

National Epidemiology Center
Department of Health



Adverse Events Following Immunization (AEFI)

A Manual of Procedure for
Surveillance and Response to AEFI



2014

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Foreword

Throughout the years, we have been implementing immunization campaigns which aim to protect the public from vaccine preventable diseases (VPD). These enormous efforts have significantly increased the chances of public's safety from acquiring VPDs. As the age of vaccines continues to progress from all global efforts in research and studies, the social awareness towards vaccine and immunization has remained vague. Therefore, we should remain vigilant in ensuring the safety and most importantly, gaining the trust of the public. We should remember that no vaccine is without risk; and we are aware that at present, though modern vaccines are considered safe; there are a number of reported cases of adverse events following immunization (AEFIs). These reports may or may not be entirely associated to vaccine itself. It may be coincidental, may have caused from mishandling of vaccines or from an error in administration.



Being front liners in public health, I present the Adverse Events Following Immunization (AEFI) manual of procedures for surveillance and response. This shall serve as a guide for our healthcare professionals in understanding immunization principles, immunization safety, new classification of AEFIs and the national AEFI surveillance system. In understanding the entirety of AEFI, we will be able to protect the public from VPDs and to encourage them to get vaccinated.

I give my thanks to World Health Organization for their continuous support to our cause; all staff of the regional, provincial city, municipal and health offices hospitals; staff of the Food and Drug Administration, national VPD surveillance and EPI team whose perseverance have immensely contributed in making the revision of this manual possible.


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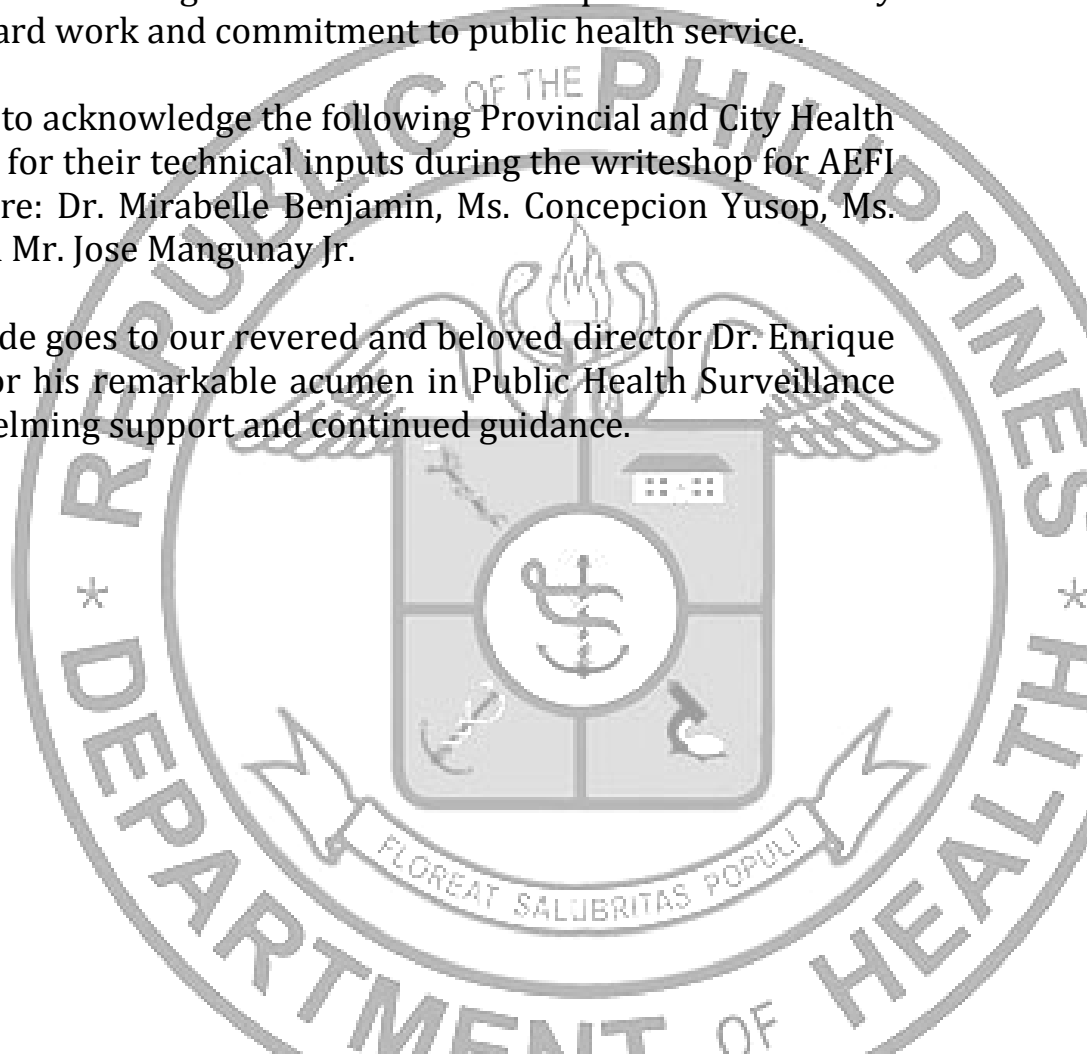
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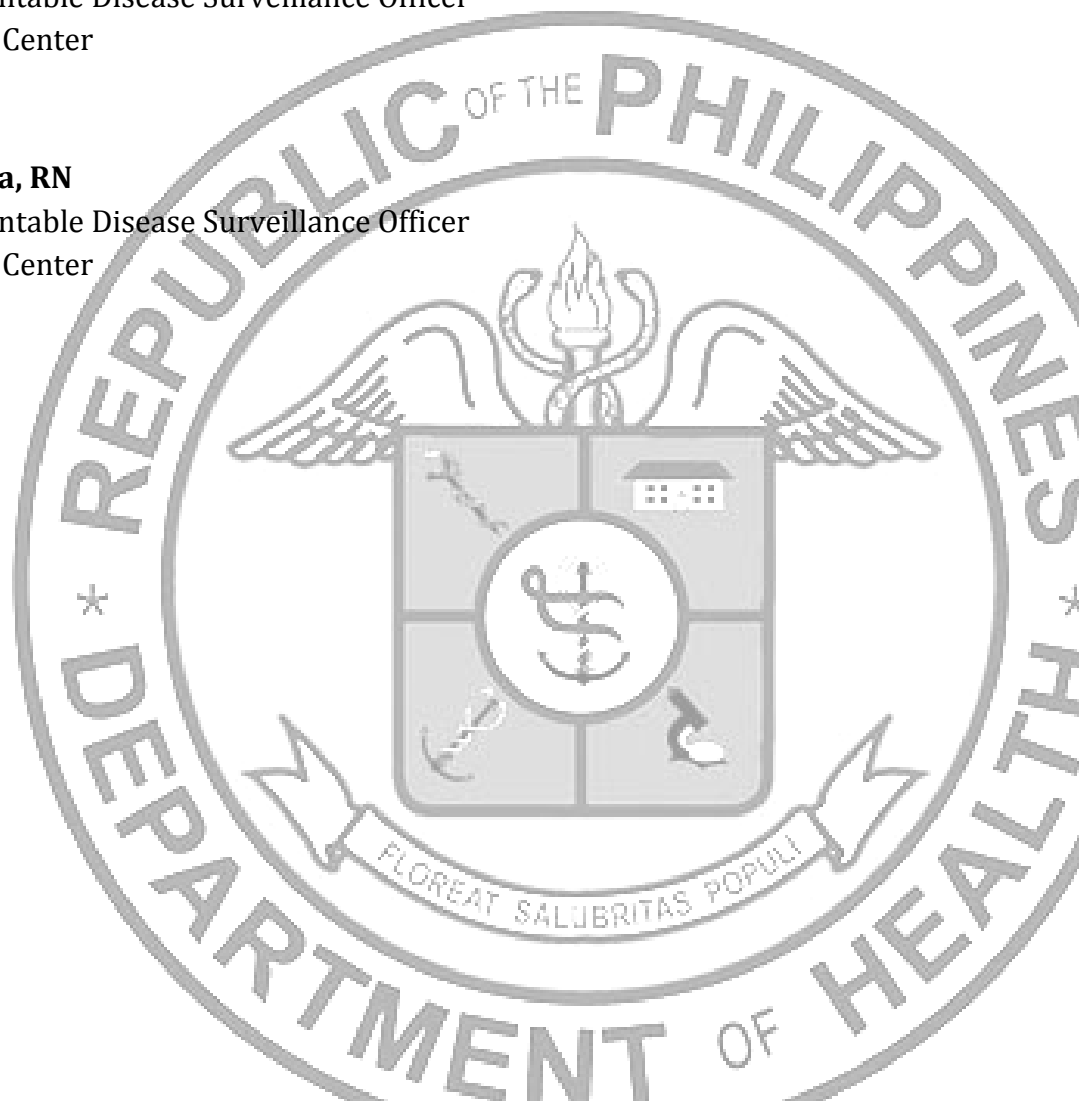
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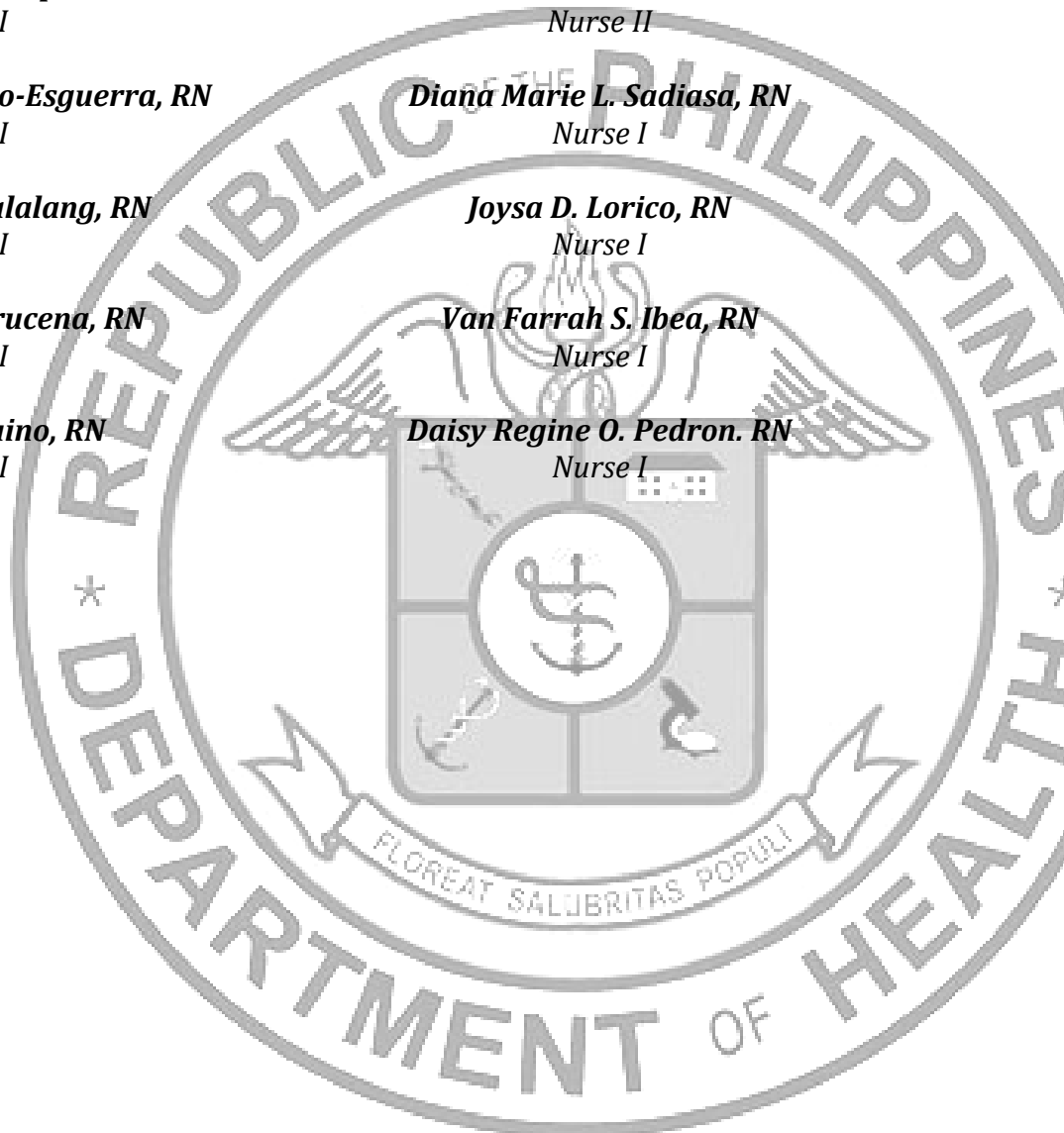
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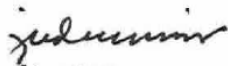
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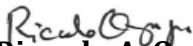
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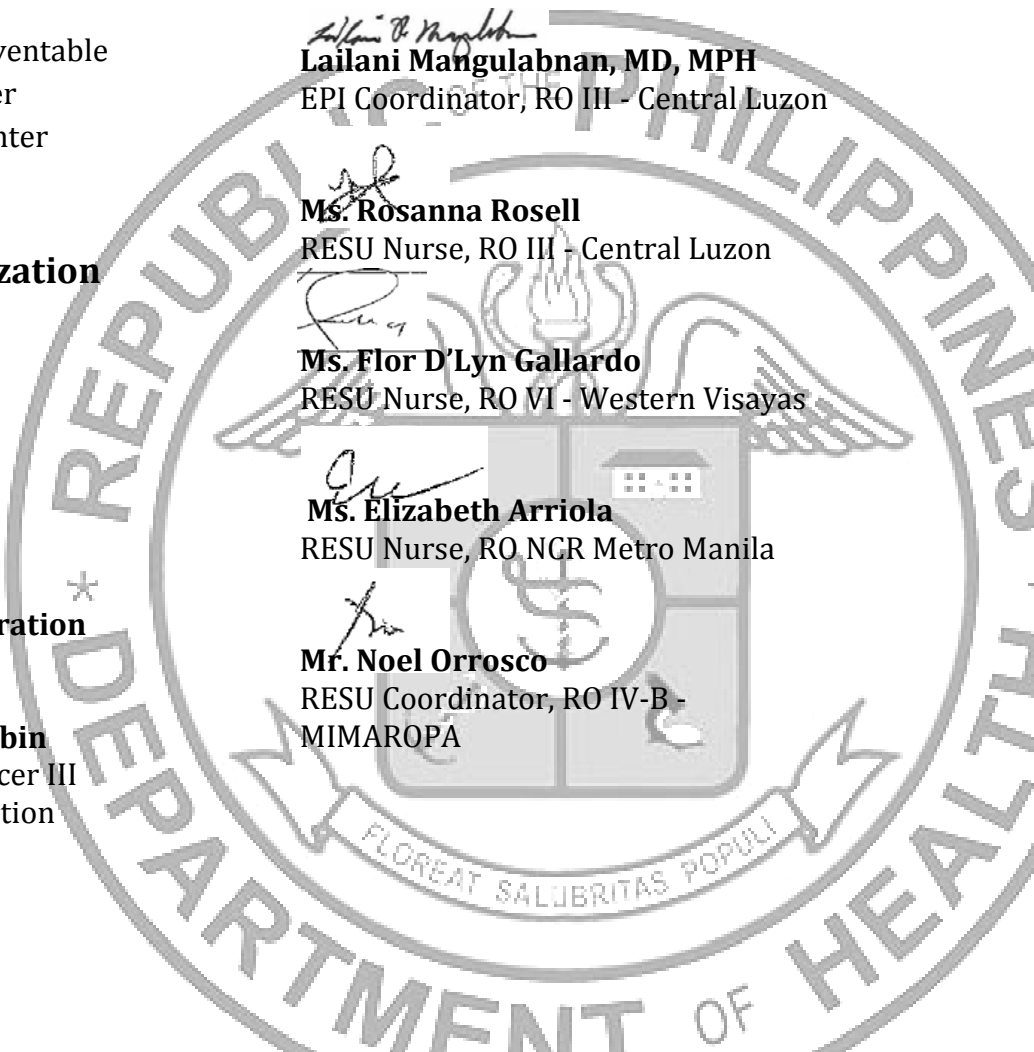
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ACRONYMS

AEFI	Adverse Events Following Immunization
BCG	Bacillus Calmette-Guerin
CIF	Case Investigation Form
CRF	Case Report Form
DRU	Disease Reporting Unit
DRA	Disease Reporting Advocate
DSC	Disease Surveillance Coordinator
DSO	Disease Surveillance Officer
DT	Diphtheria-tetanus vaccine
DTwP	Diphtheria-tetanus-pertussis (whole-cell)vaccine
EPI	Expanded Program on Immunization
ESU	Epidemiology and Surveillance Unit
FDA	Food and Drug Administration
HiB	Haemophilus influenza type B vaccine
MMR	Measles-mumps-rubella vaccine
MR	Measles-rubella vaccine
NEC	National Epidemiology Center
NRA	National Regulatory Authorities
OPV	Oral Poliovirus Vaccine
PIDSR	Philippine Integrated Disease Surveillance and Response
PV	Pharmacovigilance
PVu	Pharmacovigilance Unit
RESU	Regional Epidemiology and Surveillance Unit
TT	Tetanus Toxoid
VPD	Vaccine-Preventable Disease
VPDS	Vaccine-Preventable Disease Surveillance
WHO	World Health Organization

PURPOSE

This manual is guided by the policies issued by Department of Health to serve as guidelines for on adverse events following immunization (AEFI).

It provides guidelines for managers of the national immunization program at all levels, disease surveillance officers and others responsible for vaccine safety and quality on the following:

- strategies and systems for ensuring quality and safety of vaccines and immunization,
- the objectives of immunization safety/AEFIs surveillance
- new classification of AEFIs and understanding vaccine reactions, AEFI surveillance system: reporting, investigation and, causality assessment
- best use of surveillance data for response and follow up process
- communication strategy on immunization safety for the public and the media

INTRODUCTION

The goal of immunization is to protect the individual and the public from vaccine preventable diseases (VPD). Although modern vaccines are safe, no vaccine is entirely without risk; adverse reactions will occasionally occur following vaccination. Irrespective of the cause, when adverse events following immunization (AEFIs) occur, people become confused to the extent that they refuse further immunization of their children, making the children susceptible to VPDs which are more disabling and life-threatening.

