionals
- Laboratory professionals
- Others

6.2.3. How to report?

All SAE reports should be made on a standard AEFI reporting form (Annex 6.1). Whereas minor AEFIs should be reported using line list. However, for new vaccines all AEFI cases regardless of seriousness/severity should be reported using standard AEFI reporting form. It is a shared responsibility of the immunization service provision unit and the regulatory authority to supply

these forms. The report should be kept simple but should ensure that health workers can input essential information. It is important that all of the minimum required information should be entered into the reporting form, as this is the basis for decisions regarding the need for further investigation. Countries are strongly encouraged to maintain at least the minimum required information, so that data can be shared with regional and global partners through the WHO Program for International Drug Monitoring. For optimal vaccine safety monitoring and meaningful analysis of AEFI data, systematic and standard collection of critical parameters is essential.

A limited number of variables are required to manage AEFI information properly. These include;

- Unique identifier for the report
- The primary source of information
- Patient characteristics
- Details of the event(s)
- Details about vaccine(s) of interest and
- The possibility of collecting additional information if needed. Any additional information that is collected would be useful for investigation.

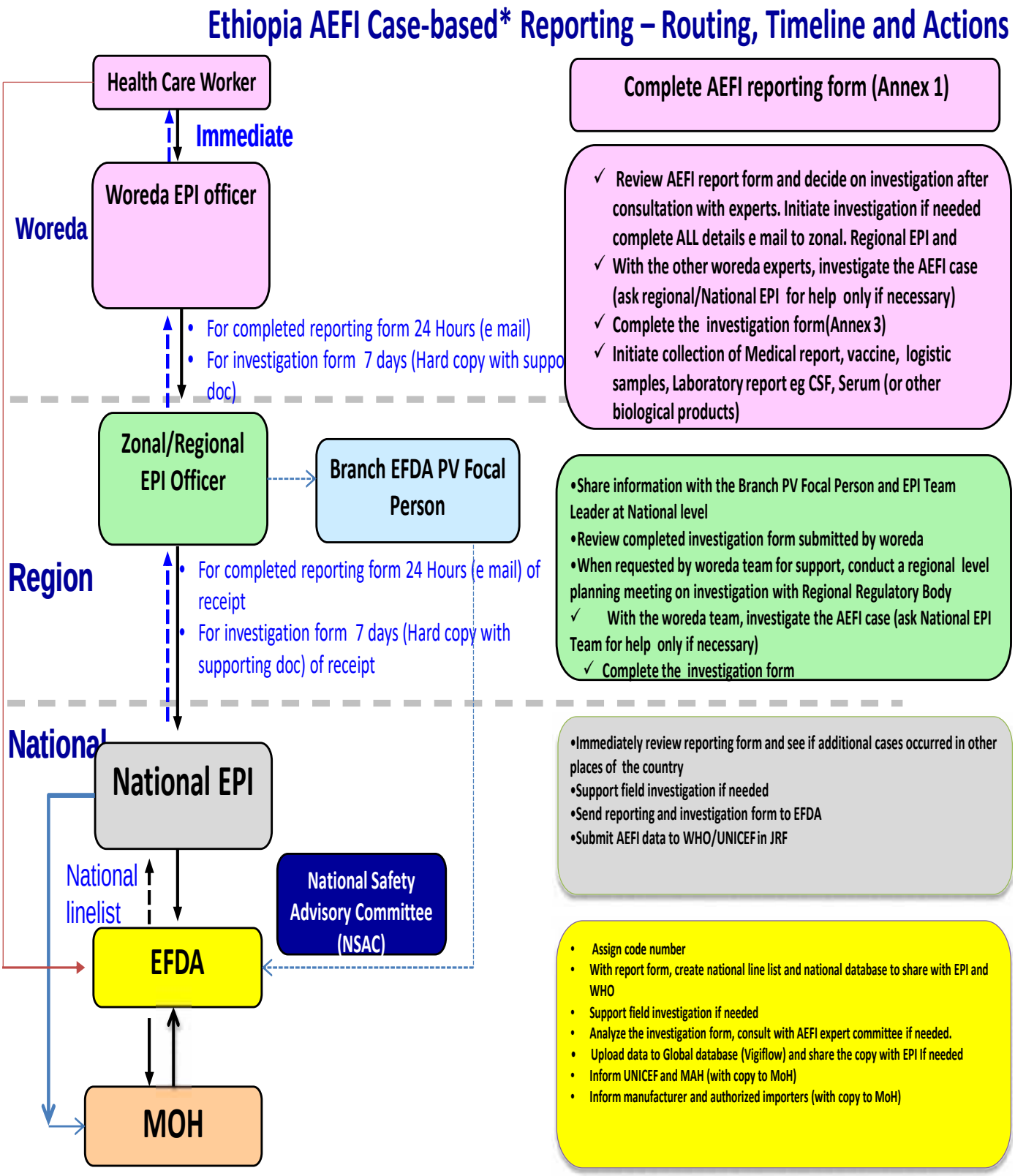


Figure 5.1 Ethiopia AEFI Reporting – Routing, Timeline and Action

6.3 Types of AEFI Reporting tools

6.3.1 Paper-based reporting tools

Reporters use the paper-based (manual) AEFI reporting format to report any suspected adverse events following immunization. All fields of the reporting template in AEFI reporting form (Annex 1) or line list form (Annex 2) should be filled in order to provide as much information as possible for subsequent investigation. The information obtained from the report will also be of great importance in order to establish causal link between the vaccine and the adverse event.

6.3.2. Electronic reporting tools

In addition to the paper based AEFI reporting form, healthcare professionals at the healthcare facility level or in the immunization program can also use electronic reporting mechanisms to report an AEFI. The Ethiopian Food and Drug Authority have developed a web-based reporting tool which is available in the authority's website (www.fmhaca.gov.et-serivces-e-Reporting). Once the report is submitted by the reporter and received at EFDA, the system will generate an automatic response to the reporter.

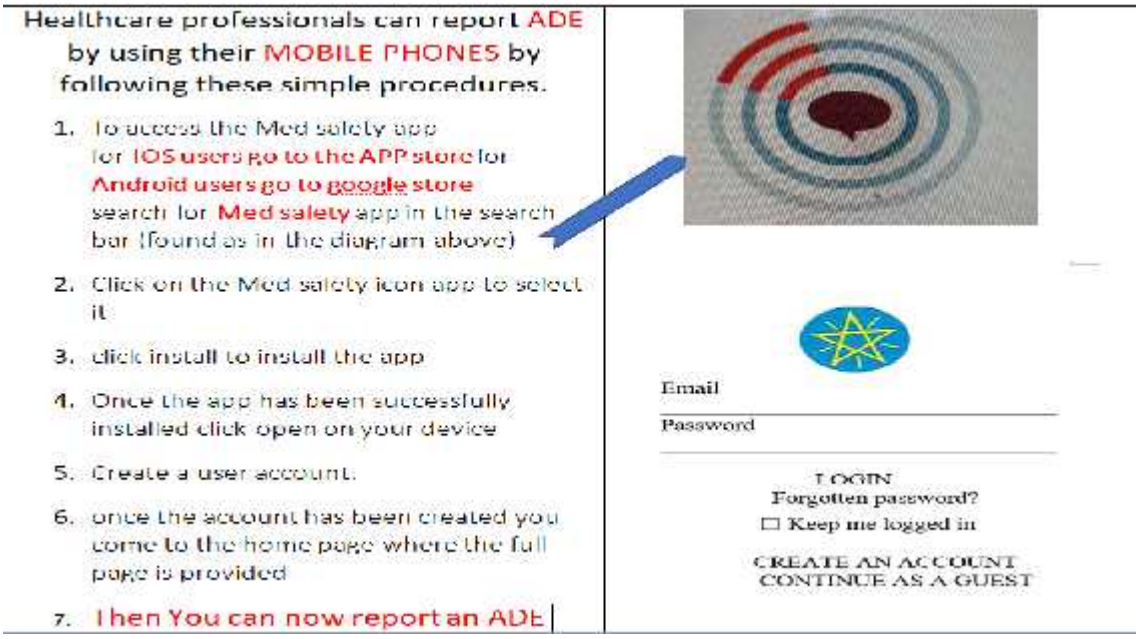
Use the following steps to report AEFIs:

	) Go to EFDA website www.efmhaca.gov.et) Click on Services) Click on the link e Reporting of ADR) You will find a page as indicated in this picture) Enter your e mail and select your qualification as indicated in this picture) Type the characters exactly as in the image) Thick I accept the term and next page) Enter all the information on the next page and submit the AEFI report

6.3.3. Mobile application

Another online reporting system which is newly added is a mobile application reporting tool which is called the Med-safety. This application can be downloaded from **Google play store** for Android phones or **the APP store** for IOS users. By creating an account using an email address, health workers and immunization officers can send an AEFI report to the authority directly.

Use the following steps on how to use the mobile app:



6.3.4. Emailing to the National pharmacovigilance center

In addition to the above reporting means any health care professionals can report an AEFI by sending scanned copy of legibly filled standard AEFI reporting form to an email address of pharmacovigilance@efda.gov.et

6.3.5. EFDA toll free service (8482)

EFDA has also availed a toll free phone call service to be used for notifying and reporting an AEFI by health care professionals, vaccine recipients and care givers as well.

6.4. Reporting AEFI during immunization campaigns

	**Reflect on the following points** - What are the AEFI reporting challenges during campaign? - What should be the role of HCP during campaign?

A campaign is an opportunity to strengthen or establish immunization safety surveillance. Proper planning to reduce immunization error-related reactions, to monitor and to respond can

prevent adverse events and their effects during an immunization campaign. Careful planning will limit the potential for negative publicity from AEFI. During mass immunization or a special immunization program, it is of utmost importance to ensure AEFI reporting for two reasons;

1) Mass immunization and special immunization programs cover a large number of individuals in a particular target group in a specified time period. Therefore, an excess number of adverse events may be reported within a short time period. The rate of events remains unchanged, but the increased number of events tends to be noticed by both staff and the public, particularly when injectable vaccines are used and at a time of high social mobilization. Unless an event is properly investigated or analyzed, it can cause concern among the public and may also affect the immunization program.
2) During special immunization program, a new vaccine may be introduced with no prior experience of, or little information on, adverse reactions. There is a possibility of detection of signals through strengthening surveillance during special immunization programs. For example, cases of intussusception were reported following the introduction of a new oral rotavirus vaccine (Rota shield) in the USA in 1998-1999.

key measures to consider for AEFI management and monitoring during campaign:

- Assess or set up AEFI monitoring system
- Develop rapid reporting channels
- Ensure the availability the necessary monitoring and evaluation tools
- Mobilizing additional resources (Financial, HR)
- Creating strong coordination and collaboration platforms
- Decide which AEFI are to be reported and which contraindications to observe
- Train health care workers to investigate and manage AEFI and respond to rumors
- Explain to key people involved in the campaign why the campaign may result in the perception of increased rates of AEFI.
- Plan and transmit media messages on the campaign which address locally perceived safety concerns.
- Form a local AEFI investigation task forces
- Creating effective communication platform and responding to “issues” and rumors

6.6 Private sector reporting

Private health care facilities have significant contribution to health care provision in Ethiopia particularly in urban areas. Vaccine recipient may visit private health care facilities for AEFI. This is a good opportunity for the HCP to detect and report AEFIs to the health offices and authorities. This endeavor has to be supported by enhancing capacity and awareness, monitoring and supportive supervision to HCP working at private health facilities.

6.5 Barriers of reporting AEFI

Immunization service providers may not report AEFI for a number of reasons, such as;

- Considering that the event did not occur after immunization (however, all events following immunization as per the definition should be reported)
- Lack of knowledge about the reporting system and process
- Apathy, procrastination, lack of interest or time, inability to find the reporting form;
- Fear that the report will lead to personal consequences
- Guilt about having caused harm and being held responsible for the event and
- Diffidence about reporting an event when not confident about the diagnosis.

It is worth emphasizing that, unless immunization service providers/units at community level generate and process reports appropriately, an adequate immunization safety surveillance system will not exist. Staff must be encouraged to report adverse events without fear of penalty. The aim is to improve systems or provide further training, and not to blame individuals. Positive feedback to health workers is essential. The feedback should include the outcome of investigations or causality assessment when these are carried out, and recommendations on the management of the vaccine, particularly with regard to the need for future vaccination. There must be an adequate supply of reporting forms. Pre-addressed and postage-paid forms may improve reporting in some countries, especially from private physicians.