Since the establishment of the Expanded Program on Immunization in 1976 in the Philippines, the immunization coverage of all individual vaccines has much improved. The immunization program ensures that all infants/children, adolescents and mothers have access to routine recommended infant/childhood/adolescent vaccines. However, public concern regarding vaccine safety has increased due to rumors and incorrect information readily available in the internet. And also, our National Immunization Program was disturbed in a few occasions in the past with unproven AEFIs. However, with successful response to those, the country's National Immunization Program has improved. For instance, the country's over-all immunization coverage for infant is about 85%. In the Philippines, all vaccines used are quality and safety assured.

As a result, more concerns on quality and safety of vaccine are highlighted and/or demanded by service providers and the public. To determine whether a vaccine is causally linked or a mere coincidence to an AEFI, detailed investigation and causality assessment are required.

In order to maintain and improve public confidence in national immunization program, all health-care providers should comprehensively be aware of all aspects of AEFI and remain prepared to respond to public concern any time. Timely response to public concerns about the safety of vaccines as well as prompt communication will protect the public and preserve the integrity of the immunization program.

The succeeding topics in this manual will easily guide us on how to conduct case detection, notification, investigation, and response; cornerstone of AEFI surveillance. Expected AEFI rates per vaccine are also included in this training manual to lead disease surveillance officers and program managers during the calculation of AEFI rates in determining vaccine safety.

This manual provide guidelines for health professionals from the public and private sectors who are providing vaccination nationwide; the Department of Health (DOH) concerned offices and attached agencies, epidemiology and surveillance units, private and government health facilities, local government units and the community involved in the surveillance and management of AEFIs to properly respond to these cases and maintain public confidence with the immunization program of the Department of Health.

Immunity

Immunity is the ability of the human body to tolerate the presence of material indigenous to the “body” (self) and to eliminate “foreign” (non-self) material. This discriminatory ability provides protection from infectious diseases, since most microbes are identified as foreign by the immune system. Immunity to a microbe is usually indicated by the presence of antibody to that organism. Immunity is generally very specific to a single organism or a group of closely-related organisms.

Two basic mechanisms for acquiring immunity:

A. Active immunity

Active immunity is stimulation of the immune system to produce antigen-specific humoral (antibody) and cellular immunity. Usually it lasts for many years, often a lifetime. One way to acquire active immunity is to survive infection with the disease-causing form of the organism. Upon re-exposure to the same antigen, these memory cells begin to replicate and produce antibody rapidly to re-establish protection.

Another way to produce active immunity is by **vaccination**. Vaccines interact with the immune system and often produce an immune response similar to that produced by the natural infection, but they do not subject the recipient to the disease and its potential complications.

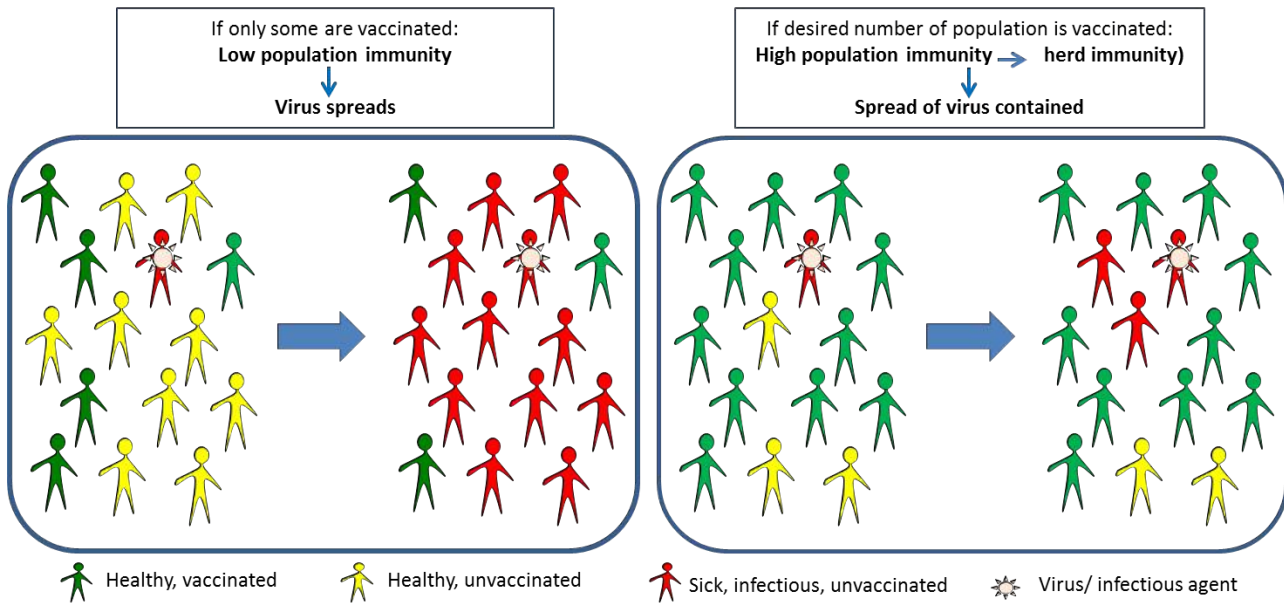
B. Passive Immunity

Passive immunity is the transfer of an antibody produced by one human or animal to another. It provides protection against some infections but is only temporary because the antibodies degrade over time. The most common form of passive immunity is the transfer of antibodies from the mother to the infant during conception, at birth and through breastfeeding. The antibodies received from the mother protect the infant from certain diseases for up to a year.

What is Herd Immunity?

Herd immunity is a type of immunity that occurs when the vaccination of a portion of the population (or ‘herd’) provides protection to unprotected individuals. This theory proposes that diseases passed from an individual to another makes it difficult to maintain a chain of infection when large numbers of population are immune. There are infections for which herd immunity is very important and those are diseases that transmitted directly from person to person (e.g. measles, rubella, varicella) and for which humans are the reservoir, or an important reservoir of infection (e.g. polio).

How herd immunity prevents virus spread?



Herd immunity threshold is the proportion of immune individuals in a population above which a disease may no longer persists. Its value varies with the virulence of the disease, the efficacy and overall coverage of the vaccines, and the contact parameter for the population.

Vaccine

A vaccine is a biological preparation that improves immunity to a particular vaccine preventable disease. It is intended to produce immunity to a disease by stimulating the production of antibodies. Vaccine typically contains an agent that resembles a disease causing microorganism or portion of it, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

Essential qualities of Vaccine:

A. Safety

Vaccines are generally very safe, but it is unlikely that a vaccine will be 100 percent free from any adverse reaction. It will produce protective immunity with only minimal side effects (such as redness and soreness at the vaccination site) for the majority of those who receive it. Discomfort caused by side effects may be acceptable depending upon the severity of the disease the vaccine is intended to prevent.

B. Immunogenicity

It must cause a strong and measurable immune response. Vaccines usually contain antigens, bits of material, sometimes from the disease-causing microbe itself that can stimulate the immune system to respond and fight off a potential infection. When a vaccine is immunogenic, it primes the recipient's immune system to recognize the disease-causing microbe and launch a counter-attack before an illness occurs. In addition, the vaccine must induce the right type of immunity. When microbes invade, they cause disease in different ways, and different parts of the immune system respond to fight them. Vaccines must stimulate the specific parts of the immune system that protect against a particular kind of organism.

C. Potency

The potency of a vaccine must remain at a high level for the vaccine to evoke an immune response. Maintaining cold chain is important to ensure the vaccine potency and therefore proper cold chain must be maintained from the time the vaccine is manufactured until the time it is administered. Storing vaccines in recommended storage temperature ensures that vaccines remain potent and shall provide the desired immune response.

Table 1: Types of Vaccines

VACCINE TYPE	DESCRIPTION	EXAMPLES
Live attenuated vaccine (LAV)	Derived from "wild" or disease-causing, virus or bacteria. These are attenuated or weakened, in a laboratory by repeated culturing. It has the ability to replicate (grow) in the vaccinated person and produce immunity but rarely cause the disease and usually it is milder. The immune response to a LAV is virtually identical to that produced by a natural infection.	<ul style="list-style-type: none">• Measles vaccine• Mumps vaccine• Rubella vaccine• Varicella vaccine• Yellow fever vaccine• Oral Poliovirus Vaccine• Influenza vaccine• Live JE vaccine Live-attenuated bacterial vaccines: <ul style="list-style-type: none">• BCG and oral typhoid vaccines
Inactivated (Killed) Vaccine	Produced by growing viruses or bacteria in culture media and then inactivating them with heat or chemicals (usually formaldehyde). Generally safer than LAV, with no risk of inducing the disease. Inactivated vaccines always require multiple doses because primary dose does not produce protective immunity but rather, only "primes" the immune system. Antibody titres against inactivated antigens diminish with time. Therefore, it may require periodic supplemental doses to increase, or "boost" antibody titres.	<ul style="list-style-type: none">• Influenza vaccine• IPV• Hepatitis A vaccine• Pertussis vaccine

Subunit Vaccines	Whole organism that is grown in culture media and further treated to purify so that only the essential components are included in the vaccine. Subunit vaccines are categorized in three groups: protein-based, polysaccharide and conjugate vaccines.	<ul style="list-style-type: none"> • Protein-based [Hepatitis B, acellular pertussis (aP)) vaccines • Polysaccharide vaccines (Meningococcal and pneumococcal polysaccharide vaccines) • Conjugated Vaccines (HiB, PCV-7, PCV-10, PCV-13 vaccines) •
Toxoid Vaccines	Produced by purifying the toxin and altering it chemically. The toxoid is still capable of inducing a specific immune response protective against the effects of the toxin	<ul style="list-style-type: none"> • Diphtheria toxoid • Tetanus toxoid

Source: Immunization Safety Surveillance, 3rd Edition, WHO Western Pacific Region

Other Components of Vaccines (Excipients)

Vaccines are made with a variety of ingredients including adjuvants, antibiotic, preservatives, and stabilizers. Knowing precisely what is in each vaccine can be helpful when investigating adverse events following vaccination and for choosing alternative products for persons who have allergies or have had an adverse event known or suspected to be related to a vaccine component.

Table 2: Components of Vaccines

COMPONENTS	DESCRIPTION	EXAMPLE
Adjuvants	A substance added to a vaccine to enhance the immune response by degree and/or duration, making it possible to reduce the amount of immunogen per dose or the total number of doses needed to achieve immunity. Adjuvants have been shown to be safe over seven decades of use. Rarely, they may cause injection site reactions, including subcutaneous nodules, sterile abscess, granulomatous inflammation or contact hypersensitivity.	The commonly used adjuvants are aluminum salts (aluminum hydroxide, aluminum phosphate or potassium aluminum sulfate). Oil-in water emulsions (AS03 and AS04) have been used as adjuvants in some vaccines developed in recent years.

<i>Antibiotics</i>	Antibiotics are used during the manufacturing phase to prevent bacterial contamination of the tissue culture cells in which the viruses are grown.	MMR vaccine and IPV each contain less than 25 micrograms of neomycin per dose (less than 0.000025 g). Persons who are known to be allergic to neomycin should be closely observed after vaccination so that any allergic reaction can be treated at once. Other antibiotics being used are streptomycin, polymyxin B, chlortetracycline and amphotericin B
<i>Preservatives</i>	Chemicals added to killed or subunit vaccines in order to inactivate viruses, detoxify bacterial toxins and to prevent serious secondary infections as a result of bacterial or fungal contamination.	Phenol derivatives, Thimerosal
<i>Stabilizers</i>	Stabilizers are used to help the vaccine maintain its effectiveness during storage. To confirm product quality (antigenicity) or stability, compounds may be added to vaccines to address problems with acidity, alkalinity (pH), stability and temperature. Vaccine stability is essential, particularly if the cold chain is unreliable. Instability can cause decreased infectivity of LAVs and loss of vaccine antigenicity.	MgCl ₂ , MgSO ₄ , lactose-sorbitol and sorbitol-gelatine.

Vaccine Contraindication and Precaution

A contraindication to vaccination is a rare condition in a recipient that increases the risk for a serious adverse reaction. Ignoring contraindications can lead to avoidable vaccine reactions. One of the worst and most serious vaccine reactions is anaphylaxis. There are two types of contra indications: absolute or relative (temporary). Most contraindications are relative or temporary, and the vaccination can be administered later. The only absolute

contraindication applicable to any vaccines is a history of a severe allergic reaction (Anaphylaxis) after a prior dose of given vaccine or to a vaccine constituent.

Precautions are not contraindications, but are events or conditions to be considered in determining if the benefits of the vaccine outweigh the risks (for example, if the recipient is an immunocompromised person or pregnant woman). There is no evidence of risk to the foetus from vaccinating pregnant women with inactivated vaccines or toxoids and for LAV, it's a theoretical risk to the foetus. Precautions stated in product labeling can sometimes be inappropriately used as contraindications, resulting in missed opportunities to vaccinate.

The safety of vaccines in immunocompromised persons is determined by the type of immunodeficiency and degree of immunosuppression. There is potential for serious illness and death if immunocompromised people are under-immunized; however, inappropriate use of LAV can cause serious adverse events in some immunocompromised people.

An Adverse Event Following Immunization is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease. Although people often think that a medical incident after an immunization was caused by vaccines, many such incidents are coincidental. This statement is supported by data from the Philippine AEFI surveillance database that has been in place since 2007.

AEFIs were previously classified into five categories: vaccine reaction, program error (programmatic error), coincidental events, injection reaction and unknown. In 2012, the Council for International Organizations of Medical Sciences (CIOMS) and WHO revised the existing categorization into a more cause-specific categorization of AEFIs. (See Table 3)

Table 3: Cause-specific categorization of adverse events following immunization

CAUSE –SPECIFIC CATEGORY OF AEFI	DEFINITION
Vaccine product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
Vaccine quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.
Immunization error-related reaction	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization.
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety

Source: Immunization Safety Surveillance, 3rd Edition, WHO Western Pacific Region

Note: “**Immunization**” as used in these definitions means the usage of a vaccine for the purpose of immunizing individuals. “Usage” includes all processes that occur after a vaccine product has left the manufacturing/ packaging site, i.e. handling, prescribing and administration of the vaccine.

The comprehensive explanations of cause-specific categorization of AEFIs are the following:



VACCINE REACTIONS

The new cause-specific categorization is important for decision making on a vaccine product, as it clearly differentiates the two types of possible vaccine reactions;

- a. **Vaccine product-related reaction-** it is caused or precipitated by a vaccine that is due to one or more inherent properties of the vaccine product.
- b. **Vaccine quality defect-related reaction-** it is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine products. All vaccine manufacturers should strictly follow the standards set by the National Regulatory Authorities (NRA) under the Philippine Food and Drug Administration (FDA) to avoid or minimize any reactions.

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.

➤ Common, minor vaccine reactions

The purpose of a vaccine is to induce immunity by causing the recipient's immune system to react to the vaccine. Local reaction, fever and systemic symptoms can result as part of the immune response. In addition, some of the vaccine's components (e.g. aluminium adjuvant, stabilizers or preservatives) can lead to reactions. A quality and safe vaccine reduces these reactions to a minimum while producing the best possible immunity. The proportion of reaction occurrences are likely to be observed with the most commonly used vaccines. (See Table 4)

- **Local reactions** include pain, swelling and/or redness at the injection site and can be expected in about 10% of vaccinees, except for those injected with DTwP, or tetanus boosters, where up to 50% can experience local reactions. . BCG causes a specific local reaction that starts as a papule (lump) two or more weeks after immunization that then becomes ulcerated and heals after several months, leaving a scar. Keloid (thickened scar tissue) from the BCG lesion is more common among Asian and African populations.
- **Systemic reactions** include fever and occur in approximately 10% or more of vaccinees, except for DTP where it is again about half. Other common systemic reactions (e.g., irritability, malaise, 'off-colour', loss of appetite) can also occur after DTP. For live attenuated vaccines such as measles/MMR and OPV the systemic reactions arise from vaccine virus infection. Measles vaccine causes fever, rash and/or conjunctivitis, and affects 5-15% of vaccinees. It is very mild compared to 'wild' measles, but for severely immunocompromised individuals, it can be severe, even fatal. Vaccine reactions for mumps (parotitis; swollen parotid gland) and rubella (joint pains and swollen lymph nodes) affect less than 1% of children. Rubella

vaccine causes symptoms more often in adults, with up to 25% suffering from joint pains. Systemic reactions from OPV affect less than 1% of vaccinees with diarrhea, headache and/or muscle pain.

It is important to note that these observed vaccine reaction rates are expected as vaccine reactions or response to vaccine antigen. Any significant increase in the observed vaccine reaction rates for any vaccine requires comprehensive investigation to exclude possible adverse reaction to the given vaccine.

Table 4: Frequency of Vaccine Adverse Reaction (VAR)

Vaccine	Vaccine Adverse Reaction (VAR)	VAR frequency rate or %	Frequency category
BCG Vaccine	▪ Injection site reaction [Papule, mild ulceration or scar]	Almost all vaccinees	Very common
	▪ Suppurative lymphadenitis	1 per 10 ³ - 10 ⁴	Uncommon to Rare
	▪ BCG osteitis	1 per 3,333 - 10 ⁶	Uncommon to Very rare
	▪ Disseminated BCG disease or systemic BCG-itis	1 per 230,000 - 640,000	Very rare
	▪ Immunine Reconstitution Inflammatory Syndrome (IRIS)	1 per 640,000	Very rare
Whole cell wP vaccine	▪ Fever 37.8°C -39°C	12.4% - 44.5%	Very common
	▪ Injection site Redness	16.4% - 56.3%	Very common
	▪ Swelling	22.4% -38.5%	Very Common
	▪ Pain (Severe-Moderate)	14.3% - 25.6%	Very common
	▪ Fussiness (Severe-Moderate)	12.4% 29.1%	Very common
	▪ Drowsiness	62%	Very Common
	▪ Anorexia	35%	Very common
	▪ Vomiting	13.7%	Very common
	▪ Persistent screaming	3.5%	Common
	▪ HHE	57-250 per100,000	Uncommon to Rare
	▪ Seizures	6 per 100,000	Very rare
	▪ Encephalopathy	0-5.3 per 10 ⁶	Very rare
	▪ Anaphylaxis	1.3 per 10 ⁶	Very rare
Acellular aP vaccine	▪ Fever 37.8°C -39°C	2.8% - 20.8%	Common to Very common
	▪ Injection site redness	3.3% - 31.4%	Common to Very common
	▪ Injection site	4.2% - 20.1%	Common to Very common

	<ul style="list-style-type: none"> swelling ▪ Pain (Severe-Moderate) ▪ Fussiness (Severe – Moderate) ▪ Drowsiness ▪ Anorexia ▪ Vomiting ▪ Persistent screaming ▪ HHE ▪ Seizures 	0.4%-6.5% 4.7%-12.4% 42.7% 21.7% 12.6% 0-0.2% 14-62 per100,000 0.5 per 100,000	Uncommon to Common Common to Very common Very Common Very Common Very Common Uncommon Rare Very rare
Oral Polio virus Vaccine (OPV)	<ul style="list-style-type: none"> ▪ VAPP <ul style="list-style-type: none"> - Recipient VAPP - Total VAPP 	1 per 6.4 million doses 1 per 2.9 million doses [Risk is higher following the first dose (1 in 750 000), and for adults and immune-compromised]	Very rare Very rare
Inactivated Polio virus Vaccine (IPV)	<ul style="list-style-type: none"> ▪ Injection site erythema ▪ Injection site induration ▪ Injection site tenderness 	0.5%-1.5% 3% - 11% 14%- 29%	Uncommon to Common Common to Very common Very Common
Hepatitis B (HepB) Vaccine	<ul style="list-style-type: none"> ▪ Fever > 37.7°C ▪ Headache ▪ Injection site pain ▪ Injection site redness ▪ Injection site swelling ▪ Anaphylaxis 	1%-6% 3% 3%-29% 3% 3% 1.1 per 10 ⁶	Common Common Common to Very common Common Common Very rare
Hib Vaccine	<ul style="list-style-type: none"> ▪ Fever ▪ Injection site reaction 	2% 10%	Common Very common
Tetanus vaccine	<ul style="list-style-type: none"> ▪ Brachial neuritis ▪ Anaphylaxis 	5-10 per 10 ⁶ 1-6 per 10 ⁶	Very rare Very rare
Measles Vaccine	<ul style="list-style-type: none"> ▪ Fever ▪ Rash ▪ Injection site reaction ▪ Febrile seizures 	5% - 10% 5% 17%-30% 1 in 2000-3000	Common to Very Common Common Very common Rare

	<ul style="list-style-type: none"> ▪ Encephalomyelitis ▪ Thrombocytopenia ▪ Anaphylaxis 	1 per 10 ⁶ 1 per 30,000 1 -3.5 per 10 ⁶	Very rare Very rare Very rare
Rubella Vaccine	<ul style="list-style-type: none"> ▪ Fever ▪ Injection site reaction ▪ Acute Arthralgia (adults) ▪ Acute Arthritis (Adults) 	2% 17%-30% 25% 10%	Common Very common Very common Very common
Mumps Vaccine	<ul style="list-style-type: none"> • Injection site reaction • Parotid swelling • Aseptic meningitis 		Very common Common Very common
Pneumococcal			
Unconjugated vaccine (PPSV)	<ul style="list-style-type: none"> ▪ Fever > 39°C ▪ Injection site reaction 	<1% 50%	Uncommon Very common
Conjugated vaccine (PCV)	<ul style="list-style-type: none"> ▪ Fever > 39°C ▪ Injection site reaction 	<1% 10%	Uncommon Very common
Japanese Encephalitis			
Inactivated Mouse brain vaccine	<ul style="list-style-type: none"> ▪ Injection site reaction ▪ Systemic reactions [Headache, malaise, myalgia, low-grade fever, nausea, vomiting, abdominal pain, rash, chills and dizziness] ▪ Allergic reaction ▪ Neurological Complications (Convulsions, Encephalitis, Encephalopathy, Peripheral neuropathy, Transverse myelitis) ▪ Anaphylaxis 	20% 5% - 30% 17 per 10 ⁶ 1 -2.3 per 10 ⁶ 1 - 2 per 10 ⁶	Very common Common to Very Common Very rare Very rare Very rare

Inactivated Cell culture Vaccine	<ul style="list-style-type: none"> ▪ Injection site reaction ▪ Headache, dizziness ▪ Fever > 38°C ▪ Urticarial rash 	4% <1% 12% 6.6 per 10 ⁵	Common Uncommon Very common Very rare
Live attenuated SA-14-14-2 vaccine	<ul style="list-style-type: none"> ▪ High Fever ▪ Skin rash 	5 – 7 per 10 ² -10 ⁴ 1 per 10 ⁴	Uncommon to Common Uncommon
Human Papiloma Vaccine (HPV) - Bivalent	<ul style="list-style-type: none"> ▪ Fever ▪ Headache ▪ Injection site pain ▪ Redness ▪ Swelling ▪ Rash ▪ Arthralgia ▪ Myalgia ▪ Fatigue ▪ Gastrointestinal disorders 	3% 30% 78% 30% 26% 1% 10% 28% 33% 13%	Common Very Common Very Common Very common Very Common Uncommon Very common Very common Very common Very common
Human Papiloma Vaccine (HPV) Quadrivalent	<ul style="list-style-type: none"> ▪ Fever ▪ Headache ▪ Injection site pain ▪ Redness ▪ Swelling ▪ Urticaria ▪ Arthralgia ▪ Myalgia ▪ Gastrointestinal disorders ▪ Anaphylaxis 	13% 26% 5.7% 5.7% 5.7% 3% 1% 2% 17% 1.7-2.6 per 10 ⁶	Very common Very Common Common Common Common Common Common Common Very common Very rare
Rotavirus Vaccine	<ul style="list-style-type: none"> ▪ Intussusception 	1-2 per 100,000 [For first dose in some populations. No apparent increase identified with subsequent doses]	Very rare
Typhoid Vaccine Ty21a	<ul style="list-style-type: none"> ▪ Fever ▪ Vomiting ▪ Diarrhoea 	0.3 % - 4.8% 0.5% - 2.3% 1.2% - 3.9%	Uncommon to Common Uncommon to Common Common
ViCPS	<ul style="list-style-type: none"> ▪ Low grade fever < 	Up to 2%	Common

Vi-TT	39°C		
	<ul style="list-style-type: none"> Local erythema Soreness Swelling 	3% - 21% 8% - 33% 2% - 17%	Common to Very common Common to Very common Common to Very Common
Varicella vaccine	<ul style="list-style-type: none"> Injection site pain Fever 	Data not available Data not available	
	<ul style="list-style-type: none"> Febrile seizures 	4 – 9 per 10,000 [the risk depends on age, with much lower risk in infants age of less than four months].	Rare
Yellow Fever vaccine	<ul style="list-style-type: none"> Fever > 39°C Injection site reaction Skin rash (local/generalized) 	15%-27% 7%-30% 3%-5%	Very Common Common to Very Common Common
	<ul style="list-style-type: none"> Vaccine-associated viscerotropic disease 	1 per 10 ⁶	Very rare

Source: WHO Fact sheets www.who.int/vaccine_safety/initiative/tools/vaccinfosheets
 Immunization Safety Surveillance, 3rd Edition, WHO Western Pacific Region

**Although encephalopathy is included as a rare possible reaction to measles, JE or DTP vaccines, it is not certain that these vaccines in fact cause encephalopathy. Hence, further scientific evaluation is necessary.*

➤ Rare, more serious vaccine reactions

An event that is causing a potential risk to the health/life of recipient leading to hospitalization, disability/incapacity, congenital abnormalities/birth defects or death defined as “serious” vaccine reaction. ‘Serious’ and ‘severe’ are often used as interchangeable terms but they are not. Severe is used to describe the intensity of a specific event (as in mild, moderate or severe). The event itself, however, may be of relatively minor medical significance. (e.g. Fever is a common relatively minor medical event, but according to its severity it can be graded as mild fever or moderate fever.) Anaphylaxis is always a serious event and life threatening. Most of the rare and more serious vaccine reactions (e.g. seizures, thrombocytopenia, hypotonic hyporesponsive episodes, persistent inconsolable screaming) do not lead to long-term problems. Anaphylaxis, while potentially fatal, is treatable without leaving any long-term effects. Although encephalopathy is included as a rare reaction to measles or DTP vaccine, it is not certain that these vaccines in fact cause encephalopathy.

Severe reactions (Not regulatory term)	
<ul style="list-style-type: none"> ✖ Can be disabling and, rarely, life threatening. ✖ Must be reported. ✖ Most do not lead to long-term problems. ✖ Severe reactions include serious reactions but also include other severe reactions. 	<div> Serious reactions (Regulatory term) <p>Any untoward medical occurrence that at any dose:</p> <ul style="list-style-type: none"> ✖ Results in death. ✖ Requires inpatient hospitalization. ✖ Results in persistent or significant disability. ✖ Is life-threatening. </div>

Source: WHO (<http://www.vaccine-safety-training.org/vaccine-reactions.html>)



Key points

- The information on observed vaccine reaction rates type of reactions for a specific antigen or vaccine used in immunization program can be used to identify if an event is related to the immunization or not.
- The antigen (vaccine) specific information sheets on observed rates of Vaccine Reactions developed by WHO are a useful tool to the managers of immunization program for decision making

Source: (http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/index.html)



Prevention and management of vaccine reactions

Vaccines are very rarely contraindicated. However, it is important to check for contraindications to avoid serious reactions.

- Vaccines are very rarely contraindicated. However, it is important to check for contraindications to avoid serious reactions. For example, vaccines are contraindicated if there is a possibility of serious allergy (Anaphylaxis) to a vaccine or its components in previous vaccination.
- **Live vaccines should not be given to immune-deficient children.**

- Advice parents on how to manage common reactions and instruct them to return to the nearest health facility if there are more serious symptoms. This will help to reassure parents about immunization and prepare them for these common reactions. (See Annex D)
- A feverish child can be cooled with a tepid sponge bath, and by wearing cool clothing. Extra fluids need to be given to feverish children. For a local reaction, a clean cold cloth applied to the site may ease the pain. Paracetamol, at a dose of up to 15mg/kg every six to eight 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 advise not to overuse Paracetamol as overdosing may harm the vaccinee.
- Practicing local remedies for any serious vaccine reaction can risk the health and life of vaccinee and are strongly discouraged. Early medical care by a qualified clinician will minimize any unwanted outcome and ensure early recovery and also save life.
- Adrenalin and other basic emergency items should be available at any health facility to provide initial emergency care. All immunization providers should develop skills and competence on managing anaphylaxis at immunization clinic/facility setting. (See Annex E)



IMMUNIZATION ERROR-RELATED REACTIONS

This AEFI type was previously categorized as Program-related errors, which is an event caused by errors in vaccine preparation, handling, storage and administration. Immunization error - related reactions are preventable and they derail the benefit of the immunization program (See Table 5). The identification and correction of these errors in a timely manner are of great importance. This type of AEFI may also lead to a cluster of events associated with immunization. These clusters are usually associated with a particular provider, or health facility, or even a single vial of vaccine that has been inappropriately prepared or contaminated. Immunization error-related reactions can also affect many vials (e.g. by freezing vaccine during transport leading to an increase in local reactions).

In the past, the most common immunization error was infection (including blood borne virus) as a result of non-sterile injection. The infection could manifest as a local reaction (e.g. suppuration, abscess), systemic effect (e.g. sepsis or toxic shock syndrome), or blood borne virus infection (e.g. HIV, hepatitis B or hepatitis C). The introduction of auto disabled (AD) syringes has reduced the occurrence of infection. Still, infection can occur in cases of mass vaccination or disaster situations particularly if there is any shortage or problems with logistics and supplies. This can be avoided by proper planning and preparedness of programme managers.

The symptoms arising from an immunization error may help identify the likely cause. For example, children immunized with contaminated vaccine (usually the bacterium *Staphylococcus aureus*) become sick within a few hours; local tenderness and tissue infiltration, vomiting, diarrhea, cyanosis and high temperature are the most frequent symptoms. Bacteriological examination of the vial, if still available, can confirm the source of the infection.

Sterile abscesses are rare (~1 per 100 000 doses) local reactions from aluminium containing vaccines, especially DTP. Inadequate shaking of the vaccine before use, superficial injection, and use of frozen vaccine increases the risk of sterile abscess and other local reactions. Contamination of vaccine or injection equipment can also lead to a **bacterial abscess**. For BCG vaccine, injection abscess can arise from improper injection (subcutaneous rather than intradermal injection).

Table 5: Immunization error-related reactions

IMMUNIZATION ERROR		RELATED REACTION
Error in vaccine handling:	Exposure to excess heat or cold as a result of inappropriate transport, storage or handling of the vaccine (and its diluents where applicable)	Systemic or local reactions due to changes in the physical nature of the vaccine such as agglutination of aluminium-based excipients in freeze-sensitive vaccines.
	Use of a product after the expiry date	Failure to vaccinate as a result of loss of potency or non-viability of an attenuated product.
Error in vaccine prescribing or non-adherence to recommendations for use	Failure to adhere to a contraindication	Anaphylaxis, Disseminated infection with LAV
	Failure to adhere to vaccine indications or prescription (dose or schedule).	Systemic and/or local reactions, Neurologic, muscular, vascular or bony injury due to incorrect injection site, equipment or technique
Error in administration	Use of an incorrect diluent or injection of a product other than the intended vaccine	Failure to vaccinate due to incorrect diluent, reaction due to the inherent properties of whatever was administered other than the intended vaccine or diluent.
	Incorrect sterile technique or inappropriate procedure with a multidose vial	Infection at the site of injection/ beyond the site of injection,

Immunization team should be clearly aware of absolute and temporary (relative) contraindications. Any uncertainty should be consulted with a higher level program manager, pediatrician or physician. However, it is equally important not to overreact to concerns of false contraindications which may lead to missed opportunity of vaccination, reduced coverage and thereby, increase the risk of disease of both individuals and the

community.

There should also be a clear understanding between contraindications and precautions. Precautions are not contraindications, but decision on vaccination requires a case-based assessment. The use of vaccines in pregnancy is limited or mostly not recommended. The vaccines which are recommended in pregnancy would benefit and protect both mother and the newborn. However, the limited use of vaccine in pregnancy is largely due to the potential risk and harm to the fetus. The risk is mostly theoretical and limited to live attenuated vaccines which have demonstrated evidence of potential risk and harm, particularly in animal models. Vaccine manufacturers include pregnancy as a contraindication not due to proven evidence, but as a precautionary measure against litigation.

Learning activity

In 2012, a 9 month old female died due to septic shock following immunization with Measles Vaccine during the nationwide mass immunization campaign. Patient was sent to a hospital and upon assessment, the patient had poor reflex, pale in appearance, had swelling of the left thigh and with lock jaw. The baby was diagnosed with Sepsis. Investigation revealed that the vaccinator used pre-filled syringes to vaccinate all her target population.

➤ **Cause:**

Immunization error related reaction: Incorrect sterile immunization procedures resulting in infection at the site of injection/beyond the site of injection.

To avoid immunization error:

- Maintaining cold chain at all levels is important and necessary
- Vaccines must only be reconstituted with specific diluent supplied by the manufacturer.
- Reconstituted vaccine should not be used for more than six hours after reconstitution and must be discarded at the end of each immunization session and never retained.
- No other drugs or substances should be stored in the refrigerator of the health facility.
- Health workers must be adequately trained and closely supervised to ensure that proper procedures are being followed. Regular updates and refresher course on safe immunization practices should be provided by the EPI.
- Cautious epidemiological investigation of an AEFI is needed to pinpoint the cause and to correct immunization practices.
- Give adequate attention on contraindications.



IMMUNIZATION ANXIETY-RELATED REACTIONS

Immunization Anxiety-Related Reactions, previously referred to as Injection Reactions, are reactions NOT related to the content of the vaccine, but to the injection. Individuals and groups can react on the sight of the syringe or in anticipation to and as a result of an injection of any kind. Clear explanations about immunization from a well-trained vaccinator will decrease the level of anxiety about the injections, and thus reduce the likelihood of an occurrence.

- Younger children tend to react in a different way, with vomiting a common anxiety symptom. Breath-holding may occur, which can end in a brief period of unconsciousness, during which breathing resumes. They may also scream to prevent the injection or run away.
- Another example is fainting which is relatively common, but usually only affects children aged over five years. Fainting does not require any management beyond placing the patient in a recumbent position. The likelihood of faints can be anticipated when immunizing older children, and reduced by minimizing stress in those awaiting injection, through short waiting times, comfortable room temperatures, preparation of vaccine out of recipient's view, and privacy during the procedure.
- Hyperventilation as a result of anxiety about the immunization leads to specific symptoms (light-headedness, dizziness, tingling around the mouth and in the hands). This is also common in mass vaccination campaigns.
- An anxiety reaction to injection can include convulsions in some case. These children do not need to be investigated but should be reassured.

It is important to note that fainting (syncope) can be misdiagnosed as anaphylaxis (see Annex E). Very careful observation and clinical judgement is necessary. However by mistake, a health care worker may administer a single dose of Adrenaline (intramuscularly) to a vaccinee with syncope; this will not cause any harm. To avoid such unnecessary medical emergency interventions, continued training and awareness for health staff is necessary.

Learning activity

In 2004, a mass school based measles-rubella immunization campaign was conducted among 12-19 years, in country D. On very first day, 44 cases school children were hospitalized with either hyperventilation or/and vomiting. Investigation concluded these events were due anxiety reactions, and except 2 cases all other were discharged from hospital on same day.