Chapter summary

- Any individual including health care professionals should report any AEFI encountered regardless of severity to the next higher health office/authority as soon as possible using the available standard reporting tools.
- Suspicion alone is sufficient for reporting, and the primary reporter is not expected to assess causality.
- Reports of SAE should reach EFDA within 24 hours.
- Locally collected AEFIs should be shared regionally and globally (via the WHO Program for International Drug Monitoring /UMC).
- Special consideration and advanced preparation is necessary during mass immunization campaigns and special immunization programs.
- Private-sector reporting is encouraged.
- Identifying barriers to reporting and taking appropriate action to address these barriers will improve reporting.

Chapter 7: AEFI investigation and causality assessment

Allocated time: 80 Minutes

Chapter Description:

This chapter introduces the basics of AEFI investigation and causality assessment of serious adverse events (SAEs) and other AEFIs of concern. The chapter emphasizes steps and procedures on how the reported AEFIs are investigated to obtain more information. In addition, it explains the need and steps for analyzing information to establish a possible causal link or relationship between the serious AEFI and the action, response, and communication that should be made.

Chapter Objective:

At the end of this chapter, participants will be able to understand and describe AEFI investigation and causality assessment.

Enabling Objectives:

- Explain AEFI investigation
- Describe AEFI causality assessment

Chapter outline

- AEFI investigation
  - Introduction about investigation and its objectives
  - What, who, and when should be AEFI investigated?
  - Steps in investigating AEFI's
  - Investigation of AEFI with fatal outcome and AEFI cluster
  - Outcome of AEFI investigation
  - Type of data that should be collected and how the data be collected and recorded

- AEFI Causality assessment
  - Introduction to causality assessment
  - Selection of cases for causality assessment
  - Preparation for AEFI causality assessment and causality assessment team
  - Steps in causality assessment
  - Categories of causally assessed AEFI cases
  - Response and action after causality assessment
- Chapter Summary

7.1. AEFI Investigation

	**Group discussion and Reflection** - What will be done once the AEFI report is received by the national PV center? - What do you understand about the term investigation and its objective? **Time: 10 mins**

7.1.1. Basics of AEFI investigation

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

General Objective of AEFI investigation:

- To seek detailed information on an AEFI and take appropriate corrective actions to maintain public confidence in the immunization program.

Specific objectives of AEFI investigation:

- To identify the cause of AEFI
- To confirm the reported diagnosis or establish a diagnosis.

- To document the outcome of the reported AEFI
- Prevent false blame from coincidental events
- To identify the details of vaccine administered and determine the timing between administration of the vaccine and the onset of the event.
- To examine the operational aspects of the program
- To determine whether a reported event was a single incident or one of a cluster
- To determine whether similar events are occurring in individuals who have not received the same vaccine
- To maintain confidence by properly responding to parent/community concerns while increasing awareness (public and professional) about vaccine risks
- To generate new hypotheses about vaccine reactions that are specific to the population
- To estimate rates of occurrence on AEFI in the local population compared with trial and international data particularly for new vaccines being introduced.

7.1.2. What should be investigated and when?

	**Group reflection** - **Do you think that all reported AEFIs undergo investigation?** - **If no, what type of AEFIs need investigation?** **Time: 10 mins**

Not all AEFI reports will need investigation. Once the report has been received, an assessment should be done to determine whether an investigation is needed. In general, the following medical incidents (trigger events) should be investigated;

- All serious cases of AEFIs
- Clusters and events above the expected rate and severity

- Evaluation of suspected signals
- Other AEFIs
  - Immunization error is suspected (e.g. injection site abscesses, sepsis
  - Significant events of unexpected cause within 30 days of vaccination
  - Events causing significant parental and community concerns (e.g. febrile seizures, hypotonic hypo-responsive episode)

Note: Any significant AEFI following vaccination should be reported and investigated irrespective of the time interval between vaccination and onset of symptoms.

7.1.3. Who should be involved in AEFI investigation?

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

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

7.1.4. What is the timeline to investigate?

Investigation should begin as soon as possible, ideally within 24 hours but maximum within seven days of notification to the health worker, to identify any immunization error(s) that might be

present, to correct them before other people are exposed to the same error, and to show members of the community that their health concerns are taken seriously.

7.1.5. What data should be collected?

An AEFI investigation follows standard epidemiological investigation principles. In addition, an investigation of the vaccine(s), administration techniques and procedures, and service in action should be conducted as shown in figure 7.1.

7.1.6. How should data be collected and recorded?

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

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

7.1.7. Steps in investigating AEFI's

An AEFI investigation follows standard epidemiological investigation steps (Figure 7.1). It is important to investigate suspected AEFIs promptly and completely. The investigators will need to look directly at the reported reaction as well as gather information from the client/parent, health workers, supervisors, and community members. The information collected (and conclusions) should be recorded on an AEFI investigation form (Annex X: AEFI investigation form)

Immunization-related errors and coincidences are the most likely causes of AEFIs. Therefore, the investigator should suspect immunization errors as the cause and examine the evidence for any errors in the storage, handling, or administration of vaccines. The investigators should seek to identify system problems rather than to find individuals to blame. For example, the investigation

may reveal that more abscesses are reported in one immunization clinic due to faulty immunization technique by a health care worker. In such case, rather than blaming the health care worker, the investigators should find reasons for why health care worker practice incorrect technique, which may be a system failure such as lack of training, lack of supportive supervision etc.

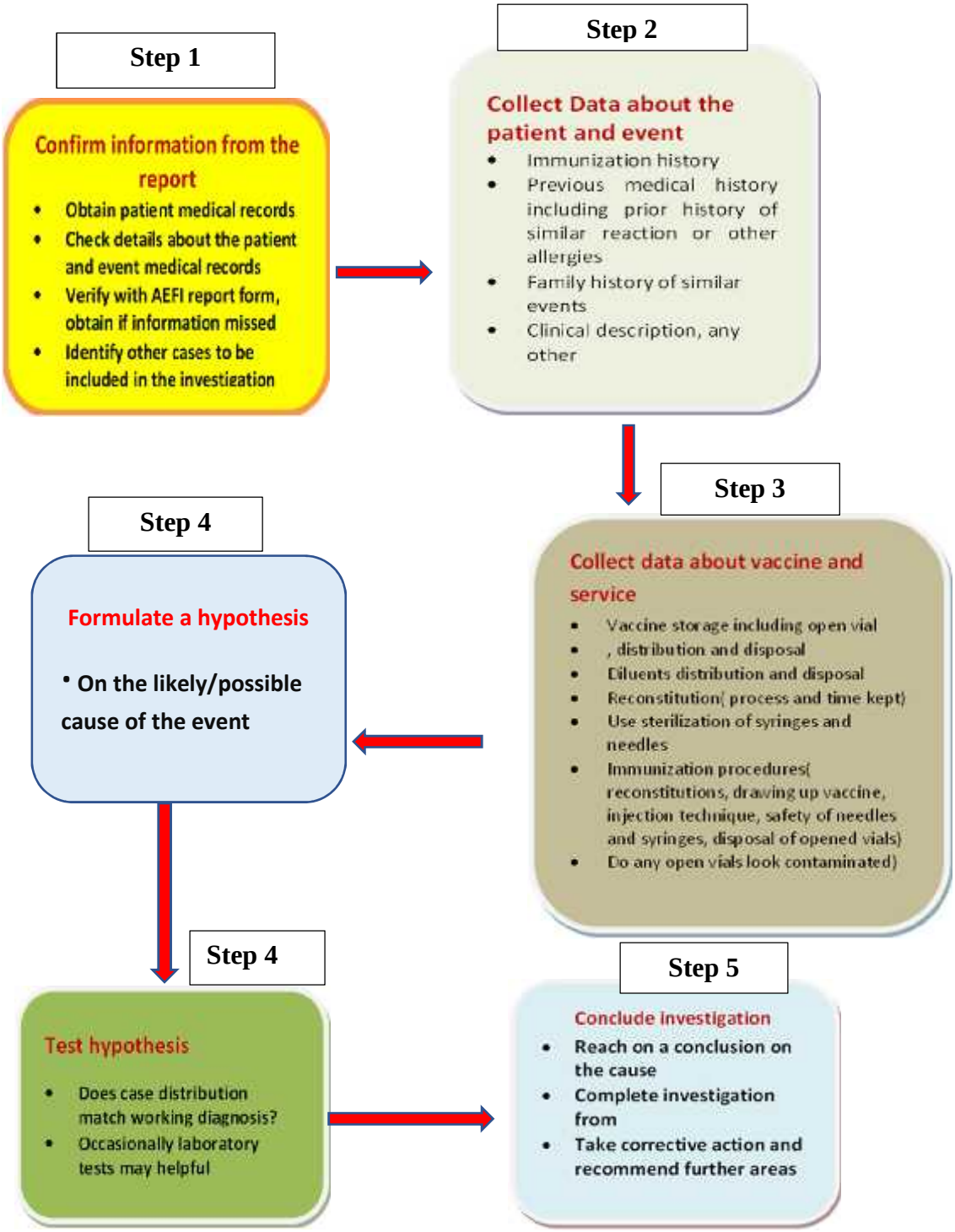


Fig 7.1. Steps in Investigation

7.1.8. Investigation of AEFI with fatal outcome

In the event of an identified death following immunization, the field investigation has to be initiated immediately. Within 24 hours, the death should be notified to all administrative levels concerned, including the Woreda, Zonal, and Regional EPI officers, the National EPI, and the EFDA. An investigation of the case should be carried out by a team of experts from relevant areas including clinicians.

As a death causally linked to immunization is extremely rare (anaphylactic reactions being one of the only 2-3 known events), major immunization errors may be involved and thus an investigation to rule those out has to be conducted without any delay to prevent additional cases.

As any fatality temporally linked to vaccination can cause panic, the public will also demand an immediate explanation. A post-mortem examination is preferred and recommended following all deaths suspected to be caused by a vaccine / immunization. A decision on autopsy should be taken within the local sociocultural, religious, political context and legal framework of the local population. If an autopsy is not possible, a verbal autopsy can be carried out using established guidelines and protocols.

7.1.8. Investigating AEFI clusters

A cluster of AEFI is defined as two or more cases of the same AEFI related in time, place or vaccine administered. Apart from checking on these three factors, the investigators should look for AEFI occurring in similar age groups and populations with genetic predisposition or disease.

Cluster investigation begins by establishing a case definition for the AEFI and related circumstances and by identifying all cases that meet the case definition. The investigators should demarcate the cluster and identify common exposure factors within the cluster.

Cluster identification (i.e. cases with common characteristics) is done by gathering details (when and where) of vaccines administered. This can be achieved by collecting and recording:

- Detailed data on each patient
- Program-related data (storage and handling, etc.)

- Immunization practices and the relevant health workers' practices.

Common exposures among the cases can be identified by reviewing:

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

When an AEFI cluster has been identified, the cause-specific definitions provide a framework for investigation and causality assessment. Usually the key considerations will be to investigate the possibility of an immunization error, vaccine reaction or a vaccine quality defect. The possibility of immunization error must be considered when events cluster in one setting without a similar change in frequency in other settings using the same vaccine. On the other hand, if an increased frequency of events is reported from multiple settings the possibility of a quality defect must be considered more strongly. For example, clusters of fainting after immunization are well-recognized immunization anxiety-related reactions during immunization programs targeting adolescent girls.

7.1.9. Outcome of AEFI investigation

On concluding the investigation, the documents and evidence collected should be compiled, a report prepared and submitted to a pharmacovigilance advisory committee.

7.2. Causality Assessment of AEFIs

7.2.1 Basics of 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 a definite relationship exists, but generally ascertains a degree of association between the reported AEFI and the vaccine/ vaccination. Nevertheless, causality assessment is a critical part of AEFI monitoring and enhances confidence in the national immunization program and regulation of the safety and quality of the product. Vaccine recipients want to know whether what they have experienced was due to the vaccine. They may believe that because one event followed another, it was causal. It can be difficult to

explain that might not have been the case. Causality assessment may provide a more descriptive explanation that may reassure the importance of the vaccine and lead to better management of the event. Performing causality assessment is important for:

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

Causality assessment of AEFI applies to investigating relationships between a vaccine and AEFI at three levels;

- At Population level: To test if there is a causal association between the usage of a vaccine and a particular AEFI;
- At individual level: To determine from evidence and case assessment if an AEFI in a specific individual is causally related to the usage of the vaccine; and
- Investigation of signals

They all depend at some level on performing an assessment for causality of individual cases.

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

- **Temporal relationship**: The vaccine exposure must precede the event occurrence. Exposure always precedes the outcome. If factor "A" is believed to cause a disease, then it is clear that factor "A" must always precede the occurrence of the disease. This is the only absolutely essential criterion.
- **Definitive proof that the vaccine caused the event**: Clinical or laboratory proof that the vaccine caused the event. **Biological plausibility**: Biological plausibility may provide

support for or against vaccine causality. In other words, the association should be compatible with existing theory and knowledge related to how the vaccine works.