➤ Cause

Immunization *anxiety related reactions*



COINCIDENTAL

Vaccines are normally scheduled early in life, when infections and other illnesses are common including manifestations of an underlying congenital or neurological condition. It is therefore possible for many events, including deaths, to be falsely attributed to vaccine through chance association. An event may occur coincidentally with immunization and at times may be falsely attributed as a result from 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. For example, Sudden Infant Death Syndrome (SIDS or cot death) incidence peaks around the age of early childhood immunization. However, available evidences have shown that the association of SIDS and immunization is coincidental and not causal.

Coincidental adverse events are predictable. The number of events to be expected depends upon the size of the population and the incidence of disease or death in the community. Knowledge of these background rates of disease and deaths, particularly *age specific disease incidence rates* allows estimation of the expected numbers of coincidental events. For instance, children aged 1-15 years are immunized in a mass campaign and the background *age specific mortality rate* for this population is 3 per 1000 per year. Then, 250 deaths can be expected in the month after immunization and 8 deaths on the day of the immunization, simply by coincidence. These deaths will be temporally associated with, even though entirely unrelated to, immunization.

Learning activity

In 2012, a 2-month old male was vaccinated with 1st dose of DPT on left thigh, 2nd dose of Hepa B on the right thigh, and 1st dose of OPV. Paracetamol 0.3ml for fever and warm compression on the injection site was advised. In the afternoon, the child became febrile, and Paracetamol 0.3ml was given. Warm compress was also applied on the injection site. The mother breastfed her infant during the night. The following day, the father discovered that his child was “paper white in color” and was not breathing. Post mortem findings do not indicate any pathology or illness. Final diagnosis indicated Sudden Infant Death Syndrome (SIDS) and upon investigation on the vaccinator and cold chain, no deviation from the standard protocol for immunization and storage were found to have caused an adverse reaction from immunization. In addition, no other case/s of AEFIs was reported in the same area wherein same lot/batch of vaccines was distributed.

➤ Cause

Coincidental Event

A similar calculation is shown in Table 6 for infant (aged under one-year) deaths in selected Western Pacific countries for the number of deaths temporally associated with routine DTP immunization. There will be many coincidental deaths in the day, week and month after immunization, which are only temporally related to immunization. The actual

number of coincidental deaths depends on the population size, infant mortality rate, the number of immunization episodes and the immunization coverage.

When comparing expected versus actual events, it is possible to do statistical analysis to ensure that differences are not simply the result of chance. Note that the expected number of death calculations presented here may be inflated as it assumes that children who are near to death will still be immunized.

Table 6: Estimated coincidental infants deaths temporally would be linked to immunization in the month, week and day after immunization of DPT/Pentavalent in selected countries in the Western Pacific Region

Country	Infant Mortality Rate per 1000 live births (IMR)	Number of births per year (N)	Estimated number of infant death in			Estimated number of DTP/ Pentavalent vaccine immunizations* in		
			a month	a week	a day	a month	a week	a day
Australia	4	307,000	102	24	3	68,799	15,877	2,262
Cambodia	36	317,000	951	219	31	68,757	15,867	2,261
China	13	16,364,000	17,728	4,091	583	3,634,035	838,624	119,475
Fiji	14	18,000	21	5	1	3,993	922	131
Japan	2	1,073,000	179	41	6	240,942	55,602	7,921
Philippines	20	2,358,000	3,930	907	129	519,939	119,986	17,094

Source: Immunization Safety Surveillance, 3rd Edition, WHO Western Pacific Region

Note: Assumes uniform distribution of deaths and children who are near to death will still be immunized.

Infant mortality and births from 2011 immunization summary, WHO/UNICEF (2013).

IMR= Infant mortality rate per 1000 live birth; IMR/1000

*Assumed here to be three doses with 90% coverage for each dose of DPT or Pentavalent vaccine

In general, coincidental events are clearly unrelated and may not require any investigation (e.g. pneumonia). However, certain serious events may be blamed on the vaccine by the parents or public or media 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 public concerns about immunization safety is important in maintaining confidence in the immunization program. Availability of information on background rates reported coincidental 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 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.

Surveillance is a process of systematic collection, consolidation, interpretation and dissemination of data on AEFI to be used for immunization program monitoring and evaluation, policy formulation, decision making, advocacy and health promotion, and planning for public health intervention.

AEFI surveillance exists at national and local level to ensure effective monitoring and prompt actions in response to AEFIs. This needs to be a collaborative venture between the National Epidemiology Center (NEC), National Center for Disease Prevention and Control (NCDPC) particularly the expanded program on immunization (EPI) and Food and Drug Administration (FDA) which is responsible for the safety of vaccines. The links with the aforementioned organization should be maintained at all time. It is also essential that the functionality of AEFI surveillance system at all level is preserved to achieve highest compliance and takes appropriate action in response to reported AEFI.

Specific objectives of the AEFI surveillance:

- To detect and timely identify problems with vaccines, which could be due to the inherent properties of vaccines
- To detect, correct and prevent immunization error-related reactions (previously classified as program errors)
- To estimate expected vaccine reaction rates (background rates) in the population (by country, region and global)
- To identify clustering or unusually high rates of AEFI even if they are considered as mild
- To ensure that coincidental events do not negatively affect the immunization program
- To ensure and facilitate causality assessment of coincidental, serious and unexpected/unusual AEFIs
- To identify signals of unknown vaccine reactions; generating new hypotheses about vaccine reactions that are specific to the given population
- To maintain the confidence of the community and health staff in the immunization program by appropriately and timely responding to their concerns about immunization safety
- To effectively communicate with parents, the community, media and other stake holders, the occurrence of AEFIs without jeopardizing the immunization program
- To collaborate and share information at WPR region and globally (through post marketing surveillance/PMS network), in order to generate new and additional information on vaccine safety

In the Philippines, the overall administration of the AEFI surveillance system for DOH was delegated to the National Epidemiology Center (NEC) of the Department of Health (DOH) with active linkage to FDA (National Regulatory Authority) and EPI.

Case Detection and Notification

Case detection is the most important first step in AEFI surveillance. The primary reporter who first reports an AEFI may be a field health worker, clinic or hospital staff, volunteer or parent or any other person who detect the AEFI.

All AEFI cases, including minor AEFIs such as local reactions, fever and self-limiting systemic symptoms should be reported to the next higher level on a weekly basis using the AEFI Case Report Form (Annex B). ***However, in cases of serious/cluster of AEFI cases, notification should be made to the epidemiology and surveillance unit of the next higher level and the National Epidemiology Center within 24-48 hours of case detection by the fastest means possible.*** Initial notification can be verbal using the telephone, text message, or via facsimile or email. This is to notify the next higher level that an in-depth case investigation is warranted. (see Annex A for AEFI Surveillance Flow)

It is intended that the case definition is broad so that the surveillance system for AEFI would be very sensitive to capture all AEFIs that are related or caused by the vaccine (Annex D; please see Case Definitions). All reported cases should provide with WHO recommended minimum core variables (Table 8). The Philippine AEFI Case Report Form is incorporated with these core variables.

To improve the detection capacity, a good knowledge in the primary reported of AEFIs, its types and purpose of AEFI surveillance is necessary.

Places and Persons Involved in Case Detection and Notification

Cases may be seen from Disease Reporting Units (DRU) such as private and government, hospitals and clinics, Municipal Health Offices [MHO], City Health Offices [CHO], Barangay Health Stations [BHS], laboratories, and in the community.

Detection of AEFI cases is everyone's responsibility. The Disease Reporting Advocates (DRA) and Disease Surveillance Coordinators (DSC) are the first to detect cases from the community, hospitals and clinics. Therefore, they should receive training in detecting cases of AEFI. In some instances, concerned individual and or parent was also encouraged to notify the vaccinator if there is untoward event happened to the vaccinee.

The detailed roles and responsibilities of the DRA and DSC are found in the Administrative Order on the Revised Guidelines on Surveillance and Response to AEFI.

Table 8: Core variables with minimum information required reporting in AEFI surveillance

ICH	Core variable
Identity	Date AEFI report first received at national level
	Country where this AEFI reported
	Location (address)
	Worldwide unique number
Case	Patient identifier
	Date of birth (or)
	Age at time of onset (or)
	Age group at onset
	Sex
	Medical History
Vaccine	Primary suspect vaccine name (generic)
	Other vaccines given just prior to AEFI
	Batch number
	Vaccine dose number for this particular vaccinee
Event	Date and time of vaccination
	Date and time of AEFI onset
	Adverse event
	Outcome of AEFI
Reporter	Name of first reporter of AEFI
	institution/location
	position/department
	e-mail Id
	Telephone
Other	Comments (if any) by national officer before the report is uploaded to Global Database

Reporting AEFIs during immunization campaigns

A campaign is an opportunity to strengthen or establish immunization safety surveillance. Proper planning to reduce immunization errors-related reaction, monitor and respond to AEFI can minimize adverse events and their effects during a campaign. Careful planning will limit the potential for negative publicity from an AEFI.

In an event of mass immunization or special immunization program, it is of utmost importance to ensure AEFI reporting for 2 reasons:

- Mass Immunization and special immunization program covers a large number of individuals in a particular target group in a specified given time period and therefore, excess number of adverse events may be reported within a short time period. Unless,

this is not properly investigated or analyzed, it can cause concern by the public and also may affect the immunization program

- During special immunization program, a new vaccine may have been introduced with no prior experience or with little information on adverse reactions. There is a possibility of detection of signals through strengthening surveillance during special immunization programs. (e.g. MR-SIA campaigns from 2011)

A specific AEFI case report form should be used to document all cases reported during mass immunization or special immunization program. This will be beneficial in tracking serious or clusters of minor AEFI cases in one particular area (see Annex B).

Barriers to reporting

Immunization service providers may not report AEFI for one or more of these reasons:

- **not considering** the event as related to immunization
- **lack of knowledge** about the reporting system and process
- **lethargy** - procrastination, lack of interest or time, inability to find the report form
- **fear** that the report will lead to personal consequences
- **guilt** about having caused harm and being responsible for the event
- **diffidence** about reporting an event when not confident about the diagnosis
- **shortage** of reporting forms

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.

Private sector reporting

All private sector and/or medical institutions handling immunization services and treating AEFI cases should report all AEFIs to Food and Drug Administration and Department of Health.

Reporting from private sector is encouraged for two reasons:

- a. Individuals seek medical care from the private sector, following vaccines received at public institutions.
- b. It is also important to monitor vaccines used in private sector and therefore reporting of all AEFIs is necessary.

To maintain the reporting of AEFI of all vaccines used in the country, it is encouraged that vaccines exclusively used in private sector are reported to the FDA and the vaccines given under the national immunization program (Expanded Program on Immunization) and other vaccines given by the DOH should be reported to the National Epidemiology Center of the Department of Health.

Zero Case Reporting

Zero case reporting refers to the reporting of “zero cases” using the AEFI Case Report Form when no cases have been detected by the reporting unit. This should be done on a monthly basis. However, zero reporting may not always mean that there are no cases in the area, but could also mean that there may be problems encountered in the surveillance system.

Possible reasons for consistently zero case reporting may include:

- Lack of attention on non-serious cases; assuming that non-serious are not reportable
- There are “missed” cases (cases that are self-managed or treated in private sectors)
- Lack of supervisions or absence of DSC, who is in-charge of AEFI surveillance

The ultimate goal of a case investigation is to find the cause of an AEFI or clustering of AEFIs and prevent the occurrence of the similar events in the future. If the cause is identified as immunization error, remedial action needs to be taken promptly. Even if the cause cannot be identified or the cause of the event was due to some other reason, the fact that staff had investigated the incident itself will increase public confidence towards immunizations.

The purpose of investigating AEFI cases are:

- To confirm the reported diagnosis or propose other possible diagnoses and clarify the outcome of the medical incident.
- To identify the details of specifications of the vaccine used to immunize the affected recipient. Most importantly, identify any vaccine related link to the given AEFI.
- To identify 'possible/likelihood' cause of the AEFI
- To examine the operational aspects of the program. Even if an event seems to be vaccine induced or coincidental, immunization errors may have increased its severity.
- To determine whether a reported event was a single incident or one of a cluster and if it is a cluster where the suspected immunizations were given and what vaccines were used.
- To determine whether unimmunized people are experiencing the same medical incidents.

Which reports should be investigated?

Not all AEFI reports will need investigation. Once the report has been received, an assessment should be done to determine whether or not an investigation is needed.

The reported AEFI must be investigated if it:

- Is a serious event of known or unknown causes; all hospitalizations
- Cluster of minor AEFI
- Events associated with newly introduced vaccine
- Suspected to be caused by immunization error
- Appears on the list of events defined for AEFI surveillance
- Is causing a significant parental or public concern
- All deaths suspected to be caused by the vaccine

Who should investigate?

The primary responsibility of investigating an AEFI lies on the City/Provincial level, depending on their capacities for AEFI case investigations. In instances when the LGU needs assistance, the Regional level shall provide technical assistance.

It is strongly recommended that AEFI investigations are conducted by a team composed of duly authorized representatives from the Epidemiology and Surveillance Unit (ESU), Regional Food and Drug Regulation Officer (FDRO) the EPI coordinator and Health Promotion Officer.

When to investigate?

Complete investigation and initial response activities shall be conducted within 48 hours upon reporting of a serious AEFI. The AEFI case investigation form (Annex C) shall be used in the investigation of cases. The completed CIF for serious AEFIs, other severe and unusual events occurring within 4 weeks after immunization and clusters of minor AEFIs shall be submitted within 48 hours of after completion of investigation to the RESU for initial causality assessment.

How to investigate?

It is important to investigate suspected AEFIs promptly and completely. An AEFI investigation follows the standard epidemiological investigation principles. In addition, investigation of the vaccine(s), immunization techniques and procedures, and service in action needs to be conducted.

During investigation, each investigating team shall have the following roles:

- a. ESU – primarily conduct epidemiologic investigation
- b. EPI – assist in AEFI investigation, document immunization practices including cold chain management
- c. FDA/ FDRO – assist in AEFI investigation, document registration of distributed vaccines including specific vaccine lot/batch number
- d. Health Promotion Officer – conduct risk communication

The investigators will need to look directly at the suspected reaction as well as gather information from the patient/parent, health workers and supervisors, and community members. The information collected (and conclusions) should be recorded in the AEFI Case Investigation Form (CIF).

Immunization errors and coincidences are the most likely causes of adverse events. Therefore, the investigator should suspect immunization errors as the cause and examine the evidence for any errors in the storage, handling, or administration of vaccines. Attention can then focus on finding out more about the particular error and taking the necessary corrective action. The investigator should seek to identify system problems rather than find individuals to blame.

Below are the steps in AEFI investigation that follows standard epidemiological investigation principles:

Table 9: Steps in an AEFI investigation

STEP		ACTIONS
1	Confirm information in report	<ul style="list-style-type: none"> Obtain patient's medical file (or other clinical record) Check details about patient and event from medical file and document information. Obtain any details missing from AEFI Report Form. Identify any other cases that need to be included in the investigation.
2	Investigate and collect data: About the patient :	<ul style="list-style-type: none"> Immunization history Previous medical history, including prior history of similar reaction or other allergies Family history of similar events.
	About the event :	<ul style="list-style-type: none"> History, clinical description, any relevant laboratory results about the AEFI and diagnosis of the event Treatment, whether hospitalized, and outcome.
	About the suspected vaccine(s) :	<ul style="list-style-type: none"> Conditions under which the vaccine was shipped, its present storage condition, state of vaccine vial monitor, and temperature record of refrigerator Storage of vaccine before it arrived at health facility, where it has come from higher up the cold chain, vaccine monitor card.
	About other people :	<ul style="list-style-type: none"> Whether others received the same vaccine and developed illness Whether others had similar illness (may need case definition); if so exposure of cases to suspect vaccine(s) Investigate the local immunization service
3	Assess the service by: Asking about:	<ul style="list-style-type: none"> Vaccine storage (including open vials), distribution, and disposal Diluents storage and distribution Reconstitution(process and time kept) Use and sterilization of syringes and needles Details of training in immunization practice, supervision and vaccinator(s) Number of immunizations greater than normal?
	Observing the service in action:	<ul style="list-style-type: none"> Refrigerator – what else is stored (note if similar containers stored next to vaccine vials which could be confused); which vaccines/diluents stored with other drugs; whether any vials have lost their label Immunization procedures (reconstitution, drawing up vaccine, injection technique, safety of needles and syringes; disposal of opened vials) Do any open vials look contaminated?
4	Formulate a working hypothesis:	<ul style="list-style-type: none"> On the likely/possible cause(s) of the event
5	Test working hypothesis	<ul style="list-style-type: none"> Does case distribution match working hypothesis? Occasionally, laboratory tests may help (see text)

6 Conclude investigation	<ul style="list-style-type: none"> • Reach a conclusion on the cause. • Complete AEFI Investigation Form (Annex B) • Take corrective action, and recommend further action
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Quantitative and qualitative aspects of data collection need to be considered. In addition, the DOH issued a Department Memorandum no. 2011-0308, which requires local ESUs to submit hospital records, laboratory results, autopsy (if patient dies), and preliminary investigation report (which consists of the current status of investigation, actions taken, and preliminary causality assessment by regional AEFI committee) for evidence-based causality assessment. Hence, securing copies of these reports during and after the investigation is necessary.

Laboratory Testing: Vaccine

Laboratory testing may sometimes confirm or rule out the suspected cause: the vaccine may be tested for sterility and adjuvant (such as aluminium salts); the diluent for sterility and chemical composition; and the needles and syringe for sterility. Testing should be requested on a **clear suspicion** and **not as routine**, and *never* before the working hypothesis has been formulated. Determining which samples to send depends on the working hypothesis for the cause of the event. If the used vial of suspect vaccine is available, it should be sent together with unused vials of the same lot.



Key points

- **Not every AEFI investigation requires testing of the implicated vaccine**
- Laboratory testing should only be considered when a causality assessment ruled out all other cases of the AEFI and upon recommendation of the National AEFI Committee and/or the Food and Drug Administration (FDA).
- Vaccine specimens will only be tested in WHO recognized national control laboratory and should be coursed through the:

Food and Drug Administration

Trunk line number: 857-1900

- For human specimen, please refer it to the clinical laboratory/facility that is capable and qualified to perform the required testing.

Tertiary Level Laboratories in Regional/Provincial Hospitals

or

Research Institute for Tropical Medicine

Trunk line number: 827-2632

- For further advice, please contact:

National Epidemiology Center

Trunk line number: 651-7800 Loc. 2930

Laboratory Testing: Human Specimens

For biochemical, histo-pathological and microbiological examination specimens should be handled at the local hospital and forwarded to the nearest laboratory, where facilities are available to carry out requested laboratory testing. If facilities for essential laboratory testing are not available at intermediate level (Region/Province/ Municipality) institutions, sending samples to national laboratory or an accredited laboratory abroad needs to be considered. However, **testing should be requested on a *clear suspicion* and not as routine.**

It is critical to properly document the date, time of collection and type of every vaccine sample collected, reports of clinical investigations and medical records related to the incident such as microbiology, biochemistry, immunology, histopathology, hematology, radiology, etc. Detailed history which includes past medical history, history of allergies and findings of medical records should also be collected. Please see table below for reference:

Table 10: Laboratory testing to investigate AEFIs by working hypothesis

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

Table 11: Guide to specimen samples obtained following selected AEFIs

Hypothesis	Specimen	Reason	Specimen collection
Suspected bacterial sepsis due to contaminated vial, needle contamination, coincidental	Whole blood	Bacterial culture	Blood 8–10 mL in each of 2 blood culture bottles.
	CSF	Differential cell count, biochemistry, bacterial and viral culture, PCR (HSV1/2, enterovirus, other)	Sterile container Viral culture media
Suspected viraemia due to vaccine virus or coincidental disease	Serum	IgM and IgG antibodies for viral pathogens	Clotted blood 5–10 mls
	CSF	Differential cell count, biochemistry, bacterial and viral culture, PCR (HSV1/2, enterovirus, other)	Sterile container Viral culture media
	Skin vesicle	Viral culture	Sterile container Viral culture media
Suspected anaphylaxis	Serum	Mast cell tryptase	Clotted blood 5–10 mL
		Specific IgE	Clotted blood 5–10 mL
Suspected toxin or drug injection/ingestion, either programme error or coincidental	Urine	Drug screen	Sterile container 1 mL
	Blood	Chemistry when indicated, liver enzymes, glucose, electrolytes	Clotted blood or in Li Heparin 5–10 mL
Suspected VAPP or coincidental encephalitis	Stool	Enterovirus and viral culture	Sterile container

Source: Immunization Safety Surveillance, 3rd Edition, WHO Western Pacific Region

Investigating AEFI clusters

A cluster of AEFI is defined as two or more cases of the same adverse event related in time, place **or** vaccine administration. The exact nature of the relationship between the adverse events (e.g. duration of time, proximity of place) will differ by nature of the events and the circumstances in which they occur. The criteria defining a cluster will depend on the context (e.g. for a globally distributed vaccine, the batch may be more important than the place) however in the case of immunization errors, the place will be an important criterion.

A cluster can be understood as a special kind of signal, where not only an increase in the AEFI reporting rate has been seen but one or more common characteristics of the AEFI reports have become apparent too. The characteristics are traditionally time, place and/or vaccine, but could also be age group, genetic predisposition, disease or other characteristic of the vaccinees which could constitute a risk factor for a certain AEFI.

Cluster investigation begins by establishing the case definition and identifying all cases that meet the case definition. The immunization programme manager should then take two actions (Figure 1).

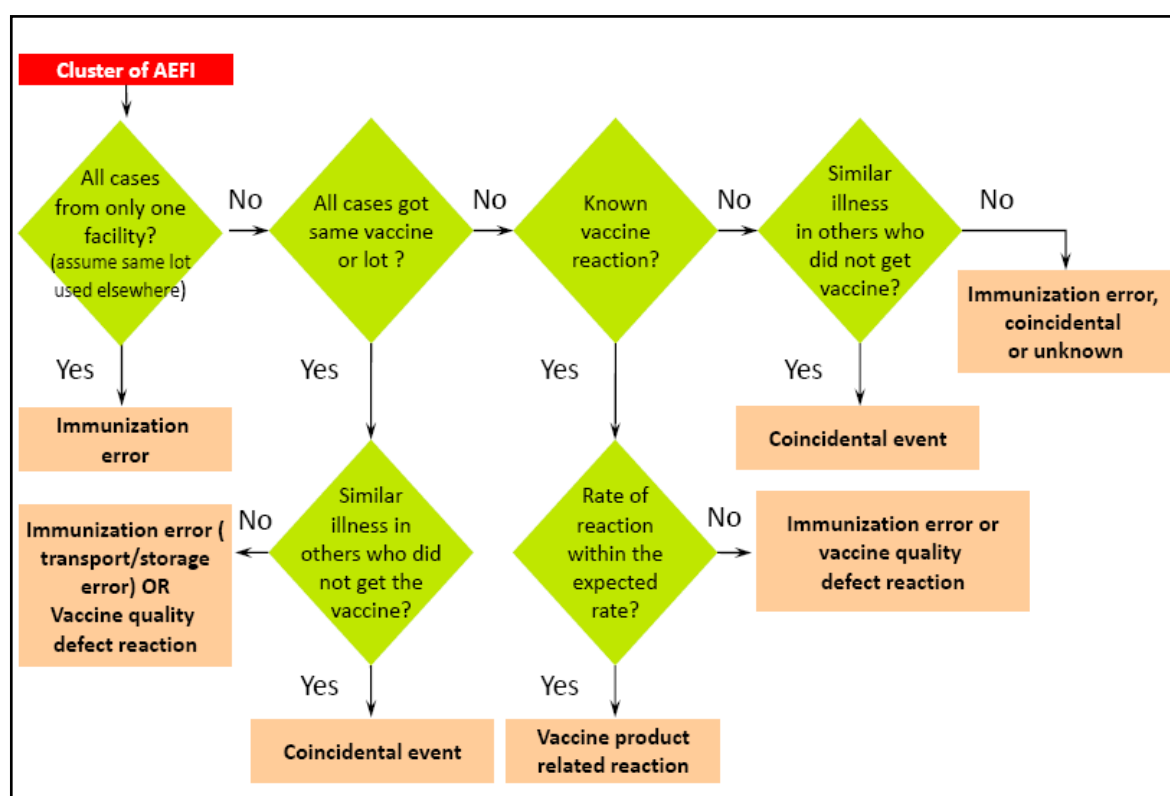
1. Identifying the common cases (the cluster cases) including details of when, where and which vaccines were given, by collecting and recording:
 - Detailed data on each case
 - Programme-related data (vaccine storage, handling, etc.), and
 - Immunization practices and the associated health worker's practices
2. Identify any common exposures among the cases, such as:
 - All data on vaccine(s) used (name, lot number, etc.), and
 - Data on other people in the area (also the non-exposed)

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 a vaccine quality defect as well as whether an immunization error may have occurred. For relatively new vaccines or established vaccines use in new target populations, a cluster may represent a previously unrecognized vaccine product-related reaction. Knowledge of the background incidence of events which may occur in causal relationship with a vaccine is, therefore, essential for assessing a cluster in terms of the strength of the signal it may provide.

Table 13. Cluster characteristics of cause-specific categories of AEFI

Cause-specific AEFI	Cluster characteristics
Vaccine reaction (product-related or quality defect-related)	<ul style="list-style-type: none"> • If all cases received the same vaccine or lot, and there are no similar cases in the community. • If an increased frequency of events is reported from multiple settings.
Immunization error-related	<ul style="list-style-type: none"> • If all cases received vaccines from the same health worker/facility and there are no other cases.
Immunization anxiety-related reaction	<ul style="list-style-type: none"> • Clusters of fainting after immunization are well-recognized immunization anxiety-related reactions during immunization programmes targeting adolescent girls.
Coincidental	<ul style="list-style-type: none"> • If cases include people from the same area in the same age group who were not immunized.

Figure 1: Identifying cause of AEFI cluster



(Source: CAUSALITY ASSESSMENT OF AN ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI), User Manual for the Revised WHO Classification. March 2013)

Investigation of Deaths

In the event of a death following immunization, the field investigation has to be initiated promptly and death should be notified at all levels concerned including national immunization program. The death investigation has to be conducted without any delay as it can cause a public panic concern. **An autopsy is preferred and recommended following all deaths suspected to cause by vaccine / immunization.**

However, in Philippine set up, conduct of autopsy examination should be within the religious, cultural acceptance and legal framework of the country. An autopsy should be done with least disturbance to the parents and the health staff should take all the possible arrangements to carry out autopsy at earliest time possible.

The autopsy should include the following: review of detailed preclinical and clinical history including laboratory and radiological findings, where possible visit to the death scene for additional evidence, radiological examination, histo-pathological examination and toxicological and microbiological examinations. Samples for microbiology, immunology, histo-pathology and virology should be collected according to the instructions given by the relevant laboratories. The adherence to a standard autopsy protocol which would enable conducting of a comprehensive causality assessment of a reported death following immunization is important and necessary³.

Causality is the relationship between two events (the cause and the effect), where the second event is a consequence of the first. A direct cause is a factor in absence of which the effect would not occur (necessary cause). Sometimes there are multiple factors that may precipitate the event (effect) or may function as co-factors so that the event (effect) occurs. Many challenges are involved in deciding whether an adverse event is actually caused by a vaccine or vaccination. Vaccines are often administered to children at ages when many underlying diseases become evident. Vaccines administered to adults can also coincide with an entirely different risk factor for an event. The fact that a vaccine was administered within a reasonable time period of the occurrence of an event does not automatically suggest that the vaccine or vaccination caused or contributed to the event.

Causality assessment, on the other hand, is the systematic review of data about an AEFI case to determine the likelihood of a causal association between the event and the vaccine(s) received. This does not necessarily establish a definite relationship, but only ascertains the level of certainties of causal association with the vaccine/vaccination. Besides, a definite causal association or absence of association often cannot be established for an individual event. This process is a critical part of AEFI surveillance and monitoring system and enhances public and health worker's confidence in the national immunization programme. Whether an AEFI is attributable or not to the vaccine or to the immunization program determines what steps need to be taken to address the event.

Causality assessment is important for:

- Identification of vaccine related problems
- Identification of immunization error related problems
- Excluding coincidental events
- Detection of signals for potential for follow up, testing of hypothesis and research
- A basis for estimation of rates of serious AEFIs
- Comparison of AEFIs between vaccine brands
- Validation of pre-licensure safety data with comparison of post marketing surveillance safety data

The quality of the causality assessment depends upon:

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

Causality assessment outcomes help raise awareness of vaccine-associated risks among health-care workers; this, combined with knowledge of benefits of immunization, forms the basis of vaccine information for parents and/or vaccine.

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 absolute criterion.
- **Definitive proof that the vaccine caused the event:** Clinical or laboratory proof that the vaccine caused the event. It is most often found in **live attenuated vaccine**
- **Biological plausibility:** Biological plausibility may provide support for or against vaccine causality. In other words, the association should be compatible with existing theory and knowledge related to how the vaccine works.
- **Strength of the association:** This is defined by the size of the association as measured by appropriate statistical tests. The stronger the association, the more likely it is that the relation of “A” to “B” is causal.
- **Consistency of the association:** The association is consistent when results are replicated in studies in different settings using different methods. That is, if a relationship is causal, we would expect to find it consistently in different studies and among different populations. This is why numerous experiments have to be done before meaningful statements can be made about the causal relationship between two or more factors.
- **Consideration of alternate explanations:** In doing causality assessment, all reasonable alternative etiologic explanations need to be considered.
- **Prior evidence that the vaccine in question could cause a similar event:** The concept of ‘re-challenge’ which is more commonly used in drug causality, but has also been helpful for certain vaccine-event considerations (for example, Guillain-Barre Syndrome or GBS occurring on three separate occasions in the same individual within weeks of administration of tetanus vaccine).

Case selection for AEFI causality assessment

Not all AEFI incidents that are reported and investigated need to have a causality assessment. Generally, it is recommended that causality assessment should focus on the following:

- **Serious AEFIs** , as per definition (i.e. event that is causing a potential risk to the health/life of recipient leading to death, life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent significant disability/incapacity, congenital abnormalities/birth defects or required intervention to prevent permanent impairment or damage.)
- Clusters of events above expected rate or severity.
- Signals: generated as a result of individual or cluster cases as they could signify a potential for large public health impact.
- Other AEFIs outlined below if the reviewing team/committee decides that causality needs to be determined as a special case or to conduct special studies:

- AEFIs 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),
- Events causing significant parental or community concern (e.g. HHE, febrile seizures).

In the Philippines, the National and Regional AEFI Committees are responsible for determining final causality of an AEFI case or clusters of AEFIs. However, investigation team may offer a “first opinion” on the causality of a particular AEFI or cluster of AEFIs. The first opinion can be derived from the result of the investigation done by the team in collaboration with key stakeholders at the regional and sub-regional levels.

Regional AEFI Committee (RAEFIC)

AEFI Committee must then be established at the Regional Level. The suggested members are composed of the following:

Regional AEFI Committee:

- Chaired by the Regional Director or Assistant Regional Director
- 4 clinical experts (Medicine/infectious disease/pediatrician)
- Research specialist (academe), pharmaco-epidemiologist
- Regional Food and Drug Authority (observers)
- EPI program manager and cold chain manager (observers)
- RESU head/staff (secretariat)

For serious AEFIs, RESU shall convene the Regional AEFI committee within 7 days after completion of investigation for causality assessment and recommendation for appropriate response.

Roles and responsibilities of the RAEFIC:

- a. Deliberate preliminary causality assessment upon receipt of complete AEFI case investigation reports from the provincial/regional investigating team. The committee should convene at least quarterly or as need arise.
- b. Provide immediate written report regarding the deliberated preliminary assessment to NEC and concerned LGU, copy furnish NCDPC and FDA.
- c. Provide information of the final causality assessment and recommendations to the Regional Offices/PHO/CHO and concerned LGU.
- d. Monitor implementation of the recommendations by the responsible program/offices.

National AEFI Committee (NAEFIC)

Cases that were not or cannot be classified by the RAEFIC are forwarded to the National Epidemiology Center (NEC) with attached investigation reports. Every quarter, NEC convenes the National AEFI Committee (NAEFIC) to provide final causality assessment for these cases and make final decisions for inconclusive investigations.

Roles and responsibilities of the NAEFIC:

- a. Review all reported serious and cluster of AEFI cases presented for expert opinion on a quarterly basis or as the need arise, and provide a final causality assessment of the AEFI cases as well as the cases that were not classified by the Regional AEFI Committee.
- b. Ensure evidence-based causality assessment by recommending further investigation and data collection as needed.
- c. Make final decisions on causality assessment of inconclusive investigations.
- d. Ensure standard protocols for AEFI surveillance and investigation are correctly followed.
- e. Engage with other national and international experts when requirements arise in establishing causality and vaccine quality issues.
- f. Provide recommendations to the National Immunization Program, NEC and National Cold Chain Manager on improving immunization service delivery, compliance with injection safety and effective vaccine management, etc. based on lessons from the AEFI cases.
- g. Serve as technical advisory group to the Secretary of health and the FDA on vaccine and immunization safety-related issue of highest consideration such as immediate recall of vaccine from market or temporary/permanent withdrawal of a vaccine from the immunization program.
- h. Serve as resource person in other AEFI related meetings, conference or capacity building activities as requested.

Prerequisites for causality assessment

AEFI are usually reported through passive or stimulated passive surveillance, and less frequently from active surveillance systems. Timely reporting of AEFI followed by appropriate and detailed investigation is the key to successful causality assessment and signal detection. An AEFI report should accomplish three prerequisites before causality assessment, namely:

- Completed AEFI case investigation. Premature assessments with inadequate information could mislead the classification of the event.
- Complete documents pertaining to the investigation such as hospital charts, laboratory and autopsy findings should be available at the time of assessment.
- There must be a “valid diagnosis” (as explained below) for the unfavorable or unintended sign, abnormal laboratory finding, symptom or disease in question.

Causality assessment method

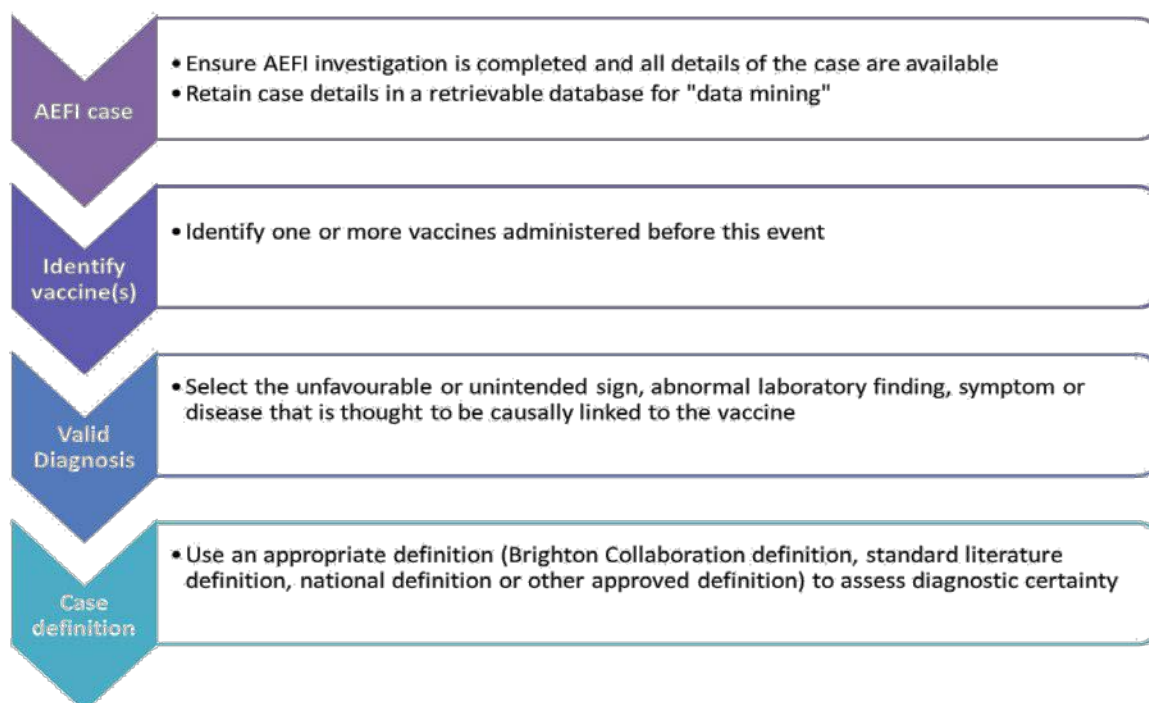
Attribution of causality to AEFI, especially those considered severe, of public importance, and programmatically disruptive are critical for ensuring vaccine safety. There is a method developed by WHO in 2012 that allows the National AEFI Committee to screen reported serious AEFI cases and assess for completeness and quality of information, ensuring the objectiveness of the assessment². Cases deemed incomplete remains pending and follow up investigation and data collection is required. A repository in the form of a database of all AEFI cases sorted through this new guideline is considered critical and recommended to allow for future signal detection and determining the need for additional epidemiological studies.