- **Strength of the association:** This is defined by the size of the association as measured by appropriate statistical tests. The stronger the association, the more likely it is that the relation of "A" to "B" is causal.

7.2.2. Selection of cases for causality assessment

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

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

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

- ✓ AEFI that may have been caused by immunization error, (e.g. bacterial abscess, severe local reaction, high fever or sepsis, BCG lymphadenitis, toxic shock syndrome),

- ✓ Significant events of unexplained cause occurring within 30 days after a vaccination (and not listed in product label), and
- ✓ Events that are causing significant parental or community concern and where a formal case assessment can provide a detailed, more reassuring explanation to the parents and/or community (e.g. febrile seizures).

7.2.3. Preparation for AEFI causality assessment

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

- The AEFI case investigation should be completed.
- Premature assessments with inadequate information could mislead the classification of the event.
- All details of the case should be available at the time of assessment
- They should include documents pertaining to the investigation as well as laboratory and autopsy findings as appropriate
- There must be a "diagnosis" (see annex xxx for case definition) for the adverse event, clinical sign, abnormal laboratory finding, symptom and/or disease in question.
  - In other words, the event being assessed should be clear ; it should be understood both which vaccine is being associated with what specific event that was reported

7.2.4. Causality assessment team

In Ethiopia, causality assessment is being done by the National Pharmacovigilance advisory Committee that is composed of health professionals with different specialties. They are

- Independent
- Free of real or perceived government, industry conflicts of interest
- Has a broad range of expertise including areas of ‘infectious diseases, pediatrics, epidemiology, microbiology, pathology, immunology, neurology, pharmacology and others as necessary
- The committee has written and signed terms of reference (ToR)

7.2.5. Steps in causality assessment

Determining causality of AEFI, particularly those considered serious, of public importance, and programmatically disruptive are critical for ensuring vaccine safety. The final classification is based on the availability of adequate information. It is for the benefit of the final classification that all relevant information should be collected ahead of time during the investigation.

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

Step 1: Confirmation of eligibility: To determine if the AEFI case satisfies the minimum criteria for causality assessment

Step 2: **Filling checklist:** To systematically review the relevant and available information to address possible causal aspects of the AEFI .

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

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

7.2.6. Categories of causally assessed AEFI cases

After AEFIs are assessed for their causality, classification will be done based on the four steps mentioned above and then the case will finally lay upon different categories which are listed below.

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

Classified as follows:

A. Consistent causal association to immunization

A1: vaccine product-related reaction or

A2: vaccine quality defect-related reaction or

A3: immunization error-related reaction or

A4: immunization anxiety-related reaction.

B. Indeterminate

- B1. Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing the event (may be new vaccine-linked event). This is a potential signal and needs to be considered for further investigation.
- B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization.

C. Inconsistent causal association to immunization (coincidental)

- C1. Underlying or emerging condition(s), or
- C2. Conditions caused by exposure to something other than vaccine.

II. A case without adequate information for causality conclusion is "Unclassifiable" and requires additional information for further review of the causality.

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

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

7.2.7. Response and action after causality assessment

The most important in causality assessment is the action that is going to be taken after the outcome of the causality assessment. The lessons learned should provide insights and a way forward for the technical, immunization program staff working at woreda, zonal and higher level.

Findings should be promptly and clearly communicated, and the messages should be clear on any next steps to be taken, including communicating reassurance or the need to take action around the program including training, research, modifying systems, refining tools, and revocation of marketing authorization and recall of the vaccine and so on to avoid and/or minimize recurrences.

Proper and early treatment should be provided to patients regardless of the diagnosis. Case management and referral will vary depending on the seriousness. Mild symptoms such as mild fever and pain are likely to be of short duration and can be managed by assuring and educating parents during immunization. If parents return to seek medical attention, these cases should be documented and reported in the AEFI case reporting form. In case patients need hospitalization, a clear system for referral should be in place.

Based on global guidelines, the following general actions for responding to AEFI need to be considered as a response to take to the different causality conclusions resulting from the assessment:

A. Consistent causal association to immunization

A1. Vaccine product-related reaction

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

A2. Vaccine quality defect-related reaction

If this reaction is related to a particular lot or batch, the distribution of the lot or batch needs to be ascertained and specific instructions must be provided on the utilization or non-utilization of the lot or batch. It is important to communicate with global partners such as WHO and UNICEF.

A3. Immunization error-related reaction

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

A4. Immunization anxiety-related reaction

Vaccination should take place in an ambient and safe environment.

B. Indeterminate

B1. Consistent temporal relationship but insufficient evidence for causality

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

B2. Conflicting trends of consistency and inconsistency with causality

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

C. Inconsistent causal association to immunization (coincidental)

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

Responding to AEFI may involve immediate short-term activities or/and long-term follow-up activities. Follow-up activities should be based on findings of investigations, causality assessments and recommendations by the investigation team/AEFI committee. Major follow-up actions may have an impact on the national immunization program as well as on regional, zonal and woreda programs and planning. Detailed follow up actions that need to be taken after investigation and causality assessment is completed are listed as follows.

Table 7.2: Follow up actions to be taken upon completion of the investigation/causality assessment

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

If AEFI causality is not established – depending on the nature of the event, its extent and whether it is ongoing – a further investigation or epidemiological study may be warranted. However, it must be accepted that in some cases the relationship to vaccine will never be clear. Communication and training are two important follow-up actions that have long term implications.

7.2.8. General guidance of action, response, and communication during AEFI surveillance

AEFI detection, investigation, and analysis must lead to action if the credibility of immunization services is to remain high. These actions include diagnosis, treatment, reporting, communication, and correction of programme error.

Table 7.2: Actions to safeguard the public during an investigation

Stage of investigation	Actions
Incident detected	- γ ∃∃ ⊠∃|ℑ⇒Ω↓⇐∇ ⊠∅⇑ℑ∅⊠∈↓∅⊣ℑ⇒⊣ℑ⇐⇔∂⇓⇐∂↓ℑ∅⊠Ω⊠⇑∂ ⊠⊠⇓⇐⊣Δ∂↑⊠⇒⊠ | - σ ⇓∃∃↓ℵ⇒ |∀ΔℑΔℑ⇒⊗⇐⊠∃Δ∃⇐⊠⊠∇ℑ⊠⊠⇐⊠
Investigation starts	- η⇒∃Δ∂ ⊠∅⇒ℑ⊗∅⇒⊠↓⇐∇ ⊠∅⇑ℑ∅⊗∂|⇒ℑ∃|ℑΩ⊠∀ΔℑΔ∅⊠∂ ⊠⇓Δ∂⊠⊠⊠⊠⇓∇↓Ω⊠⇑⇓∂ ⊠↓⇐⊠⊠Ω⊠Ω - λ⇒⊠ ⊠ℑ∃ ⊠∃Δ∂∇ ⊠↓⇐⇐ℑ⇒⊠⊠∅⇓|↓Ω⊠⇐⊗⇐ |∃⇑↓⇐ℑ∂|⊠ℑ∃ ⊠⊠|↓⇐⊣ℑ⇒Ω⇓ΔΩ⇓⇐⊣∅⇒⊠ℑ∂ ⊠ℑ| - ζ ⊠⇐↓⇒⊠ℑ⇒ |∃Δ∃⇐⊠⊠⊠∇ℑ⊠⊠⇐⊠
Investigator develops working hypothesis	- ζ ⇓|⇒⇓⊠⊠⇓⇑⇑Δ⇒⊠⊠ℑ∅⊠∈⇓∂↵↓⇐⊣|→ ⇔⇓∅⇒⊠⊠⊣|Δ⇒⊗⇐⊠⊠⇒⇓∂⇑ ⊠Ω - λ⇐⊣⇔∂⇓⊣∂ℑ⇑| ⊠∂⇓∂∃|ℑ∂ ⊠∈⇓∂↵↓⇐⊣|→ ⇔⇓∅⇒⊠⊠⊣⊠⊠⇓∂∂ ⊠⊠⊠∅⇒⊠⇑| - λ⇐⊣ℑ|∇ℑ⊠⊠⇐⊠⇔∂⇓ℵ⇒⊠⇑|⊠⊣|∃Δ∃⇐⊠⊠⊠⊠⊠∀ΔℑΔℑ⇒⊗⇐⊠∃Δ∃⇐⊠⊠⊠∇ℑ⊠⊠⇐⊠
Investigator confirms working hypothesis	- γ Ω∇⊠ ⊠⊠⊠⇓⇑⇑Δ⇒⊠∅ |⇓⇐⊣⊠⊠Δ∃ ⊠⊠ℑ⇒Ω⇓⇐⊣⇔ℑ⇒⊠Ω∂ ⊠⊠⇔⇓⇒∃ ⊠

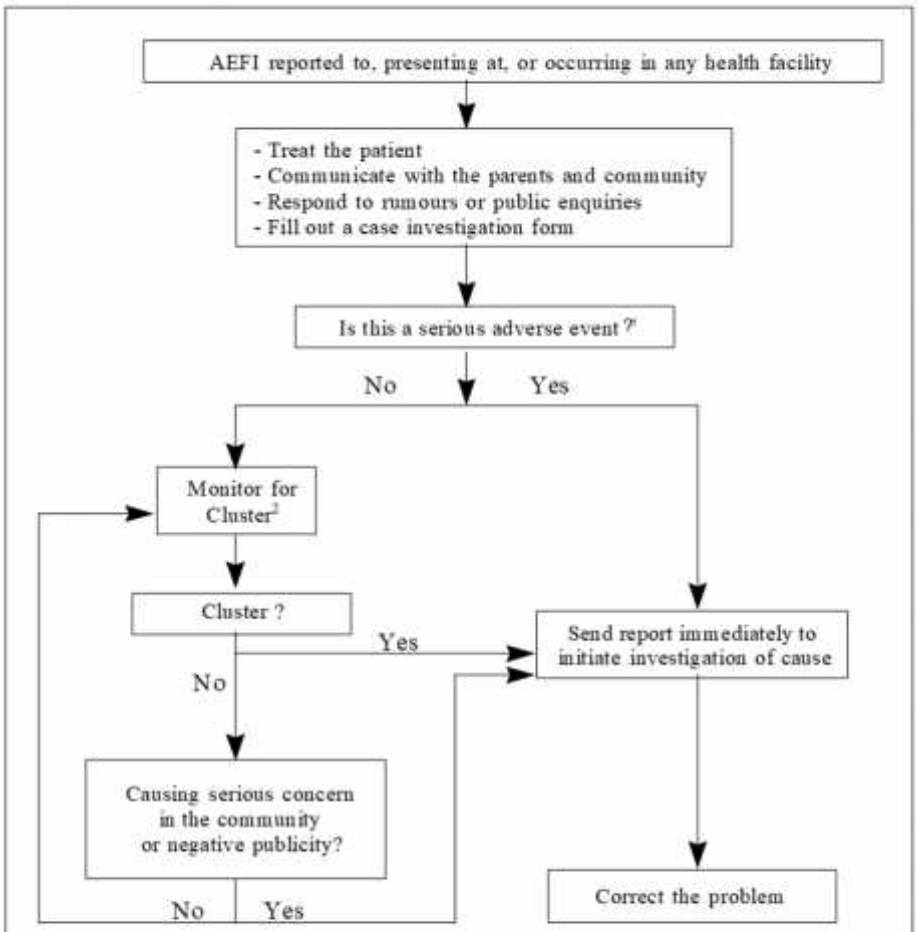
Depending on the nature of the event(s), the number of people affected, and community perceptions, an investigation may be conducted. In general, it is not advisable to discontinue the immunization programme while awaiting the completion of the investigation. If AEFI causality is not established – depending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

⎫ Action by the peripheral health worker

Even though serious AEFIs are rare, the health worker must know how to diagnose and treat serious AEFIs, and report a serious AEFI at once. They are much more likely to see less serious AEFIs such as abscess, redness at the injection site or lymphadenitis. Ideally, each event should be listed on a form such as the AEFI line list form. However, staff may be reluctant to report such

events to report to focal person, fearing they will be penalized for "poor vaccination technique". WHO encourages a relationship based on mutual trust, in which peripheral health workers are comfortable reporting incidences to their supervisors, who will assist them in fixing any programme error that may have contributed to the incidents. Peripheral health workers may initiate corrective action themselves if it is clear what to do (e.g., improve safe injection practices in the case of an abscess). However, corrective action will usually be in response to guidance from the EPI focal person or other staff member at a higher level. Actions taken by peripheral health workers are set out and summarized in the flow chart on figure 7. 2.