Four steps in causality assessment:

Step 1: Eligibility

To proceed with causality assessment, it is necessary to have a valid diagnosis for the reported AEFI. The Brighton Collaboration provides every standard case definition and should ideally be used if available. This can be accessed online at <https://brightoncollaboration.org/public>. However if this is not possible, case definitions can be adopted from standard medical literature, national guidelines or adopted locally. If the reported event does not have a valid diagnosis, the AEFI cannot be classified and additional information should be collected to arrive at a valid diagnosis.

Figure 2: Causality assessment method- eligibility



(Source: CAUSALITY ASSESSMENT OF AN ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI), User Manual for the Revised WHO Classification. March 2013)

Step 2: Checklist

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

1. Is there strong evidence for other causes?
2. Is there a known causal association with the vaccine / vaccination?
 - a. Relationship with vaccine ingredients
 - b. Immunization Error related
 - c. Injection Reaction (Immunization related anxiety)

If the response to question 2 was “yes”, then it is necessary to ask, “Is the event within the time window of increased risk?”

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

Once the checklist is systematically completed, the answers in the checklist are applied to the algorithm.

Figure 3: Causality assessment method- checklist

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

Was there exposure to a potential risk factor or toxin prior to the event?		
Was there acute illness prior to the event?		
Did the event occur in the past independently of vaccination?		
Was the patient taking any medication prior to vaccination?		
Is there a biological plausibility that the vaccine could cause the event?		

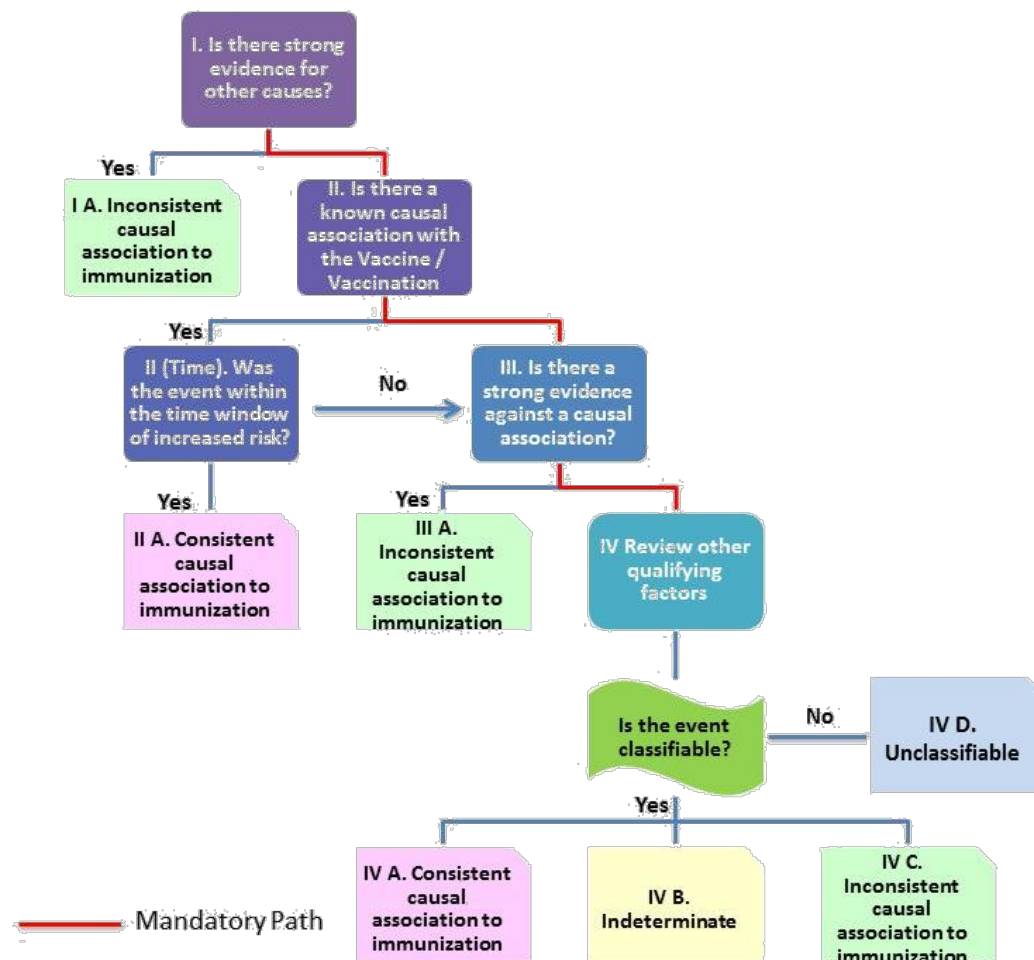
Note: Y: Yes; N: No; UK: Unknown; NA: Not applicable.

(Source: CAUSALITY ASSESSMENT OF AN ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI), User Manual for the Revised WHO Classification. March 2013)

Step 3: Algorithm

The algorithm is based on key questions given in the checklist. Stepwise approach in algorithm helps determine if the AEFI could be consistent or inconsistent with an association to immunization, indeterminate or unclassifiable. Responses IA, IIA and IIIA have greater strength and these conclusions have greater weight. When the conclusion is “unclassifiable”, the reviewers should determine the reasons why classification was not possible and all attempts should be made to obtain the necessary supporting evidence for classification.

Figure 4: Causality assessment method- Algorithm



(Source: CAUSALITY ASSESSMENT OF AN ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI), User Manual for the Revised WHO Classification. March 2013)

Step 4: Classification

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

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

C. Inconsistent causal association to immunization (Coincidental)

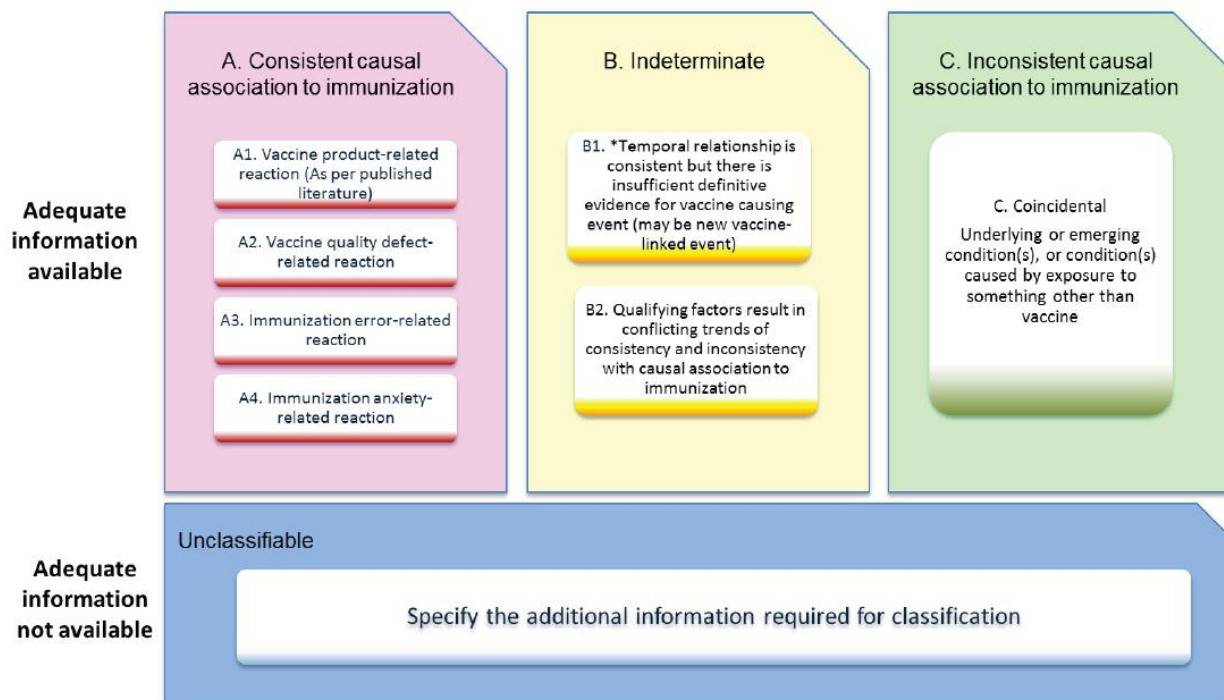
- C1: Underlying or emerging condition(s), or

**B1: These are potential signals and maybe considered for investigation*

II. 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 kept in the electronic database which should be periodically reviewed to see if additional information is available for classification and to perform analyses for identifying signals.

Final classification (step 4) is critical, as it hints the follow-up actions. It is important to note that final classification of a given AEFI may change with updated knowledge and information. During the causality assessment process, in addition to this newly introduced method, it is recommended to check: *Causality assessment of an adverse event following immunization (AEFI) – User manual for the revised WHO classification 2013* (http://www.who.int/vaccine_safety/publications/aevi_manual.pdf).

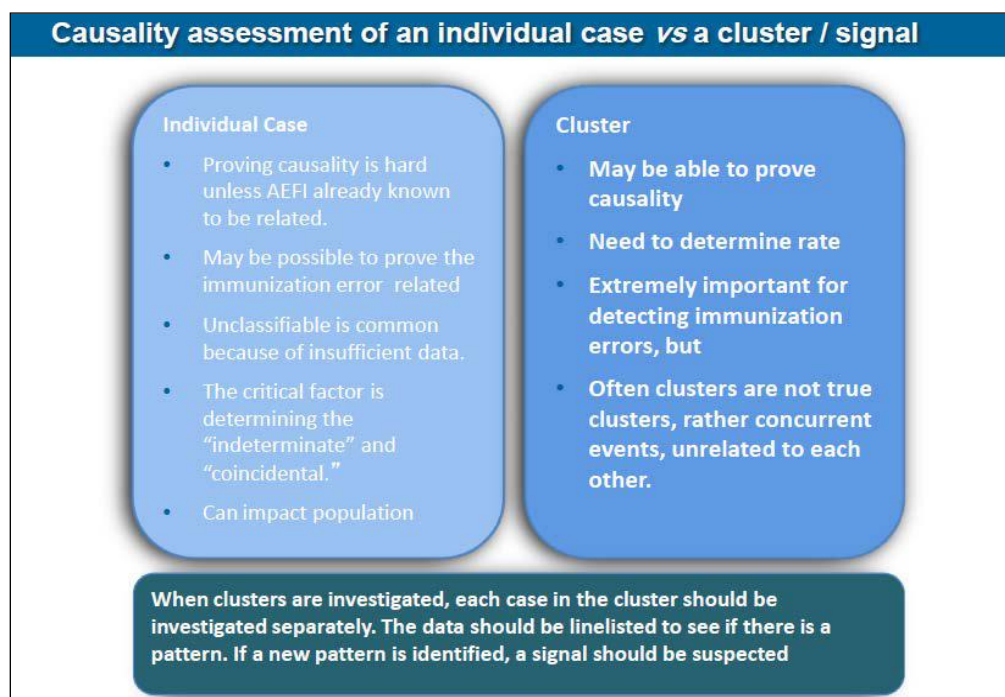
Figure 5: Causality assessment method-classification



*B1 : Potential signal and maybe considered for investigation

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

Figure 6: Causality assessment of an individual case vs. a cluster/signal



Challenges and pitfalls to causality assessment

1. Information of AEFI investigation report is incompleted therefore causality assessment cannot be done.
2. Lack of experts at the regional level responsible for formal causality assessment undermines credibility.
3. Non-analysis of the AEFI by regional responsible authorities in the context after causality assessment may delay recognition of clusters and possible program errors.

Data management is one of the core activities in AEFI surveillance. Data management system supports efficient data capture and information flow, and that can provide a master list of up-to-date case-based information. Through this process, identifying clusters can be facilitated as well as monitoring of control measures can be done. The purpose of surveillance data is to rationally utilize empowering decision makers to lead and manage more effectively by providing timely and useful evidence – data for action!

The use of computer-based data storage and analysis is highly recommended in all reporting units (RHU/CHO/PHO/RO). However, while some LGUs are still acquiring the means and capacity for computerization, a paper-based reporting system and information management should be used.

There are three main principles in data management:

- Production of complete data
- Production of accurate data
- Production of timely data

From the data management perspective, data collection is complete if all the cases are reported with all required details available. The details reflected in the data should be correct. The data should be available on time (depending on the surveillance activity) for effective and efficient implementation of interventions.

Five basic steps of data management:

- 1. Data collection** – Data should be collected weekly from ESUs and DRUs. It is important that all units are aware of established deadlines for reporting and submitting reports. Track submission by ESUs/DRUs through a use of a weekly submission register to be able to identify units that are consistently reporting and those that are considered “silent”.
- 2. Consolidation** – If the unit encodes data from the peripheral levels, ensure that forms submitted by ESUs/DRUs are compiled.

When merging data, ensure data files are complete and free from errors by reviewing data for double entries and data inconsistencies. Compile paper copy of CIF to level where data encoding was made for reference, particularly during the data cleaning process.

- 3. Data analysis** – Data analysis is largely focussed on identifying vaccine-related issues, as it will lead to operational and policy decisions on vaccine procurement and management. It also has an impact at the international level. Therefore, quality of investigations and data analysis is important.

Basic analysis using the line listing should be composed of vaccine given, dose (1st, 2nd, 3rd), time (by month), geographical location (barangay/province/city), type of reaction/s (i.e. seizures, abscess). It is important that at regional and national level that basic analysis should further expand to estimate antigen-specific AEFI reporting rates.

Data analysis should include, but not limited to the following information:

- Number of AEFI reported
- Geographic and temporal distribution of AEFI reported looking for clustering
- Number of adverse events reported by antigen and type of adverse event by antigen (i.e. injection site abscess, high fever, allergic reaction, nodule, seizures, severe local reactions, lymphadenitis, arthralgia, shock)
- Geographic distribution of abscesses and possible immunization error - related adverse events.
- Clustering of adverse events according to batch/lot

Who should analyze the data?

Data analysis should be carried out at different levels in the immunization safety surveillance system; PESU/CESU, RESU, and national level. Analysis of data at immunization service provider level is very important to identify the immunization errors. This is largely to carry out corrective action in a timely manner. The extent and purposes of analysis will vary by different level. (See Table 14)

How to analyze the data?

Step 1: Initial line listing is the basis for data analysis. It will help to initial identification of clustering or any unusual or significant reporting events, those need further analysis.

Step 2: Tabulating AEFI data by place, person and time and by antigens by type of reported adverse events (high fever, abscess). This step further filtered the AEFI by different variables and help program managers to generate clues for further analysis. Even at this step, it is possible to identify common program errors. (e.g., increased number of abscess by one immunization centre is more likely due to the immunization error). However, further investigation of such observation is necessary to confirm the causality.

Step 3: Calculating AEFI rates. Number of doses administered for each antigen is the denominator for calculating reported AEFI rates for each antigen in a given time period (by month, quarter or year). Analysis shall expand to the AEFI rates by first or second or third dose, when the antigen is administered more than once. For this, the number of doses administered of the given antigen by first, second or third need to be used as the denominator.

The most challenging selection is to use a proper denominator. There are a few options for selecting a denominator.

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

In the Philippines, the information of the denominator, i.e. vaccine doses administered/ doses used / doses distributed, is available at the National EPI Program. Therefore, at each administrative level, it is important to receive necessary data from respective EPI units

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

For example, in a city X, the registered under-1 year child population is 5000. The coverage of measles vaccine is 90%. During the same year, 20 febrile seizures were reported following measles vaccination. How do you calculate rate of febrile seizures?

The numerator for this vaccine reaction (febrile seizures) is 20. Since no other data is available, this example can use measles vaccine coverage (90%) to get the denominator.

Denominator = Target population x coverage
 = 5,000 * 90%
 = 4,500

The reported febrile seizures rate is $20/4,500 \times 100 = 0.44\%$

Multiplier: Use of proper multiplier in data analysis is important and also varied by purpose and level of analysis. At local level, percentage (%) is the best choice, whereas at intermediate and national levels, may use 1000, 100,000 or million as multiplier. For common, minor vaccine reactions, percentage is used and for rare serious reactions, 10,000 (10^4), 100,000 (10^5) or 1,000,000 (million) can be used. (Refer Table 4)

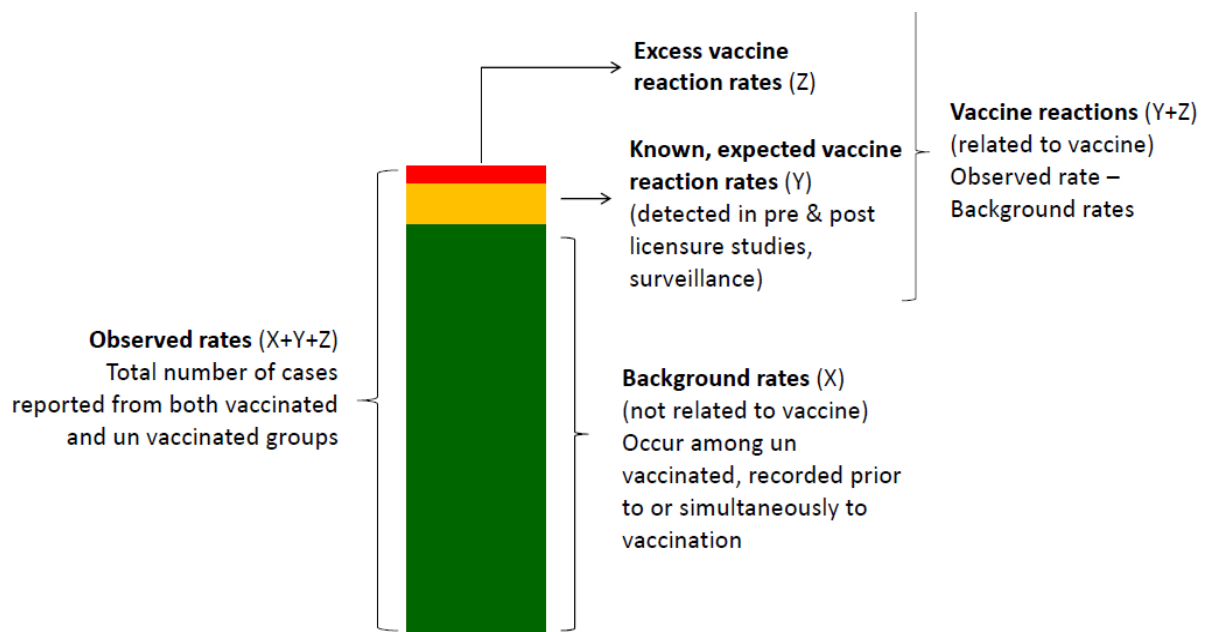
The immunization program also provides the denominator on vaccine use that helps to interpret AEFI reports. The number of reports cannot be interpreted without accurate data on the use of that vaccine or specific lot, and its distribution to different areas. Therefore, collection of vaccine distribution data is needed for immunization safety surveillance.

Step 4: Comparison and interpretation of rates

Available expected vaccine reaction rates for each type of AEFI for a given antigen (Tables 4) give a guide to make a decision on corrective action to be taken on reported AEFIs. It is also important to know about background rates of reported medical events in the country. Background rates are independent and not related with the vaccine. Observed (reported) rates include both background rates and vaccine-related rates. Comparison of background rates with reported rates of AEFI will lead to a valid conclusion on possible type of AEFI.

$$\text{Vaccine-related rates} + \text{Background rates} = \text{Observed (reported) rates}$$

The following graphic shows a comparison of the background rate with the observed rate of an event to determine the vaccine reaction rate (i.e. the rate of



events that are actually caused by the vaccine).

(Source: Global Manual on Surveillance of AEFI, WHO, 2014)

Vaccine reaction rates are further divided into two subcategories: expected vaccine reaction rates (Y) and excess vaccine reaction rates (Z). The WHO vaccine reaction information sheets give the “expected” vaccine reaction rates (the “Y” component in figure), which are based on pre-licensure and post-licensure data. These expected vaccine reaction rates are known rates due to the inherent properties of the vaccines and the response by recipients. If the values exceed the known, expected vaccine reaction rates, it needs to be considered if this is a true increase of vaccine reaction rate or whether the values are due to other factors.

Comparison of background rates with reported rates of AEFI will guide to a possibility of hypothesis of a coincidence. (e.g. febrile seizures are common among young children with many etiologies and may also be possible for other vaccines as well.) Therefore it is important to know the rate of febrile seizures due to other reasons and expected rates following a given antigen. This comparison will essentially lead to describe the causality.

Background rates differ from country to country because of difference in national surveillance systems. Understanding the background rates in a specific population is useful for monitoring the sensitivity of the AEFI surveillance system in detecting changes in the frequency of vaccine reactions. Program managers are encouraged to use information sheets on Observed rates of vaccine Reactions worldwide, which is published by the WHO in this link:

http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/index.html

If the values exceed the expected vaccine reaction rates, it needs to be considered if this is a true increase of vaccine reaction rate or whether the values are due to other factors.

Factors to consider when comparing rates of AEFIs*

a. Vaccines

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

b. Age

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

c. Vaccine Dose

The same vaccine given as a ‘primary dose’ may have a different reactogenicity profile than when it is given as a ‘booster dose’. For example, the DTaP vaccine given

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

d. Case Definition

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

e. Surveillance Methods

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

f. Background conditions

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

Table 14: Purpose of analysis at different level

Program implementation level	What data to analyze?	Purpose of data analysis at given level
Local level (RHU, health centers or other health facilities providing immunization service)	<ul style="list-style-type: none"> Reported AEFIs by Place (clinics, barangay hospitals), Persons & time Reported AEFIs by antigen 	<ul style="list-style-type: none"> Will assess indicators (timeliness, completeness) of programme operation Identification of immunization errors will lead to corrective action.
Intermediate level (CESU, PESU, RESU)	<ul style="list-style-type: none"> Number of reports by Local levels Reported AEFIs by Place (clinics, hospitals), Persons & time Cluster analysis Reported AEFIs by antigen 	<ul style="list-style-type: none"> These are program operation indicators (timeliness, completeness) at local level Identify immunization errors and thereby will lead to corrective action. Cluster analysis too lead to identify immunization errors, but also coincidence and vaccine reactions Will identify vaccine reactions and coincidence.

National level (NEC, FDA)	Number of reports by <ul style="list-style-type: none"> • Region, Province, City, Municipality • Reported AEFIs by Place (clinics, hospitals or barangay), Persons & time • Cluster analysis • Reported AEFIs by antigen 	<ul style="list-style-type: none"> • These are program operation indicators (timeliness, completeness) at intermediate level • Cluster analysis too lead to identify immunization errors, but also coincidence and vaccine reactions too. • Will identify vaccine reaction rates (antigen and age specific) • Signal detection • Lead to take operational and policy decisions on vaccine and immunization safety
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Although the epidemiology and surveillance unit of the different levels are taking the lead in the epidemiological analysis, engagement and close coordination with the corresponding EPI managers and FDA staff are necessary and highly recommended as they could provide additional information (e.g. number of children immunized, status of vaccine pre-qualification, international rates, etc.) that will make the analysis more comprehensive.

It is critical to share the data and results of analysis to the FDA because they are mandated to report to the WHO/Uppsala Monitoring Center where rates of different adverse events of different vaccine antigens are closely monitored globally.

How should a cause be determined?

Until the investigation is complete a 'working a hypothesis' is all that can be formulated. Later it will be possible to analyze the data and assign a 'cause' and classified into the one of the categories of AEFI. For a few medical events, the diagnosis itself will show the cause whether it is immunization error related or vaccine-related or coincidental or injection reaction. In others, additional information evidence may be required to identify the cause.

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

Data analysis is important to identify problems, generate hypothesis and decision-making. Interpretation of data needs to be cautious: compare rates, but not

absolute numbers, and give attention to case definitions and used denominators. WHO information sheets on vaccine reaction rates provide rates of reactions of specific vaccines that can be helpful when comparing rates. Comparing background data with observed vaccine reaction data does not conclude the causality. It only generates the hypothesis. To conclude that a vaccine causes a vaccine reaction, it is necessary to demonstrate that the risk in vaccinated individuals is greater than that in the non-vaccinated.

4. **Production of Reports** – Surveillance data should be reported in regular or on-going basis and should be provided promptly for rapid and efficient response.
5. **Dissemination** – Surveillance reports should be disseminated to stakeholders who can use the data to take public health action. The findings should also be reviewed regularly and reported back to the ESUs and DRUs where the data was gathered from. This activity is called feedback. This will be discussed further in the next section.

Avoiding data management crisis

Data management crisis is a situation where the data is not being available when needed. The data manager may have left suddenly or the computer bugged down. The following is recommended to prevent such a situation:

1. Appoint a *backup data manager*; another member of staff should familiar himself or herself with the data management procedures and the whereabouts of documentation
2. Ensure that *data back up procedures are* made regularly on a medium external to the computer or that copies should be kept in a safe place, e.g. in a locked drawer.
3. Ensure that *all procedures are adequately documented* and that the documentation is easily accessible. Update the documentation whenever changes are made—it is clearly not desirable to discover during a crisis that the documented procedures describe a system no longer in use.

The term feedback refers to the process of sending back information, in the form of reports, results of data analysis, guidance, outcomes of causality assessment, recommendations, etc. to the different levels of the AEFI surveillance system where the information is needed. Feedback is essential to modify or guide the next action or to verify accuracy of information. There is a need to institute regular and timely feedback within and between levels of the health delivery system. Data should be reported routinely from the lower to higher levels of the health system and vice versa.

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 child/recipient especially concerning the need for future vaccination.

The reasons for providing feedback to reporting/periphery sites are:

- To facilitate the use of data by providing an analysis in greater depth. For example, if the peripheral levels are not computerized, the central level may provide computerized tables and graphs
- To place local data in the context of regional data, to allow comparison of disease incidence and program performance; allow enhanced surveillance and preventive measures in cases where disease is reported in the surrounding region but has not been seen in that area; and improve performance by showing national progress towards public health goals and comparing performance between regions
- To increase motivation of data providers by acknowledging their hard work and making them aware that the data are analyzed and used
- Verify accuracy and completeness of data received by regional and other ESUs

A Feedback may come in two forms: verbal and written.

1. **Verbal feedback** from one health unit to another and can take place in various venues, as follows:

- Telephone calls
- Meetings: weekly, monthly, quarterly, half-yearly and annually
- Health education activities

2. **Written feedback** may be in the form of the following:

- Investigation and causality assessment report
- Weekly Disease Surveillance Reports by NEC
- EPI Accomplishment Reports
- Any feedback reports produced by regions

Below is the recommended feedback process from the local, regional to the national level.

Unit/ Receiver	Data Information Needed	Provider of Feedback	Frequency
NEC	<ul style="list-style-type: none"> Complete AEFI Investigation reports Request for technical assistance Final classification of cases by the RAEFIC Conclusions and recommendations by the RAEFIC Outcome of AEFI response interventions EPI coverage reports (number of doses given) AEFI cases from private sectors/ vaccine manufacturers Status/results of vaccine pre-qualification International vaccine rates 	RESU RESU/EPI EPI FDA	As needed Quarterly As needed Quarterly As needed
FDA	<ul style="list-style-type: none"> AEFI surveillance database Final classification of cases by the RAEFIC/ NAEFIC Conclusions and recommendations by the RAEFIC and NAEFIC 	NEC	Monthly
EPI	<ul style="list-style-type: none"> AEFI surveillance reports (including AEFI rates) Final classification of cases by the RAEFIC/ NAEFIC Conclusions and recommendations by the RAEFIC and NAEFIC Status/results of vaccine pre-qualification International vaccine rates 	NEC FDA	Quarterly
RESU	<ul style="list-style-type: none"> Laboratory results Final classification of cases by the NAEFIC Conclusions and recommendations by the RAEFIC Investigation report Request for technical assistance Outcome of AEFI response interventions 	Laboratory/ FDA NEC PESU/CESU	As needed Quarterly As needed
PESU/ CESU	<ul style="list-style-type: none"> Laboratory results Final classification of cases by the RAEFIC/NAEFIC Conclusions and recommendations by the RAEFIC/NAEFIC 	RESU	As needed Quarterly
RHU/ MHO/ HOSPI- TALS	<ul style="list-style-type: none"> Laboratory results Final classification of cases by the RAEFIC/NAEFIC Conclusions and recommendations by the RAEFIC/NAEFIC Problems encountered in surveillance 	PESU/CESU	As needed Quarterly As needed

Response and Follow-up activities

Responding to AEFI may be immediate short-term and/or long-term follow-up activities. Response and follow-up activities should base on findings of investigations, causality assessments and recommendations by the investigation and expert committees. Withdrawal of the implicated vaccine and/or suspension of its corresponding immunization activity is not done following reports of AEFI unless upon declaration of the Secretary of Health in consonance with FDA and Expanded Program on Immunization and with the recommendations of the expert committees. Major follow-up actions may have impact on national immunization program and as well as regionally and globally.

The epidemiology and surveillance unit leads the team in epidemiological investigation and comprehensive data analysis. But, in terms of response activities, the EPI program managers and FDROs in their corresponding levels shall take the lead to provide corrective actions and monitor outcomes of response interventions.

Corrective actions

Patient care: Treatment must be the first response to an AEFI. Mild symptoms such as mild fever, pain are likely to be of short duration and can be managed by assuring and educating parents during immunization. Health workers need to know how to recognize, treat, and report AEFI – immediately, if serious. It is of utmost importance to ensure that proper and early treatment is received by affected vaccinees (patients).

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

Table 15: Actions to safeguard the public during an investigation

Stage of investigation	Actions
Incident detected	<ul style="list-style-type: none"> Assess and investigate with appropriate degree of urgency Possibly quarantine suspect vaccines Start communicate with all concern parties
Investigation starts	<ul style="list-style-type: none"> Ensure that investigator has adequate resources, provide more if needed (Refer to chapter 5) Increase surveillance to identify similar cases in and out of Area: some time it requires enhanced or

	<p>active surveillance to gather more information/data</p> <ul style="list-style-type: none"> • Define any suspect vaccine • Keep continue communication with all concern parties on process of investigation: do not suggest any hypothesis.
Investigator develops working hypothesis	<ul style="list-style-type: none"> • Do not communicate working hypothesis until confirmed • If immunization errors are working hypothesis, correct them • If vaccine problem suspected, quarantine suspect vaccines
Investigator confirms working hypothesis	<ul style="list-style-type: none"> • Advise community of cause, and of planned response • Communicate with all concern parties on findings

If AEFI causality is not established, depending on the nature of the event, its extent and whether it is ongoing, a further investigation or epidemiological studies may be needed. However, it must be accepted that in some cases the relationship to vaccine not clear.

Table 16: Actions to be taken upon completion of the investigation

Type of AEFI	Follow-up action
Vaccine related - reaction	<p>If a higher reaction rate than expected from a specific vaccine or lot then obtain information from the manufacturer and consult with WHO /WPR regional office to consider:</p> <ul style="list-style-type: none"> ▪ withdrawing that lot ▪ changing manufacturing specifications or quality control ▪ obtaining vaccine from a different manufacturer. <p>These are mainly the responsibility of the Philippine FDA</p>
Immunization errors	<p>Correcting the cause of the error. This may mean one or more of the following:</p> <ul style="list-style-type: none"> ▪ change in logistics for supplying vaccine ▪ change in procedures at the health facility ▪ training of health workers ▪ intensified supervision <p>Whatever action is taken, it is important to review at a later date to check that the immunization errors have been corrected.</p> <p>These are mainly the responsibility of the NEC/EPI programme.</p>

Coincidental	<p>Main task is communication to ensure that people are persuaded that the link is just coincidental. This communication can be challenging when there is widespread belief that the event was caused by immunization.</p> <p>Sometimes, it may be useful to enlist further expert investigation to convince/ensure that the event truly was coincidental. The potential for coincidental events to harm the immunization program through false attribution is immense.</p>
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Strengthening Immunization Program

a. Vaccine Cold Chain and Logistics

Immunization supply chain, injection safety and waste management are part of immunization safety surveillance. Any AEFI case report that can be attributed to gaps in management of cold chain management or supplies and logistics should be used as an opportunity to promote improvement of effective vaccine and logistics management throughout the supply chain (immunization supply chain, injection safety and waste management etc.).

In vaccine-related reactions, decisions should be carefully thought out. The impact on the immunization programme, alternate sources of vaccine, and the reliability of the evidence on which the decision is based needs careful scrutiny. Communication and coordination with the (FDA), vaccine manufacturer and WHO is advisable before making any decision.

b. Review/Supportive Supervision

- Regular reviews at each administrative level to monitor and evaluate performances of AEFI surveillance (Section 10) and EPI services
- Regular and continued supportive supervisions to ensure detecting and reporting of AEFI cases, implementation of recommendations followed by AEFI investigations and other corrective actions

c. Training and awareness

AEFI is an opportunity for training and awareness for staff. Irrespective of type or outcome of AEFI, it can use to update knowledge and develop skills and confidence among the staff. Awareness can expand to involving all stakeholders link to the immunization program such as: NEC, EPI, medical professionals, academe, teachers, volunteers, NGOs, policy makers, politicians and media.

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

Trust is a key component in the exchange of information at every level. Any overconfidence about risk estimates that are later shown to be incorrect contributes to a breakdown of trust among people involved. Admit uncertainty of AEFI, investigate fully, and keep the community informed. Avoid making a premature statement about the cause of the event before the investigation is complete. If the cause is identified as immunization error related event, it is vital not to lay personal blame on anyone, but to focus on system- related problems that resulted in the immunization error(s) and steps being taken to correct the problem.

COMMUNICATING GOALS

The goal of vaccine safety communication is to maintain public trust in vaccines and immunization safety toward sustaining the immunization programme with high immunization coverage's to prevent and control vaccine preventable diseases in the country.

In communicating with the community, it is useful to develop links with community leaders and the peripheral health workers so that information can be rapidly disseminated. Maintaining lines of communication with the community is important throughout the investigation. Upon completion of the investigation, the cause of the event(s) needs to be communicated to the community. This communication must include information about the steps being taken to remedy the situation and to prevent a recurrence, if such steps are needed.

Communication with parents and community

Key points to consider when communicating with the parents/ relations of the recipient, community, health staff:

- Listen empathetically to parents and their concerns.
- Reassure and support the parent or recipient but do not make false promises.
- Assist the parents/guardian for hospitalization, if necessary.
- Communicate frequently with the parents/guardian regarding the progress of the patient.
- Prepare a factsheet on adverse events for parents, community, health staff and media.

- Build up and maintain relationship among health staff, community, and the media.
- Inform individual parent about possible common adverse events and how to handle them.
- Continuously communicate with parents and community during the investigation period to assure understanding the risk-benefit of vaccination.
- Do not blame the health worker(s) but focus on the correction and quality of the NIP system.

Communication with health staff

Communicate among all level of health authorities involved.