Taking Action by Peripheral Level Health Worker



[1] Defined as **serious** if it results in a) death or b) hospitalization.

[2] A **cluster** is defined as an AEFIs which occur with unusual frequency, by vaccine, by type of reaction, or by locality/facility. A more precise definition may be decided upon by national programme managers.

Fig 7.2. Taking action at peripheral level

) Response to AEFI

The goals of ‘‘Response” is to verify the AEFI, identify the cause (s) of the AEFI cases, and determine if an intervention is needed (e.g., remove the vaccine batch). This section also stresses the importance of using of existing reporting systems, engaging stakeholders, and ensuring that local experts or consultants are involved in verifying the occurrence of AEFI. It emphasizes maintaining the same positive message on the safety of vaccines and the importance of engaging partners to ensure transparency.

Treatment must be the first response to an AEFI. Mild symptoms such as fever are likely to be of short duration, and can be treated by parents or health workers. Treatment suggestions for such mild symptoms are given in Immunization in Practice, (EPI/WHO), and other publications. Health workers must also know how to diagnose, treat and when to refer, serious AEFIs. Some health facilities which would otherwise charge, will normally provide free treatment to those who suffer an AEFI, especially if it appears to be caused by programme error or is vaccine-induced. A framework for preparing for and responding to clusters of AEFI comprises six steps.

Preparedness

1. Understand context for AEFI reported after vaccine administration, including local rates and causes of serious AEFIs.

2. Develop strategies for surveillance of adverse events following vaccine administration.

3. Develop a comprehensive risk communications strategy and build capacity to respond to an AEFI reported after administration.

Response

4. Verify and investigate the cause(s) of AEFI cases, including clinical and epidemiological investigations.

5. Proactively and regularly engage with news media and affected populations to share information on key aspects of the investigation and to respond to questions.

6. Monitor vaccination coverage and public response, and adapt the response to emerging data

- **Communication with Parents and Other Members of the Community**

Communication with parents, health workers not involved in the investigation and other people in the community must take place no matter what the circumstances of the event. Rumors or public inquiries must be responded . This is particularly important when public anxiety is high.

The EPI focal person or another responsible person in EFDA should set up the means for continuous communication between health workers (investigators, peripheral health workers, supervisors, and managers) and the community, directly and through the press. The public should be informed frequently about what is being done during an investigation. When it is over, conclusions and recommendations should be shared, and the public told what is being done to remedy any problems found.

The key to maintaining confidence in health services is to be honest. If the cause of the AEFI has not been identified, people should be told. If the cause has been insufficient sterilization of needles and syringes or some other programme error, the actions being taken to remedy the problem should be explained.

When death occurs because of a programme error, special precautions may have to be taken to protect health workers from harm by the community. Health workers who are implicated in the error might have to be removed from the scene before the findings are communicated.

A vaccine-induced AEFI can be a sensitive communication problem. The public needs to be assured that severe vaccine-induced events are rare, even though this may not comfort the patient's family. In some cases, managers may find it appropriate to provide technical information on the low incidence of these events. In many contexts, however, statistics may be almost meaningless and the best that can be done is to show genuine sympathy and concern.

- **Correction of the problem**

If an AEFI was caused by programme error (e.g., such as improper handling of vaccines or faulty immunization technique) the actions to be taken will probably include one or more of the following:

- ✓ Logistics

Improving logistics will be the appropriate response if programme errors can be traced to the lack of supplies or equipment or to a failure in the cold chain. Managers should investigate suspected breaks in the cold chain to find the cause and take appropriate measures. These might include training or supervision or the problem might be solved by providing more or better supplies or equipment (needles, syringes, sterilizers, vaccine carriers, cold packs) or by providing more vaccine or diluent.

- ✓ **Training**

Solving operational problems through training will deal with lack of skills and knowledge and with poor attitude. Effective immunization services call for health workers who can detect AEFIs and provide immunization services safely and who care about doing so. When an AEFI has been caused, or made worse, by service delivery errors and the investigator identifies the specific error, training can focus on correcting that error. If the investigator tracks an error to one health worker, that health worker's immunization activities should be terminated immediately, at least until he or she masters the missing skill.

- ✓ **Supervision**

Wherever AEFIs are reported, supervision should be intensified. Supervisors throughout the country should watch for any problem (e.g., in sterilization of equipment or vaccine storage) that has caused a cluster of AEFIs. If past training or supervision in the relevant skill has been weak, the problem could be widespread. See Training for Midlevel Managers: Help to Make it Work, WHO / EPI Geneva, for materials on how to plan and schedule supervisory visits.

7.3. Chapter Summary

- AEFI investigation will attempt to confirm or propose an alternative diagnosis of the reported event, identifies the specifications of the administrated vaccines, and examines the operational aspect of the program.

- The ultimate goal of the AEFI investigation is to find out the cause of an AEFI and implement the follow-up action.
- The extent of the investigation depends on the nature of the reported AEFI. The investigation can be a simple assessment or a more rigorous scientific evaluation of the reported AEFI to recognize its possible causes.
- Once an AEFI report is received, an assessment will be made to determine whether an investigation is needed.
- The reported AEFI must be investigated if is a serious event, belongs to a cluster of AEFI events, previous unrecognized event, involves an increased number or rates, suspected immunization error, appears on the list of events defined events for AEFI surveillance, and causes significant parental or public concerns.
- Investigations of death following immunization have to be conducted without delay to as the death can cause significant community concern
- 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.
- Performing causality assessment is important for the identification of vaccine-related, immunization error-related problems, coincidental events, and detection of signals for potential follow-up.
- Causality assessment is done for serious AEFI, clusters of events above an expected rate or level of severity, signals generated, AEFI that may have been caused by immunization error, significant events of unexplained cause occurring within 30 days after a vaccination (and not listed in product label), and events that are causing significant parental or community concern.
- Before causality assessment is done, the AEFI case investigation should be completed with full documents.
- The National Pharmacovigilance advisory committee that is composed of health professionals with different specialties is doing causality assessment.
- The four steps in causality assessment are; confirmation of eligibility, filling checklist, using an algorithm, and classification of the cases into different categories is done which are consistent with immunization, indeterminate, and inconsistent with immunization when it is classifiable with adequate information and unclassifiable when there is no adequate information.

- Actions, responses, and communication on AEFI surveillance need to be performed with caution and in collaboration with all stakeholders involved.

Annex ((xxx for case definition)): Case definitions of commonly reportable AEFIs'

AEFI	Case definition	Vaccine
Anaphylaxis	A clinical syndrome characterized by sudden onset (within one hour), rapid progression of signs and symptoms involving multiple (more than two) organ systems : - **Skin** – urticaria (Hives), angioedema (swelling of face/body), - **Respiratory** – persistent cough, wheeze, stridor, - **Cardiovascular** – low blood pressure (hypotension) or reduced circulation (fast weak pulses), - **Gastrointestinal** – vomiting, abdominal pain.	All
BCG Osteitis/ Osteomyelitis	Inflammation of the bone with isolation of Mycobacterium bovis BCG strain.	BCG
Disseminated BCG infections	Widespread infection occurring within 1 to 12 months after BCG vaccination and confirmed by isolation of Mycobacterium bovis BCG strain. Usually in immuno-compromised individuals.	BCG
Encephalopathy	Acute onset of major illness characterized by depressed or altered level of consciousness and/or distinct change in behavior lasting for one day or more	Measles, Pertussis

AEFI	Case definition	Vaccine
Fever	The fever can be classified (based on rectal temperature) such as • Mild fever: 100.4 ^{0}F to 102 ^{0}F (38 to 38.9Oc), • Moderate fever: 102 ^{0}F to 104.7^{0}F (39 to 40.4^{0}C) and • Severe fever: 104.7^{0}F or higher (>40.5^{0}C).	All
Hypotonic, Hyporesponsive Episode (HHE or shock-collapse)	Event of sudden onset occurring within 48 [usually less than 12] hours of vaccination and lasting from one minute to several hours, in children younger than 10 years of age. All of the following must be present: • limpness (hypotonic) • reduced responsiveness (hypo responsive) • pallor or cyanosis – or failure to observe/ recall	Mainly DPT, rarely others
Injection site abscess	Fluctuant or draining fluid-filled lesion at the site of injection. Bacterial if evidence of infection (e.g. purulent, inflammatory signs, fever, positive bacterial culture), Sterile abscess if no evidence of bacterial infection on culture. Sterile abscesses are usually due to the inherent properties of the vaccine.	All injectable vaccines
Intussusception	The invagination of one segment of the intestine into a segment of distal intestine which is physician-diagnosed .Temporal criteria: IS occurring within 42 days following immunization.	Rotavirus

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

AEFI	Case definition	Vaccine
	• Requires hospitalization. Local reactions of lesser intensity occur commonly and are trivial and do not need to be reported.	
Toxic shock syndrome (TSS)	Abrupt onset of fever, vomiting and watery diarrhoea within a few hours of immunization. Often leading to death within 24 to 48 hours.	All injectable vaccines
Vaccine Associated Paralytic Poliomyelitis (presenting as AFP)	Acute onset of flaccid paralysis and neurological deficits, compatible with diagnosis of poliomyelitis, with isolation of vaccine virus and absence of wild virus in stool.	OPV
Serious AEFI: Any AEFI causing • Death • Hospitalization • Disability, congenital anomaly • Other severe and unusual events	No time limit, if they are thought by health workers or the public to be related to immunization	

Annex XXX: AEFI investigation form

AEFI CASE INVESTIGATION FORM			
Section A	**Basic details**		
Region	**Zone**	**Woreda**	**Case ID**
Place of vaccination ( ): Govt. health facility/Private health facility/Other (specify) _____ Vaccination in ( ): Campaign/Routine/Other (specify) _____			
Name and Address of vaccination site:			
Type of site ( ) Fixed Mobile Outreach Other _____			
Name of Reporting Officer:	Date of investigation: __ __ / __ __ / __ __ __ __ Date of filling this form:__ __ / __ __ / __ __ __ _		
Designation/ Position:			
Telephone #:	Mobile:	e-mail:	
Patient Name	Sex: M / F		
(use a separate form for each case in a cluster) Date of birth (DD/MM/YYYY):__ __ / __ __ / __ __ __ __***OR*** *Age at onset: __ __years __ __months __ __ __days* ***OR*** *Age group: < 1 year 1-5 years> 5 years* Patient's full address with landmarks *(Kebele, Gott name, house number, locality, phone number etc.)***:**			

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

				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent

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

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

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

Status on the date of investigation : Died ()Disabled()Recovering()Recovered completely()Unknown()

If died, date and time of death*(DD/MM/YYYY)*:__ __ / __ __ / __ __ __ __ (*hh/mm):* __ __ / __ __

Autopsy done? ()Yes(date)_____ No Planned on (date)_____ Time_____

Attach report (if available)

Section B	**Relevant patient information prior to immunization**	
Criteria	**Finding**	**Remarks (If yes provide details)**
Past history of similar event	Yes / No/ Unkn	
Adverse event after previous vaccination(s)	Yes / No/ Unkn	
History of allergy to vaccine, drug or food	Yes / No/ Unkn	
Pre-existing illness (30 days) / congenital disorder	Yes / No/ Unkn	
History of hospitalization in last 30 days, with cause	Yes / No/ Unkn	
Patient currentlyon concomitant medication? (If yes, name the drug, indication, doses &treatment dates)	Yes / No/ Unkn	
Family history of any disease (relevant to AEFI) or allergy	Yes / No/ Unkn	

For adult women

- Currently pregnant?Yes (weeks) _____/ No/ Unknown
- Currently breastfeeding? Yes / No

For infants

The birth was: Full-term Pre-term___ Post-term. Birth weight:

Delivery procedure was: Normal___ Caesarean___ Assisted (forceps, vacuum etc.)____

With complication (specify)_____

Place of birth: Home__ Health facility_____

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

Source of information (*all that apply*): **Examination by the investigator__ Documents___ Verbal autopsy___**

Other_____ *If from verbal autopsy, please mention source (e.g. parents)*_____

Name of the person who first examined/treated the patient:_____

Name of other persons treating the patient: _____

Other sources who provided information (specify): _____

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

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

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

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

Provisional/Final Clinical Diagnosis:

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

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

**Write name of vaccine(s) given on the same vaccination day at the site ** Write total doses administered for each vaccine*	
• When was the patient immunized? (Tick the box the below and respond to ALL questions)	
Within the first vaccinations of the session Within the last vaccinations of the session Unknown	
In case of multidose vials, was the vaccine given within the first few doses of the vial administered? Within the last doses of the vial administered? Unknown?	
• Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes/ No
• Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?	Yes/ No/ Unable to assess
• Based on your investigation, do you feel that the vaccine's physical condition (e.g. colour, turbidity, foreign substances etc.) was abnormal at the time of administration?	Yes / No/ Unable to assess
• Based on your investigation, do you feel that there was an error in vaccine reconstitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	Yes / No/ Unable to assess
• Based on your investigation, do you feel that there was an error in vaccine handling (e.g. break in cold chain during transport, storage and/or immunization session etc.)?	Yes / No/ Unable to assess
• Based on your investigation, do you feel that the vaccine was administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size,not following good injection practice etc.)?	Yes / No/ Unable to assess
• Number immunized from the concerned vaccine vial/ampoule	
• Number immunized with the concerned vaccine in the same session	
• Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations:_____	
• Is this case a part of a cluster?	Yes / No/ Unkn
• If yes, how many other cases have been detected in the cluster?	
• Did all the cases in the cluster receive vaccine from the same vial?	Yes / No/ Unkn
• If no, number of vials used in the cluster (enter details separately)	

Section E Immunization practices at the place(s) where concerned vaccine was used
(Complete this section by asking and/or observing practice)

Syringes and needles used:

Are AD syringes used for immunization?	Yes	No	Unkn
If no, specify the type of syringes used: Glass___ Disposable____ Recycled disposable_____ Other _____			

Specific key findings/additional observations and comments:			
Reconstitution: (complete only if applicable, √NA if not applicable)	Status		
Reconstitution procedure (√)	Yes	No	NA
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA
Same reconstitution syringe used for reconstituting different vaccines?	Yes	No	NA
Separate reconstitution syringe for each vaccine vial?	Yes	No	NA
Separate reconstitution syringe for each vaccination?	Yes	No	NA
Are the vaccines and diluents used the same as those recommended by the manufacturer?	Yes	No	NA
Specific key findings/additional observations and comments:			
Section F Cold chain and transport ***(Complete this section by asking and/or observing practice)***			
Last vaccine storage point:			
• Is the temperature of the vaccine storage refrigerator monitored?	Yes	No	Unkn
oIf "yes", was there any deviation outside of 2–8° C after the vaccine was placed inside?			
oIf "yes", provide details of monitoring separately.			
• Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes	No	Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes	No	Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes	No	Unkn
• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes	No	Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes	No	Unkn
Last vaccine storage point:			
• Is the temperature of the vaccine storage refrigerator monitored?	Yes/No		
oIf "yes", was there any deviation outside of 2–8° C after the vaccine was placed inside?	Yes / No		
oIf "yes", provide details of monitoring separately.			
Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes	No	Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes	No	Unkn

• Were any partially used reconstituted vaccines in the refrigerator?	Yes	No	Unkn
• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes	No	Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes	No	Unkn
Specific key findings/additional observations and comments:			
Vaccine transportation:			
• Type of vaccine carrier used	Yes	No	Unkn
• Was the vaccine carrier sent to the site on the same day as vaccination?	Yes	No	Unkn
• Was the vaccine carrier returned from the site on the same day as vaccination?	Yes	No	Unkn
• Was a conditioned ice-pack used?	Yes	No	Unkn
Specific key findings/additional observations and comments:			
Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes	No	Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes	No	Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes	No	Unkn
Section G Community investigation (Please visit locality and interview parents/others)			
Were any similar events reported within a time period similar to when the adverse event occurred and in the same locality? If yes, describe:	Yes	No	Unkn
If yes, how many events/episodes?_____			
Of those effected, how many are • Vaccinated:_____ • Not vaccinated:_____ • Unknown:_____			
Other comments:			
Section H: Other findings/observations/comments			

Chapter 8: Vaccine Risk Communication

Allocated time: 60 minutes

Chapter description: This course is to designed to provide participants an insight on vaccine risk communication

Primary Objective: The primary objective of this chapter is to equip trainees with the technical knowledge on appropriate vaccine risk communication.

Enabling objectives:

By the end of this session, participants are expected to:

- Explain the concept of vaccine risk communication and principles of effective communication
- Explain the benefits and challenges of vaccine risk communication
- Discuss communication with different stakeholders
- Discuss communication with media
- Discuss media management post AEFI

Session Outline

- Activity 1: Introduction
- Activity 2: Principles of effective communication
- Session 3: Communication with Stakeholders
- Session 4: Communicating with media
- Activity 5: Media management post AEFI
- Session 6: Session Summary

8.1 Background

Many vaccine fears have some basis in reality. However, there is often mismatch between people's fear and reality. Moreover, there is little evidence on the knowledge of risk assessed by professional, which influence the way public perceives and responds to risks and dangers. Risk communication is communication process that the communicator hopes to provide service (for the audience) with information about the expected type (good or bad) and magnitude (weak or strong) of an outcome from a behavior or exposure. It is the science of understanding scientific and technological risk and how it is communicated within a socio-political structure. which attempted to offer a scientific basis for thresholds of risk which would be accepted by the public.

8.1.Principles of effective communication

Principles of effective communication contains seven C's of effective communication

1. **Completeness-**The communication must be complete. It should convey all facts required by the audience. The sender of the message must take into consideration the receiver's mind set and convey the message accordingly. A complete communication has following features:
    - Complete communication develops and enhances reputation of an organization.
    - Moreover, they are cost saving as no crucial information is missing and no additional cost is incurred in conveying extra message if the communication is complete.

- A complete communication always gives additional information wherever required. It leaves no questions in the mind of receiver.
- Complete communication helps in better decision-making by the audience/readers/ receivers of message as they get all desired and crucial information.
- It persuades the audience.

2. **Conciseness-** Conciseness means wordiness, i.e., communicating what you want to convey in least possible words without forgoing the other C's of communication. Conciseness is a necessity for effective communication. Concise communication has following features:
    - It is both time-saving as well as cost-saving.
    - It underlines and highlights the main message as it avoids using excessive and needless words.
    - Concise communication provides short and essential message in limited words to the audience.
    - Concise message is more appealing and comprehensible to the audience.
    - Concise message is non-repetitive in nature.
3. **Consideration-**Consideration implies "stepping into the shoes of others". Effective communication must take the audience into consideration, i.e., the audience's view points, background, mind-set, education level, etc. Make an attempt to envisage your audience, their requirements, emotions as well as problems. Ensure that the self-respect of the audience is maintained and their emotions are not at harm. Modify your words in message to suit the audience's needs while making your message complete. Features of considerate communication are as follows:
    - Emphasize on "you" approach.
    - Empathize with the audience and exhibit interest in the audience. This will stimulate a positive reaction from the audience.
    - Show optimism towards your audience. Emphasize on "what is possible" rather than "what is impossible". Lay stress on positive words such as jovial, committed, thanks, warm, healthy, help, etc.
4. **Clarity-** Clarity implies emphasizing on a specific message or goal at a time, rather than trying to achieve too much at once. Clarity in communication has following features:
    - It makes understanding easier.

- Complete clarity of thoughts and ideas enhances the meaning of message.
- Clear message makes use of exact, appropriate and concrete words.

5. **Concreteness-** Concrete communication implies being particular and clear rather than fuzzy and general. Concreteness strengthens the confidence. Concrete message has following features:
    - It is supported with specific facts and figures.
    - It makes use of words that are clear and that build the reputation.
    - Concrete messages are not misinterpreted.
6. **Courtesy-** Courtesy in message implies the message should show the sender's expression as well as should respect the receiver. The sender of the message should be sincerely polite, judicious, reflective and enthusiastic. Courteous message has following features:
    - Courtesy implies taking into consideration both viewpoints as well as feelings of the receiver of the message.
    - Courteous message is positive and focused at the audience.
    - It makes use of terms showing respect for the receiver of message.
    - It is not at all biased.
7. **Correctness-** Correctness in communication implies that there are no grammatical errors in communication. Correct communication has following features:
    - The message is exact, correct and well-timed.
    - If the communication is correct, it boosts up the confidence level.
    - Correct message has greater impact on the audience/readers.
    - It checks for the precision and accurateness of facts and figures used in the message.
    - It makes use of appropriate and correct language in the message.

Awareness of these 7 C's of communication makes you an effective communicator.

Good communication has the following key benefits

- Improves vaccine decision-making
- Improves patient understanding and care
- Improves vaccination coverage
- Promotes transparency and accountability
- Builds trust with individuals, parents, community leaders, health workers, health officials and policy- makers

Challenges of risk communication include among others:

- Authorities/Government lose their monopoly on communication and information (diverse voices)
- Level public trust in authorities - country context
- Explosion of new technology and the use of mobile phone, internet, newspaper - reach more, reach wide, reach fast”

8.2 Communication with Stakeholders

	Ask the participants about the need of communication 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 below will be given preliminary information at initial stage and final report after completion of investigation and causality assessment at a later stage.

- Ethiopian Food and Drug Authority (EFDA)
- Ministry of Health (MoH)
- AEFI focal person and/or EPI focal person at all levels
- Regional EFDA branch offices
- Policy-makers/Politicians
- Manufacturers
- Professional associations
- University and Hospitals
- International agencies (e.g., WHO, UNICEF) and collaborative partner

8.3 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;

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

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 rumors spreading.

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

- Communicate immediately with the MoH and other high officials.
- Provide the parents with factual information. Remember that some parents may seek information elsewhere and you may lose credibility if you do not provide a trustworthy and technically sound response. The public and the other stakeholders have a right to know exactly what happened.

- Reassure parents, caregivers and adults that necessary measures are being taken so that the members of the community and caregivers are informed of what is happening.
- Communicate the results of the investigation to the programme managers and to the EPI officers at all levels.
- If the AEFI was caused by immunization error, tell the public what steps are being taken to prevent similar events in the future.
- Broadcast an official statement about the event on radio and television and publish a statement in newspapers.
- Repeat the message to dispel all fears.
- Constantly reassure the public of the safety of vaccines.

8.4 Communication with health care staff

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

8.5 Communication 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 benefits and to motivate families and communities to make use of immunization services.

Advance preparedness

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

A database of journalists

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

Information packages

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

Draft media release

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

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

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

A spokesperson system

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

Orientation workshops and field visits for media

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

Media Management during AEFI crisis

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

Monitoring of media

When an AEFI occurs, media should be monitored for authenticity of their reporting. The AEFI Committee should move very quickly to correct any inaccuracies. The AEFI Committee could take the following immediate actions:

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

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;

- An outline of actions taken or planned (such as the AEFI investigation).
- A description of the cause of the event (but only when this is known with certainty).

- An assurance that corrective action has been taken or will be taken.
- Reference to any relevant publication, video material or web site.
- Sender's name and spokesperson's details.
- Limited to one page of matter (400-500 words max).
- Short sentences (not exceeding two lines).

Quotes from key officials may be used after seeking their permission. The quotes must be positive and carry the key messages.

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.

Media Management post AEFI

Keeping promises to the media

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

Providing answers to unanswered questions

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

Keeping media informed about subsequent developments

If any decision or action is taken at the highest levels following AEFI investigations or during the investigations and the public must know about it, keep the media informed though a press release or hard copy document. The website of the Ministry of Health can also be used to update the media.

Dealing with rumors 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. Rumors 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 rumors:

- "Vaccines are a contraceptive to control population or to limit the size of a certain ethnic group."
- "Vaccines are contaminated by the AIDS virus or mad cow disease."
- "Children are dying after receiving vaccines."

Unless the rumor 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.

Common causes of Rumors

- Inadequate information sharing by health care providers or
- Failure to communicate correct information about vaccine effects and schedules,
- Failure to check whether caregivers know and understand information,
- Failure to give clients opportunities to ask questions
- Parents/caregivers' negative attitudes about immunization services

What you can do at the health facility

Under the direction of your supervisor:

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

Words of advice

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

Chapter summary

- Principles of effective communication contains seven C's of effective communication, namely, completeness, conciseness, consideration, clarity, concreteness, courtesy, and correctness
- Depending on the need stakeholders mentioned below will be given preliminary information at initial stage and final report after completion of investigation and causality assessment at a later stage.
- Parents, other members of the community, health staff and media should be kept informed about important aspects of ADEs, investigation, results and action taken
- building partnerships with the media is key to keep the public regularly informed about immunization, its benefits and to motivate families and communities to make use of immunization services.

Chapter 9: AEFI for COVID-19 Vaccines

Allocated time: 100 min

Chapter description:

This chapter provides participants with concept of different COVID-19 vaccine development platforms and familiarize with common characteristics. In addition it will enable participants to understand commonly reported AEFIs and Adverse Event of Special Interest (AESI) following the use of these vaccines.

Chapter Objectives

At the end of this chapter, participants will be able to identify common AEFIs/AESI related to COVID-19 vaccination.

Enabling Objectives

At the end of this session, the participant will be able to:

- Understand various types of COVID-19 vaccines development platforms
- Discuss the common characteristic of COVID-19 vaccines
- Identify common AEFIs related to COVID-19 vaccines
- Identify AESIs related to COVID-19 vaccines

Chapter Outline

- Types of COVID-19 vaccines
- Characteristics of COVID-19 vaccines
- Common AEFIs related to COVID-19 vaccines
  - General AEFIs related to COVID-19 vaccines
  - Vaccine Specific AEFIs related to COVID-19 vaccines
- Adverse Events of Special Interest to COVID-19 vaccines
- Homologous Boosting and Heterologous mixing of COVID-19 vaccines
- Summary

9.1 Types of COVID-19 vaccines, development platforms and mechanisms

Discuss and reflect:

- Type of COVID-19 vaccine you know
- How COVID-19 vaccines work

9.1.1 Types of COVID-19 vaccines and development platforms

Currently, there are 4 types of COVID-19 vaccines based on the platforms they are made (Table 9.1): whole virus, subunit, viral vector and nucleic acid (mRNA and DNA). In Ethiopia, as of August 2022, EFDA provided EUA for SII/Covishield (AstraZeneca), Sinopharm, Janssen/Ad26.COV and Pfizer/BioNtech.

Table 9.1: Types and attributes of COVID19 vaccines

Platform/Types	Attributes	Vaccine candidate (Manufacturer)
mRNA	Fast development speed; low- to-medium manufacturing scale	- BNT-162b2 (Pfizer, BioNTech) - mRNA-1273 (Moderna)
DNA	Fast development speed; medium manufacturing	- INO-4800 (Inovio)
Viral vector (Adenovirus based)	Medium development; high manufacturing scale	- AZD-1222 Ad5-CoV (AstraZeneca; Oxford University) - Ad26.COV2.S (Johnson &
Protein subunit	Medium- to-fast development; high manufacturing scale	- NVX-CoV2373 (Novavax)
Whole virion inactivated	Ability to quickly produce large amounts of vaccine	- Covaxin (Bharat Biotech) - Sinopharm and Sinovac

9.1.1 How does COVID-19 vaccines work

COVID-19 vaccines help our bodies develop immunity to SARS-CoV-2 without having to get the illness. Different types of vaccines work in different ways to offer protection. But with all types of vaccines, the body is left with a supply of “memory” T-lymphocytes as well as B-lymphocytes that will remember how to fight that virus in the future. It takes a few weeks after vaccination for the body to produce T-lymphocytes and B-lymphocytes. Hence, it is possible that a person could be infected with the virus that causes COVID-19 just before or just after vaccination. Sometimes,

after vaccination, the process of building immunity can cause symptoms, such as fever, which are normal and signs that body is building immunity.

9.2 Characteristics of COVID-19 vaccines

Various COVID-19 vaccines have different efficacy against various virus variant, require different dose and schedule. Some of these vaccines require ultra-cold temperature others can be kept in conventional vaccine cold chain (2-8°C).

Table 9.2 important Characteristics of common COVID-19 vaccines

Vaccine type & efficacy against SARS-Cov-2	**Dose and schedule**	**Effectiveness in variants**	**Storage**
Oxford/AstraZeneca COVID-19 vaccine ≈ 63.09% efficacy	- Two doses (0.5 ml, each) within 8 to 12 weeks.	Surveillance on their potential impact on vaccine effectiveness is required.	Maximum shelf life is 6 months stored in a refrigerator (2 to 8°C) Once punctured, the vial must be used within 6 hr Must not be frozen
The Janssen Ad26.COV2.S COVID-19 vaccine	- one dose (0.5 ml, each)14 days between other	Efficacious against B1.351 (first identified in South Africa) and P.2 (first identified in Brazil)	Store unpunctured multi-dose vials at 2°C to 8°C and must not be frozen. Once punctured (2 to 8°C), use
Sinopharm COVID-19 vaccine ≈79% Efficacy	-Two doses (0.5 ml, each) with 3–4 weeks interval	Has not yet been evaluated in the context of circulation of widespread variants of concern.	Store in the original packaging in a refrigerator at +2 to +8 °C. Once punctured, the vial must be used within 6 hr Needs easy storage requirements
Sinovac COVID-19 vaccine ≈ 51% efficacy from symptomatic infection	Two doses (ml, each) at interval of 2–4 weeks	Effective in an observational study in the presence of P1 variant circulation.	Once puncture, use within 6 hr Do not shake the vial roughly. It is refrigerated suspension stored between 2°C to 8°

Pfizer-BioNTech ≈ 94.1% efficacy	Two doses (0.3 ml) Between 21-28 days	Suppress variants such as B.1.351.	Store an ultra-cold freezer, thermal shipping container Maximum shelf life is 6 months (-80°C to -60°C) 31 days at 2-8°C after thaw (assign immediately after removing from freezer) May be stored at 2 to 25°C for 2 hours prior to dilution Once diluted may be stored at 2 to 25°C for a further 6 hours vaccine cannot be re-frozen
The Moderna COVID-19 (mRNA-1273) vaccine ≈ 94.1% in protecting against COVID-19	- Two doses (0.5 ml or 100 µg, each) 28 days apart. - May be extended to 42 days.	New variants of SARS-CoV-2, do not alter the effectiveness of the Moderna mRNA vaccine.	Maximum shelf life is 7 months at -25°C to -15°C and 30 days at 2 to 8°C May be stored between 8 to 25°C for up 12 hours Once punctured, the vial must be used within 6 hours The vaccine cannot be re-frozen

9.3 Common AEFIs related to COVID-19 vaccines

Vaccines used in national immunization programs are extremely safe and effective. However, no vaccine is perfectly safe, and AEs can occur following immunization. In addition to the vaccines themselves, the process of immunization is a potential source of AEs.

	Group Discussion

During COVID-19 vaccination, what type of common adverse effects are encountered by patients in your facility?

Do these adverse effects differ from other routine vaccines?

Time: 3 Minutes

9.3.1 General AEFIs related to COVID-19 vaccines

Due to limited administration of the vaccines in the development and clinical trial phase, some side effects particularly those that are **very rare** only emerge during widespread use. The rapid development of COVID-19 vaccines, due to the urgency of the pandemic has led to unfounded rumors that COVID-19 vaccines are linked to various post-vaccination adverse effects. Even though, COVID-19 vaccines developed and produced based on technological advancements, existing vaccine candidates have contributed to the emergence of many rumors.

Like any vaccine, COVID-19 vaccines can cause side effects, most of which are mild or moderate and go away within a few days on their own. Most COVID-19 side effects reported to date have been general events, such as 'flu-like conditions', headache, pain at the injection site, chills, fatigue, nausea, fever, dizziness, weakness, myalgia, and tachycardia. Generally, these reactions are not associated with the more serious illness. The chances of any of these side effects occurring after vaccination differ according to the specific vaccine. These events occur within seven days of vaccination and are not associated with serious illness.

Serious reactions such as allergic and anaphylactic reactions are very rare and usually occur soon after vaccination, with a sudden onset. However, even though they are very rare, clinical trials and post marketing surveillance results have shown that serious or long-lasting side effects are possible.

9.3.2 Vaccine Specific AEFIs related to COVID-19 vaccines

Local reactions at the injection site were found to be common after vaccination with the **COVID-19 mRNA Vaccine BNT162b2 (Pfizer BioNTech)** during clinical trials. Over 80% of trial participants reported pain at the injection site. This occurred within 7 days after the injection and was resolved after a few days. **In clinical trials**, the most frequently reported systemic reactions in participants include;

- Tiredness (>60%)
- Headache (> 50%)

- Muscle aches (> 30%)
- Chills (> 30%)
- Raised temperature (pyrexia) (> 10%)
- Joint pain (> 20%) and

The above symptoms were usually mild or moderate in intensity and resolved within a few days after vaccination. If required, symptomatic treatment with analgesic and/or antipyretic medicinal products (e.g., paracetamol-containing products) may be used. There is no significant reported serious reactions including anaphylaxis.

The majority of AEs reported during the clinical trials of the **AstraZeneca COVID-19 vaccine** were mild to moderate and short-lasting, usually resolving within a few days of vaccination. When compared with the first dose, adverse reactions reported after the second dose were milder and reported less frequently. More than 60% of AstraZeneca vaccine **trial participants** reported tenderness at the injection site with redness, swelling, itching, warmth, and pain. The most frequently reported systemic reactions were;

- Headache and tiredness (>50%)
- Muscle aches and feeling generally unwell (>40%)
- Raised temperature (pyrexia) and chills (>30%)
- Joint pain and nausea (>20%)

The most frequently reported adverse reactions to the **COVID-19 Vaccine Moderna** were:

- Injection site pain (92%)
- Fatigue (70%)
- Headache (65%)
- Myalgia (62%)
- Arthralgia (46%)
- Chills (46%)
- Nausea/vomiting (23%),
- Axillary swelling/tenderness (19.8%)
- Fever (15.5%)
- Injection site swelling (14.7%)
- Redness (10%)

The most common side effects reported by people 17 to 21% of who received various doses of **Sinovac (CoronaVac) vaccine** were injection site pain and soreness. Other reported side effects included fatigue, diarrhea and muscle weakness. Most of these side effects were mild and lasted for only 2 days. Furthermore, clinical trial data for the vaccine has shown that trial participants

who received the Sinovac vaccine reported a lower occurrence of fever in comparison to mRNA vaccines like the Pfizer-BioNTech and Moderna vaccine.

People reported mild side effects of **Sputnik V (Gam-COVID-Vac)**. Local and systemic, flu-like reactions were more common including local pain, asthenia, headache, and joint pain were most frequently encountered AEs usually go away within 24 to 48 hrs. A comprehensive analysis of AEs during clinical trials and over the course of mass vaccinations with the Sputnik V vaccine showed no cases of cerebral venous sinus thrombosis.

As of August 30, 2022 globally more than 4.2 million AEFIs were reported to WHO Uppsala Monitoring Center (UMC). The following are commonly reported AEFIs following COVID-19 vaccines

Reaction (MedDRA)	Count	Percentage
PT: Headache	962 464	22.8
PT: Pyrexia	783 090	18.6
PT: Fatigue	684 069	16.2
PT: Myalgia	508 027	12.1
PT: Chills	495 165	11.7
PT: Nausea	408 619	9.7
PT: Arthralgia	334 503	7.9
PT: Malaise	328 815	7.8
PT: Dizziness	322 901	7.7
PT: COVID-19	307 780	7.3
PT: Injection site pain	287 932	6.8
PT: Pain in extremity	267 135	6.3
PT: Pain	238 598	5.7
PT: SARS-CoV-2 test	212 677	5.0
PT: Vaccination site pain	192 262	4.6
PT: Vaccination failure	190 205	4.5
PT: Dyspnoea	184 004	4.4
PT: Asthenia	171 742	4.1
PT: Lymphadenopathy	152 232	3.6
PT: Vomiting	138 495	3.3

In Ethiopia as of August 30, 2022 more than 41,678 AEFIs were reported. However only 11,262 AEFIs were shared to WHO UMC. The following are list of commonly reported AEFIs.

Uppsala Monitoring Centre

VigiLyze ET Food, Medicine & Healthcare Admin and Control Authority

Reported preferred terms (MedDRA)

Reaction (MedDRA)	Count	Percentage
PT: Headache	4 060	36.1
PT: Injection site pain	3 245	28.8
PT: Pyrexia	2 340	20.8
PT: Adverse drug reaction	2 255	20.0
PT: Fatigue	1 499	13.3
PT: Arthralgia	1 384	12.3
PT: Chills	763	6.8
PT: Myalgia	495	4.4
PT: Back pain	417	3.7
PT: Nausea	358	3.2

9.4 Adverse Events of Special Interest to COVID-19 vaccines

Definition: An AESI is a pre-specified 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 special studies.

AESIs 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:

- Vaccine-associated enhanced disease
- Multisystem inflammatory syndrome in children
- Acute cardiovascular injury (microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia, myocarditis)
- Coagulation disorder (thromboembolism, hemorrhage)
- Acute respiratory distress syndrome
- Acute kidney injury

- Generalized convulsion
- Guillain Barré Syndrome (GBS)
- Acute liver injury
- Anosmia, ageusia
- Single organ cutaneous vasculitis
- Erythema multiforme
- Anaphylaxis
- Acute aseptic arthritis
- Meningoencephalitis
- Acute disseminated encephalomyelitis (ADEM)
- Thrombocytopenia

All AESIs should be reported to the next higher health office or health authority as soon as possible using the available standard report tools.

Selected adverse events of special interest

Thrombotic and thromboembolic events after COVID-19 vaccination

A very rare new type of AE called Thrombosis with Thrombocytopenia Syndrome (TTS), involving unusual blood clotting events associated with low platelet counts have been reported after vaccination with adenovirus viral vector vaccines including AstraZeneca, Janssen and Sputnik COVID-19 vaccines. Some patients developed deep venous thrombosis (DVT), pulmonary emboli, or acute arterial thrombosis. The patients had low platelet counts at diagnosis, but the onset and rate of platelet decrease preceding the thrombotic event are unknown.

The majority of the events have occurred in between 5 and 12 days with median duration of 9 days following vaccination. Approximately 59% of cases were females. Median age was 42 years.

Considerations for health workers in the context of TTS

- Clinicians should be alert to any new, severe, persistent headache or other significant symptoms, such as severe abdominal pain and shortness of breath, with an onset between 4 to 20 days after adenovirus vectored COVID-19 vaccination.
- At a minimum, clinicians are encouraged to measure platelet levels and conduct appropriate radiological imaging studies as part of the investigation of thrombosis

- Clinicians should also be aware that although heparin is used to treat blood clots in general, administration of heparin in TTS may be dangerous, and alternative treatments such as immunoglobulins and non-heparin anticoagulants should be considered.

Myocarditis and pericarditis

Worldwide, there have also been recent, rare cases of myocarditis or pericarditis (inflammation of the heart) reported after the mRNA based vaccines including Pfizer BioNTech and Moderna COVID-19 vaccines. The reported rate appears to be highest in those under 25 years of age and males, and after the second dose. Onset is within a few days of vaccination and most cases are mild, recovering within a short time following standard treatment and rest without any sequalae. Vaccinated individuals should be advised to seek immediate medical attention if they experience a new onset of chest pain, shortness of breath, palpitations, or arrhythmias.

9.5 Homologous Boosting and Heterologous mixing of COVID-19 vaccines

Mix and Match use of COVID-19 vaccines

E-NITAG recommends heterologous priming (mix and match) use of COVID 19 vaccines only for the two vaccines - AstraZeneca and Pfizer. If either of the vaccines are stock out at a given facility or vaccine delivery point, mix and match of AstraZeneca and Pfizer is allowed. However, it is not recommended to use the mix and match of the vaccines if the facility has adequate stock of the same vaccine to complete the primary series. Based on the Global SAGE recommendations and E-NITAG guidance, other types of COVID-19 vaccines may be included in the mix and match approach.

Mix and Match		
1st dose	**2nd dose**	**Booster dose**
AstraZeneca	AstraZeneca	AstraZeneca
J & J		J & J
Pfizer	Pfizer	Pfizer
Sinopharm	Sinopharm	Sinopharm

Booster Dose

E-NITAG recommends COVID-19 vaccine booster dose for those who completed the primary vaccination series and passed 6 months and above. The booster dose can be given by the same vaccine type (Homologous) or with a different type of COVID-19 vaccine (Heterologous) as shown in the table below.

Table: XX summary of Booster dose vaccination in Ethiopia

Homologous Boosting			Heterologous Boosting		
1st dose	**2nd dose**	**Booster dose**	**1st dose**	**2nd dose**	**Booster dose**
AstraZeneca	AstraZeneca	AstraZeneca	AstraZeneca	AstraZeneca	Pfizer
J & J		J & J	J & J		Pfizer
Pfizer	Pfizer	Pfizer	Pfizer	Pfizer	AstraZeneca
Sinopharm	Sinopharm	Sinopharm	Sinopharm	Sinopharm	Pfizer

9.6 Chapter Summary

- COVID-19 vaccines were developed in short period of time using new technology and platforms. These are adenovirus vector vaccines, mRNA vaccines, protein subunit, and whole virion inactivated platforms.
- Due to different development platforms various COVID-19 vaccines do have different characteristic regarding efficacy, protection against variants, dosing, schedule and storage requirements.
- All AEFIs/AESI related to COVID-19 are reportable.

Chapter 10: Monitoring and Evaluation of AEFI Activities

Allotted time: 45 minutes

Chapter description:

This chapter describes the essence of monitoring and evaluation to answer what and why monitoring and evaluation (M&E), importance of M&E for AEFI surveillance system, list of indicators to be used for monitoring and evaluation of AEFI surveillance system at different levels, with description of AEFI indicators.

Primary Objective:

By the end of this chapter, participants will be able to monitor and evaluate AEFI surveillance system and related activities in different immunization program levels and beyond.

Enabling Objectives:

- Recognize the significance of monitoring and evaluation in AEFI surveillance system
- Understand selected performance indicators in AEFI surveillance system

Chapter Outline

10.1 Introduction: Concepts and significance of monitoring and evaluation for AEFI

10. 2 AEFI surveillance Indicators and their descriptions

10.3 Chapter summary

10.1 Introduction: Concepts and significance of M&E for AEFI

	Brainstorming questions (5 minutes)
	) What is monitoring and evaluation (M&E)?) Have you any experience in AEFI? What is the importance of M&E for AEFI Surveillance

Like any other effort, AEFI surveillance system have its objective or outcome and exhibit processes or activities to meet some target by consuming resources/inputs. In this connection, all these steps need to be monitored and evaluated to check **where** we are, and to know the worth of such efforts (why). Then, what do M&E mean?

Monitoring is an ongoing process by which stakeholders obtain regular feedback on the progress being made towards achieving their goals and objectives. Different formats for tracking the planned activities can be used including monthly, quarterly, semiannual, and annual reports.

Evaluation is a rigorous and independent assessment of either completed or ongoing activities to determine the extent to which they are achieving stated objectives and contributing to decision making. In other words, Evaluation is to determine the relevance and fulfillment of objectives, developmental efficiency, effectiveness, impact and sustainability.

M&E is a process of continual gathering of information and assessment of it in order to determine whether progress is being made towards pre-specified goals and objectives, and to highlight whether there are any unintended (positive or negative) effects from a project and its activities. M&E in AEFI provide valuable information to stakeholders about immunization and vaccine safety surveillance.

Why M&E?

Monitoring and evaluation help to track progress, identify and respond to barriers to progress, and to inform course of corrective measures to increase impact and value for money. It is also needed for accountability within national, regional or individual levels which includes reporting of AEFI.

The importance of Monitoring and evaluation includes:

- it provides the only consolidated source of information showcasing performance progress;
- it allows actors to learn from each other's experiences, building on expertise and knowledge;
- it often generates (written) reports that contribute to transparency and accountability, and allows for lessons to be shared more easily;
- it reveals mistakes and offers paths for learning and improvements;
- it provides a basis for questioning and testing assumptions;
- it provides a means for agencies seeking to learn from their experiences and to incorporate them into policy and practice;
- it provides a way to assess the crucial link between implementers and beneficiaries on the ground and decision-makers;
- it adds to the retention and development of institutional memory;
- it provides a more robust basis for raising funds and influencing policy.

Safety monitoring is essential for medicines and crucial to vaccines (AEFI) due to the peculiarities in vaccines. The immunization safety surveillance system should be continuously monitored and also regularly evaluated to identify gaps and rectify them in order to strengthen the AEFI surveillance system, thereby contributing to the enhancement of immunization program. As a country, Ethiopia is expected to monitor safety of vaccines through active and passive surveillance, report AEFI, communicate signals and related issues to the global community in addition to the different measure it takes locally on the responsible actors and protecting citizens. also are medicines. The flow of data starts from report and health professionals have duty of reporting timely of adverse events of medicines (vaccines) through the designed channel. At the regional level, it is envisaged that there will be forwarding of reports and conducting investigation if there is SAE, as well as reporting of progress of AEFI to the national level. Hence, each administrative level is expected to plan AEFI surveillance activities and monitor performance using appropriate indicators. The following session describes those indicators to be used at different levels.

10.2 Performance Indicators for AEFI surveillance system

	**Group Activity:** Question and answer, reflection and discussion - What is an indicator? - Based on the knowledge you get on AEFI surveillance give Indicators for monitoring AEFI monitoring activities and explain it.

In simple terms, indicator is what we use to measure the extent of performance using **qualitative** or **quantitative** variables.

The GACVS states the there are no globally accepted indicators which could demonstrate the functionality of an AEFI surveillance system. Meanwhile, GACVS considered number of principles in deriving a set of indicators for AEFI surveillance. Three types of indicators are proposed: (i) to monitor the volume of AEFI reports; (ii) to monitor the quality of those reports; and (iii) to monitor the quality of the response to serious AEFI[1]. The proposed general indicator by GACVS is the ratio of AEFI reports per 100 000 surviving infants per year. Cognizant to this and customizing to the national context, the following are list of performance indicators recommended to be monitored for AEFI related activities:

1. Input and activity indicators for system functionality
   - 1.1. Availability of dedicated office/ team/ focal person
   - 1.2. Availability of trained personnel
   - 1.3. Existence of plan for monitoring AEFI
   - 1.4. Availability budget/fund for the AEFI monitoring
   - 1.5. Availability of reporting forms/formats, line list and guideline for AEFI
   - 1.6. Inclusion of AEFI performance in the institutions' periodic performance monitoring
   - 1.7. Existence of regional taskforce coordinating the AEFI surveillance.
   - 1.8. Presence/practice of supportive supervision at different levels

[1] https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/aefi/performance-indicators

1.9. Availability of AEFI database at national level

2. System Performance monitoring (Report Quantity and type)

2.1 AEFI reporting rate per 100 000 population per year

2.2 Ratio of AEFI reports per 100 000 surviving infants per year.

2.3 AEFI reporting rate per 100 000 < 5 population per year

2.4 AEFI reporting rate per 1 000 000 distributed doses of vaccines per year

2.5 AEFI reporting rate per 1 000 000 administered doses of vaccines per year

2.6 Percentage of serious AEFI cases versus total AEFI reports

3. Indicators for system quality or proficiency of AEFI monitoring:

3.6 Completeness of reports

3.7 Timeliness of reporting of suspected AEFIs (% of serious AEFI reports received as per specified time);

3.8 Timeliness of investigation of notified SAEs

3.9 Number (%) of AEFI investigation conclusions supported by findings of special tests (clinical specimens, Post-mortem findings (among AEFI deaths), lab findings for vaccine samples)

3.10 Number (%) SAEs reviewed by National pharmacovigilance committee and not assessable due to lack of information.

4. Monitoring Response Systems

4.8 Response for reported AEFI (minor) – acknowledging the receipt timely

4.9 Timeliness of case investigation: % of serious AEFI cases investigated within 48 hours of occurrence.

4.10 % of SAEs with causality assessment done where feedback was provided within 7 days of case classification

This list of indicators is identified from the global practice, Covid-19 vaccination experience and the national guideline. It is to be noted that there are many indicators included here but not included in the national guideline. Still, AEFI fatality Rate, Case management and follow up for SAE victims etc could also be considered as indicators. Hence, the list could also be further enriched or amended in the future depending on the prevailing conditions and the revision of

the national guideline. Most of the indicators are self-explanatory whereby detail description may not be needed. Nonetheless, technical description is given for few of indicators as example and making consistent approach for such indicators.

Examples:

1. **AEFI reporting rate per 100 000 population per year**

Indicator	**AEFI reporting rate per 100 000 population per year**						
Definition	This indicator shows the level of performance of the system effectiveness in detecting and reporting cases.						
Formula	The AEFI reporting rate per 100 000 population per year could be calculated as: $\text{Reporting Rate} = \frac{T \quad N \quad o \quad R \quad i \ the\ y}{T \quad p} x\ 100{,}000$						
Interpretation	The more the number the better the performance and vice versa						
Disaggregation	By woreda, zone, region, and by time (trend)						
Sources	Numerator: Case based AEFI reports from linelist or reporting forms. Denominator: the current statistical data of the place or coverage of the HF						
Frequency of Reporting		Hospital	WorHO	ZHD/ ScHO	RHB	EFDA	FMOH
		Biannually	Biannually	Biannually	Biannually	Annually	NA

2. **Existence of Functional Regional AEFI Taskforce**

Indicator	**Existence of Functional Regional AEFI Taskforce**						
Definition	This indicator shows the availability of functional Regional AEFI Taskforce. It applies to Regional Health Bureaus and City Administrations.						
Formula	The functional Regional AEFI Taskforce should have: - Approved ToR with list of members, - Regional AEFI Taskforce plan according to the guideline - Availability, and proper use of formats (investigation and report) - Conduct regular meeting with minutes documented						
Interpretation	If TF complies to all the above criteria mentioned (and beyond) it is fully functional, while missing one or two could be labelled as partial and fair respectively. One implies non functional but existent while zero implies non existent.						
Disaggregation	Regions						
Sources	Signed TOR with list of members, Minutes (archived document review)						
Frequency of Reporting		Hospital	WorHO	ZHD/ ScHO	RHB	EFDA	FMOH
		NA	NA	??	Biannually	NA	NA

3. **Ratio of AEFI reports per 100 000 surviving infants per year**

Indicator	**The ratio of AEFI reports per 100 000 surviving infants per year**						
Definition	This indicator is a general one estimating the number of all AEFI cases reported per 100,000 surviving births in that year.						
Formula	The ratio of AEFI reports per 100 000 surviving infants per year could be calculated as: $\textbf{Reporting Rate U5} = \frac{T \quad N \quad o \; R \quad ti \; a \; y}{T \quad s \quad b \quad hs \; d \quad the \; Sc \quad y} x\, 100{,}000$						
Interpretation	The minimum target for this indicator is 10 AEFI cases per 100,000 live births						
Disaggregation	By woreda, zone, region, and by time (trend)						
Sources	Numerator: Case based AEFI reports from linelist or reporting forms Denominator: Number of live births from records						
Frequency of Reporting		Hospital	WorHO	ZHD/ ScHO	RHB	EFDA	FMOH
		Biannually	Biannually	Biannually	Biannually	Annually	NA

Similar approaches could be used for those requiring description with the understanding such as:

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

AEFI case fatality Rate: This measures the quality of care for responding to SAEs reported. It is the percentage (%) of deaths occurred per AEFI cases reported.

Proportion of SAEs classified by causality assessment committee: it measures the presence and functionality of an independent vaccine safety monitoring advisory committee that reviews and classifies all serious cases. It is calculated as number of cases reviewed and classified per

serious cases reported to the national level. It could be further qualified as number (%) of SAEs classified within 30 days of receipt of all documentation from districts.

Target: All serious cases should be reviewed and classified within one month of report.

Frequency of Vaccine Safety Monitoring Meetings: A quarterly meeting (e.g. AEFI taskforce, casualty assessment committee, etc.) is expected to be held for monitoring AEFI and other vaccine safety issues.

10.3 Chapter summary

eM&E is an essential and integral part of any activity, task, project, or program.

- AEFI is an important safety monitoring system involving different important steps to be monitored and evaluated periodically.
- Results of monitoring and evaluation enable to measure, assess its performance and improve the next steps.
- Different performance indicators are identified for M&E of AEFI surveillance system to be used at different levels
- Good understanding of M&E of AEFI surveillance system significantly contributes to performance improvement nationally, the performance at country level is also be reflected in the global level.

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Annexes

Annex 1. AEFI reporting form

REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Patient Name or initials:	***AEFI reporting number:***
Patient's full Address:	***Reporter's Name:***
	Institution:
Telephone:	Designation & Department:
Sex: ☐ M ☐ F (Pregnant ☐ Lactating ☐)	Address:
Date of birth : _ _ / _ _ / _ _	
OR Age at onset: ☐☐ *Years* ☐☐ *Months* ☐☐☐ *Days*	Telephone & E-mail:
OR Age Group at onset: ☐ *<1 Year* ☐ *1 to 5 Years* ☐ *>5 Years-15 Years* ☐ *>15 years-60 Years* ☐ *>60 years*	Date patient notified event to health system: _ _ / _ _ / _ _
	Today's date : _ _ / _ _ / _ _

Health facility (place or vaccination center) name & address:

Vaccine							***Diluent (if applicable)***			
Name of vaccine	***Brand Name incl. Name of Manufacturer***	***Date of vaccination***	***Time of vaccination***	Dose (1st, 2nd, etc.)	***Batch /Lot number***	Expiry date	Name of diluent	***Batch /Lot number***	Expiry date	Date and time of reconstitution

Adverse event(s):	Date AEFI started : _ _ / _ _ / _ _
☐ Severe local reaction ☐ *>3 days* ☐ *beyond nearest joint*	Time _____
☐ Seizures ☐ *febrile* ☐ *afebrile*	Describe AEFI (Signs & Symptoms):
☐ Abscess ☐ Sepsis ☐ Encephalopathy ☐ Toxic shock syndrome ☐ Thrombocytopenia ☐ Anaphylaxis ☐ Fever ≥38°C ☐ Other (specify).....	

Serious: Yes / No; ➔ If Yes ☐ Death ☐ Life threatening ☐ Persistent or significant disability ☐ Hospitalization ☐ Congenital anomaly ☐ Other important medical event (specify).....

Outcome: ☐ Recovering ☐ Recovered ☐ Recovered with sequela ☐ Not Recovered ☐ Unknown

☐ Died If Died, date of death : _ _ / _ _ / _ _ Autopsy done: ☐Yes ☐No ☐Unknown

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

First Decision making level to complete:

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

National level to complete:

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

**Compulsory field*

Email address: pharmacovigilance@efda.gov.et

Annex 2: COVID-19 vaccine AEFI line listing form

Source	S.No	Patient Name /Identifier	AEFI Reporting ID Number	Patient Location (Village /Town	Patient Location (District)	sex (m/f)	Pregnant (y/N)	Lactating (Y/N)	Age (date of Birth or age of an est)	Vaccine/s Brand	Manufacture Rum	Dose	Vaccine Batch No	Diluent Batch No	Adverse Event	Place of Vaccination	Date of Vaccination (DDM)	Date of event	Date of Notification (DDM)	Date of Reporting (DDM)	Serious (y/N)	Reason for Serious	outcome	Autopsy Consulted in Case Death (y/N)	Reported by	Reporter Location 1	Reporter Location 2	Investigation Planned (y/N)	Data Reported at National Level

Annex 3: AEFI investigation form

AEFI CASE INVESTIGATION FORM			
Section A	**Basic details**		
Region	**Zone**	**Woreda**	**Case ID**
Place of vaccination ( ): Govt. health facility/Private health facility/Other (specify) _____ Vaccination in ( ): Campaign/Routine/Other (specify) _____			
Name and Address of vaccination site:			
Type of site ( ) Fixed Mobile Outreach Other _____			
Name of Reporting Officer:	Date of investigation: __ __ / __ __ / __ __ __ __ Date of filling this form:__ __ / __ __ / __ __ __ _		
Designation/ Position:			
Telephone #:	Mobile:	e-mail:	
Patient Name	Sex: M / F		
(use a separate form for each case in a cluster) Date of birth (DD/MM/YYYY):__ __ / __ __ / __ __ __ __***OR*** *Age at onset: __ __years __ __months __ __ __days* ***OR*** *Age group: < 1 year 1-5 years> 5 years* Patient's full address with landmarks *(Kebele, Gott name, house number, locality, phone number etc.)***:**			

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

				Vaccine	Vaccine
				Diluent	Diluent

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

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

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

Status on the date of investigation : Died ()Disabled()Recovering()Recovered completely()Unknown()

If died, date and time of death*(DD/MM/YYYY)*:__ __ / __ __ / __ __ __ __ (*hh/mm):* __ __ / __ __

Autopsy done? ()Yes(date)_____ No Planned on (date)_____ Time_____

Attach report (if available)

Section B	**Relevant patient information prior to immunization**	
Criteria	**Finding**	**Remarks (If yes provide details)**
Past history of similar event	Yes / No/ Unkn	
Adverse event after previous vaccination(s)	Yes / No/ Unkn	
History of allergy to vaccine, drug or food	Yes / No/ Unkn	
Pre-existing illness (30 days) / congenital disorder	Yes / No/ Unkn	
History of hospitalization in last 30 days, with cause	Yes / No/ Unkn	
Patient currentlyon concomitant medication? (If yes, name the drug, indication, doses &treatment dates)	Yes / No/ Unkn	
Family history of any disease (relevant to AEFI) or allergy	Yes / No/ Unkn	

For adult women

- Currently pregnant?Yes (weeks) _____/ No/ Unknown
- Currently breastfeeding? Yes / No

For infants

The birth was: Full-term Pre-term___ Post-term. Birth weight:

Delivery procedure was: Normal___ Caesarean___ Assisted (forceps, vacuum etc.)____

With complication (specify)_____

Place of birth: Home__ Health facility_____

Section C	**Details of first examination** of serious AEFI case**	
Source of information (*all that apply*): **Examination by the investigator__ Documents___ Verbal autopsy___** **Other**_____ *If from verbal autopsy, please mention source (e.g. parents)*_____		
Name of the person who first examined/treated the patient:_____ Name of other persons treating the patient: _____ Other sources who provided information (specify): _____		
Signs and symptoms in chronological order from the time of vaccination:		
Name and contact information of person completing these clinical details:	Designation:	Date/time
****Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports) and then complete additional information NOT AVAILABLE in existing documents, i.e.** • ***If patient has receive dmedical care*** attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write only the information that is not available in the attached documents below • ***If patient has not received medical care***–obtain history, examine the patient and write down your findings below (add additional sheets if necessary) **Provisional/Final Clinical Diagnosis:**		

Section D Details of vaccines provided at the site linked to AEFI on the corresponding day										
Number immunized for each antigen at session site. Attach record if available.	Vaccine name*									
	Number of doses**									
**Write name of vaccine(s) given on the same vaccination day at the site ** Write total doses administered for each vaccine*										
• When was the patient immunized? (Tick the box the below and respond to ALL questions)										
Within the first vaccinations of the session Within the last vaccinations of the session Unknown										

In case of multidose vials, was the vaccine given within the first few doses of the vial administered? Within the last doses of the vial administered? Unknown?	
• Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes/ No
• Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?	Yes/ No/ Unable to assess
• Based on your investigation, do you feel that the vaccine's physical condition (e.g. colour, turbidity, foreign substances etc.) was abnormal at the time of administration?	Yes / No/ Unable to assess
• Based on your investigation, do you feel that there was an error in vaccine reconstitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	Yes / No/ Unable to assess
• Based on your investigation, do you feel that there was an error in vaccine handling (e.g. break in cold chain during transport, storage and/or immunization session etc.)?	Yes / No/ Unable to assess
• Based on your investigation, do you feel that the vaccine was administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size,not following good injection practice etc.)?	Yes / No/ Unable to assess
• Number immunized from the concerned vaccine vial/ampoule	
• Number immunized with the concerned vaccine in the same session	
• Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations:_____	
• Is this case a part of a cluster?	Yes / No/ Unkn
• If yes, how many other cases have been detected in the cluster?	
• Did all the cases in the cluster receive vaccine from the same vial?	Yes / No/ Unkn
• If no, number of vials used in the cluster (enter details separately)	

Section E Immunization practices at the place(s) where concerned vaccine was used
(Complete this section by asking and/or observing practice)

Syringes and needles used:

Are AD syringes used for immunization?	Yes	No	Unkn

If no, specify the type of syringes used: Glass___ Disposable____ Recycled disposable_____ Other _____

Specific key findings/additional observations and comments:

Reconstitution: (complete only if applicable, √NA if not applicable)	Status		
Reconstitution procedure (√)	Yes	No	NA

Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA
Same reconstitution syringe used for reconstituting different vaccines? Separate reconstitution syringe for each vaccine vial?	Yes	No	NA
Separate reconstitution syringe for each vaccination?	Yes	No	NA
Are the vaccines and diluents used the same as those recommended by the manufacturer?	Yes	No	NA
Specific key findings/additional observations and comments:			
Section F Cold chain and transport ***(Complete this section by asking and/or observing practice)***			
Last vaccine storage point:			
• Is the temperature of the vaccine storage refrigerator monitored?	Yes	No	Unkn
oIf "yes", was there any deviation outside of 2–8° C after the vaccine was placed inside?			
oIf "yes", provide details of monitoring separately.			
• Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes	No	Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes	No	Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes	No	Unkn
• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes	No	Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes	No	Unkn
Last vaccine storage point:			
• Is the temperature of the vaccine storage refrigerator monitored?	Yes/No		
oIf "yes", was there any deviation outside of 2–8° C after the vaccine was placed inside?	Yes / No		
oIf "yes", provide details of monitoring separately.			
Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes	No	Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes	No	Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes	No	Unkn
• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes	No	Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes	No	Unkn
Specific key findings/additional observations and comments:			

Vaccine transportation:			
• Type of vaccine carrier used	Yes	No	Unkn
• Was the vaccine carrier sent to the site on the same day as vaccination?	Yes	No	Unkn
• Was the vaccine carrier returned from the site on the same day as vaccination?	Yes	No	Unkn
• Was a conditioned ice-pack used?	Yes	No	Unkn
Specific key findings/additional observations and comments:			
Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes	No	Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes	No	Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes	No	Unkn
Section G Community investigation (Please visit locality and interview parents/others)			
Were any similar events reported within a time period similar to when the adverse event occurred and in the same locality? If yes, describe:	Yes	No	Unkn
If yes, how many events/episodes?_____			
Of those effected, how many are • Vaccinated:_____ • Not vaccinated:_____ • Unknown:_____			
Other comments:			
Section H: Other findings/observations/comments			