- Reassure the staff confidence on immunization programme: quality of the vaccine, partial investigation.
- Reassure their knowledge, ability, skills and performances.
- Do not blame the health worker(s) but focus on the correction and quality of the NIP system.
- Keep updating on investigation process, progress, and findings.

Communicating with stakeholders

Vaccine safety information needs to be shared with other stakeholders in order to ensure dissemination of correct information and, by doing so, ensure the smooth functioning of national immunization programme in the country. This may be done at two stages: sharing preliminary information at initial stage and sharing the final data/report after completion of investigation/causality assessment at a later stage. The stakeholders may include:

- Department of Health
- Food and Drug Administration
- National and Local Government authorities
- Professionals / Academe
- Civil society
- International agencies: WHO, UNICEF
- Manufacturers

Communicating with the media

The media (newspaper, radio, television and the internet) play an important role in public perception. Understanding what the media want from a story will assist communication with them. In certain situations, media coverage can lead to public concern about immunization. In these situations, it is important to coordinate with professional organizations, health professionals and workers before responding to or addressing the media. The coordination should include preparation on how to deal with public concern on this issue, in order to minimize any potential harm. It is also useful to have other groups and individuals that merit public respect and authority to publicly endorse and strengthen key messages.

Advance preparation

Effective communication with the media includes advance preparation. This is part of a communication plan. This is important particularly before a new vaccine is introduced or before/during an immunization campaign or even as part of the on-going communication support to routine immunization programmes. A good media plan consists of the following:

Table 17. Media Plan

Plan activity	Details of Activities
A database of journalists	<ul style="list-style-type: none"> • A list of print and electronic media journalists covering health (local, national, international) with contact information. • Use of a database where updating can be done immediately. • Updating regularly any changes in the media list.
Information packages	<ul style="list-style-type: none"> • An information package may contain the following documents both in hard copy and e-copies: <ul style="list-style-type: none"> • Frequently Asked Questions (FAQs) on immunization in general, for specific disease, and AEFIs. • A factsheet or a technical brief on a specific vaccine preventable disease. • Recent updates: statistics, progress made in country, the Western Pacific Region, globally. • Contact addresses of spokespersons (experts) in the ministry.
The draft media release	<p>Must specifically answer the six Ws for journalists:</p> <ul style="list-style-type: none"> • Who is affected/or responsible? • What happened? What is being done? • Where did it happen? • When did it happen? • Why did it happen? • Will it happen again?
Information specific to media characteristic	<ul style="list-style-type: none"> • Local media: read and believed by more people in the community than national media. • National media: has a wider reach and influences national agendas. • International media: can influence national agendas.
A spokesperson system	<ul style="list-style-type: none"> • Identify in advance an appropriate spokesperson (or several spokespersons in the different agencies). • Share contact details of spokesperson (or several spokesperson in the different agencies). • Ensure spokesperson(s) has experience or some training in dealing with the media.

Crisis management

A crisis is a situation in which a real or potential loss of confidence in the vaccine or in the immunization programme is triggered by information about an AEFI. Often, crises can be avoided through foresight, care and training. If managed properly, the crisis will strengthen the immunization programme and boost public confidence and acceptance.

How to manage a crisis?

- Anticipate: do not wait until a crisis occurs. Prepare for the unavoidable.
- Develop a good relationship with the media.
- Good public awareness is necessary.
- Train staff at all levels to respond adequately: develop confidence responding to the public and the media (particularly to local media) properly and correctly.
- Confirm all facts before making any public comments.
- Prepare a plan to react to a crisis when it occurs. This has to be done in advance, identifying responsible persons to handle the crisis and preparing all supporting documents and information

The immunization safety surveillance system should be evaluated regularly to determine its effectiveness. This evaluation should be based on the following criteria:

- a. The data reported by the AEFI surveillance system
 - Overall reporting rate of AEFI; this will help to understand the functionality of the AEFI system and also, can use for comparisons. However, since this is a crude indicator, interpretation and comparison of this overall AEFI reporting rate need a precaution.
 - Number of adverse reactions reported
 - by type of adverse reaction; non serious (e.g; high fever, local reactions etc.,) and, serious
 - by vaccine(s)
 - by types of adverse reaction and by vaccine (most important technical indicator on vaccine performances)
 - by age groups (under one, under 5 years, etc.,)
 - by geographical sites (e.g; (i) by sub national level; regions, provinces, districts (ii) Programme implementation level) : important to identify performances by level/places/institutions

To calculate rates for each above category, refer to options for denominators recommended section 7.

- b. Timeliness, completeness and accuracy of AEFI reporting: Monitoring information from reports and site visits;
 - Comparing reports with the facility patient register; and
 - Talking to health workers and observing their work. (Refer to Training for Mid-Level Managers: Disease Surveillance WHO/IVB/08.08)
- c. Timeliness, completeness of investigations: Checking reports to ensure that those meeting the investigation criteria were investigated;
 - Checking that investigation began within the defined time criteria; and
 - Confirming the adequacy of the investigation and soundness of the conclusion reached and corrective action recommended.
- d. Audit of corrective action: Review by national/regional assessor to check that corrective action recommended has been done, and adequacy of change in practice to prevent AEFI, particularly Immunization error related events.

PHASES OF SUPPORTIVE SUPERVISION/ MENTORING VISITS

I. Preparatory Phase

Planning regular visit for supportive supervision

Planning the visits for supportive supervision should be an integral part of the annual/quarterly planning activities. It is important to use the data to determine areas where the visits should be conducted.

The plan should indicate:

- Where to conduct visits – this may include priority areas with the following criteria:
 - areas with cluster of AEFI
 - areas with known mishandling of previous AEFI case
 - areas with relatively high rate of AEFI
 - area with consistent AEFI case report
 - silent areas
 - area where AEFI reporting and response are usually delayed or there is lack of cooperation from the local health staff
 - area where AEFI cases are often determined by media first indicating lack of sensitivity of the AEFI surveillance system
- When to conduct visits – the frequency of visits will vary on the situation and purpose of the visit. For example, frequent supervision is needed if upon assessment, the motivation of staff needs to be improved. AEFI surveillance may be incorporated in the VPD program monitoring and supportive supervision that both aims to strengthen over-all capacity of the new staff for implementing surveillance. This may also be combined with the EPI program monitoring and supportive supervision as it may provide opportunities to monitor and reinforce safe immunization practices.

These are the steps involved in planning the visit:

1. Determine areas to visit
2. Communicate – prepare correspondence to inform areas about the visit
3. Coordinate – create a travel itinerary in coordination with the local units, arrangements on accommodations and transportations can also be made.
4. Prepare materials and logistics
 - a. Data and Powerpoint presentations – prepare surveillance data and orientation slides that could be used during courtesy calls with PHOs/CHOs, directors, chiefs and unit heads. This could also be used for on the spot orientations.
 - b. Laptop
 - c. Case investigation forms/ WHO Guide Questionnaires
 - d. Copy of guidelines and DOH issuances

II. Conducting the visit

The following activities should be done during the visit:

1. Courtesy call
 - a. Explain reason of visit and activities that will be done
 - b. Present data and expected outcomes
2. Collecting information – Below are the information that can be collected and assessed during the visit:

LEVEL	AREAS TO BE ASSESSED
NATIONAL: NEC FDA EPI	<p>It is important that the monitors assess the following indicators during monitoring and supportive supervision at the National Level:</p> <ul style="list-style-type: none"> • Timeliness, completeness and accuracy of AEFI reporting • AEFI report (total number of serious and minor) • Presence of comparison of vaccine reaction rates • Capacities for data management and analysis • Presence of risk communication plan • Availability of quarterly report/causality assessment report • Feedback reports and documentation of NAEFIC meetings • Functionality of NAEFIC • Proper implementation of safe immunization service • Presence of monitoring and supportive supervision activities • Need for trainings and capability building activities
REGIONAL: RHO-RESU FDRO REG'L EPI COORDINATORS	<p>The following indicators should be assessed at the regional level:</p> <ul style="list-style-type: none"> • Timeliness, completeness and accuracy of AEFI reporting • AEFI report (total number of serious and minor) • Presence of comparison of vaccine reaction rates • Capacities for data management and analysis • Presence of risk communication plan • Availability of quarterly report/causality assessment report of RO • Feedback reports and documentation of RAEFIC meetings • Functionality of RAEFIC • Presence and understanding of AEFI guidelines, immunization safety and other relevant guidelines that will ensure proper implementation of immunization service • Presence of monitoring and supportive supervision activities • Need for trainings and capability building activities

PROVINCIAL: PHO-PESU PROV'L EPI COORDINATORS	The following indicators should be assessed at the provincial level: <ul style="list-style-type: none"> • Timeliness, completeness and accuracy of AEFI reporting • AEFI report (total number of serious and minor) • Presence of comparison of vaccine reaction rates • Capacities for data management and analysis • Presence of risk communication plan • Presence and understanding of AEFI guidelines, immunization safety and other relevant guidelines that will ensure proper implementation of immunization service • Presence of monitoring and supportive supervision activities
LOCAL: CITIES/ MUNICIPALITIES CHO/RHU HEALTH CENTERS	The following indicators should be assessed at the local level: <ul style="list-style-type: none"> • Timeliness, completeness and accuracy of AEFI reporting • AEFI report ((total number of serious and minor) • Health worker's capacity to investigate, respond and communicate to reported AEFI cases • Presence and understanding of AEFI guidelines, immunization safety and other relevant guidelines that will ensure proper implementation of immunization service • Capacity to supervise and monitor the health center/s to ensure quality immunization service delivery at this level

All DSO/DSCs, EPI coordinators, and FDROs should not limit their roles on the above table. Activities may also include assessment of the health worker's understanding on AEFI surveillance (guidelines, case definition, reporting flow, etc.) and provide on-site mentoring if there is need for further capacity building. Areas of concerns such as barriers in reporting may also be monitored and addressed.

3. Problem-solving and feedback

Describe the findings to the health staff and its impact. Gather ideas and possible solutions with the staff; make sure that solutions are acceptable and feasible.

III. PRESENTATION OF RESULTS/FINDINGS

After each visit, a feedback presentation and report with specific doable recommendations should be made. The report is vital in planning corrective actions and will serve as a reference for future supervisory visits. It should inform unit heads, program managers and other stakeholders of the results of the visit.

IV. CONDUCT FOLLOW UP VISITS

Supportive supervision does not end with the conducted visit, follow-up should be planned. Follow up visits provide continuity between previous and future visits, in the following ways:

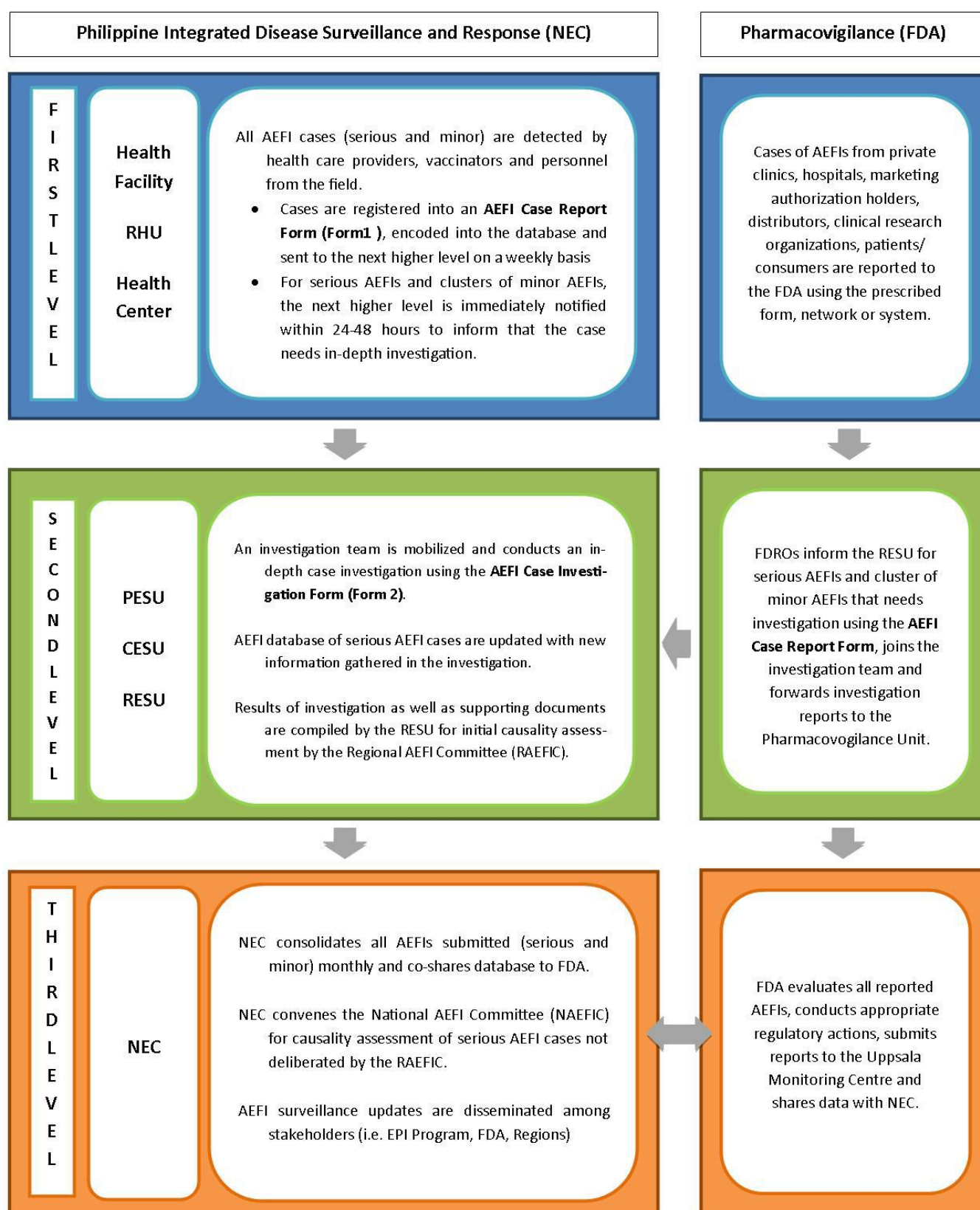
- determining resolution to problems previously identified
- reinforcing to the units visited that the findings found are relevant and still important
- providing support the health worker on how recommendations can be further implemented or modified as needed

Who is responsible for monitoring?

The role of monitoring is delegated to all health units. It includes the DOH – Central Office, Regional Office, Provincial Health Office, City Health Office and Rural Health Units. The offices shall be accountable for monitoring their own performance based on the set criteria. In addition, monitoring shall be done by person/s knowledgeable with AEFI surveillance and safe immunization practices who can easily track discrepancies and give immediate action to it. Hence, an Epidemiologist, DSO/DSCs, EPI coordinators, and FDROs shall be responsible of monitoring the system.

	ANNEXES
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ANNEX A. AEFI Surveillance Flow



[illegible]

LIST OF REPORTABLE SERIOUS AEFIs

Reportable Serious AEFI	Onset time interval*
<ul style="list-style-type: none"> Anaphylactoid reaction (acute hypersensitivity reaction) Anaphylaxis Persistent (more than 3 hours) inconsolable screaming HHE Toxic shock syndrome (TSS) 	Within 24 to 48 hours of immunization
<ul style="list-style-type: none"> Severe local reaction Sepsis Injection site abscess (bacterial/sterile) 	Within seven days of immunization
<ul style="list-style-type: none"> Seizures, including febrile seizures (6-12 days for measles/MMR; 0-2 days for DTP) Encephalopathy (6-12 days for measles/MMR; 0-2 days for DTP) 	Within 14 days of immunization
<ul style="list-style-type: none"> Acute flaccid paralysis (4-30 days for OPV recipient; 4-75 days for contact) Brachial neuritis (2-28 days after tetanus containing vaccine) Intussusception (commonly within 21 days after rota vaccines) Thrombocytopenia (15-35 days after measles/MMR) 	Within 3 months of immunization
<ul style="list-style-type: none"> Lymphadenitis Disseminated BCG infection Osteitis/Osteomyelitis 	Between 1 and 12 months after BCG immunization
<ul style="list-style-type: none"> Death Hospitalization Disability Any other severe and unusual events that are thought by health workers or the public to be related to immunization 	No time limit
*Onset time interval information it is recommended to refer to the Brighton Collaboration case definitions (www.brightoncollaboration.org) and WHO position papers and observed rates information sheets (available at http://www.who.int/vaccine_safety/initiative/tools/vaccineinfosheets/en/index.html).	

ANNEX C. AEFI Case Investigation Form



Philippine Integrated Disease
Surveillance and Response

Case Investigation Form (Only for Serious AEFI - Death/ Disability/ Hospitalized/ Cluster of Minor AEFI)



Version 2014

Name of DRU:		Type: <input type="checkbox"/> RHU <input type="checkbox"/> CHO <input type="checkbox"/> Gov't Hospital <input type="checkbox"/> Private Hospital <input type="checkbox"/> Clinic							
Address:		<input type="checkbox"/> Gov't Laboratory <input type="checkbox"/> Private Laboratory <input type="checkbox"/> Airport/Seaport							
I. PATIENT INFORMATION	EPIID Number	Patient's First Name	Middle Name Last Name						
Complete Address:		District	ILHZ						
Sex: <input type="checkbox"/> Male <input type="checkbox"/> Female	Date of Birth: MM/DD/YYYY	Age <input type="checkbox"/> Days <input type="checkbox"/> Months <input type="checkbox"/> Years	Admitted? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown						
Name of hospital/health facility:		Date Admitted/ Seen/Consult : MM/DD/YYYY							
Date onset of AEFI/ present illness MM/DD/YYYY TIME (hh:mm:sec) _____ AM / PM		Date next higher level notified ____/____/____							
Name & Designation of Reporter	Institution:		Contact #/email:						
Name & Designation of Investigator	Institution:		Contact #/email:						
II. SUSPECTED VACCINE									
Suspected Vaccine/s (Please indicate Generic and Brand Name)	Date of Vaccination	Time of Vaccination	Dose No. (e.g. 1st, 2nd, 3rd)	Site of Injection (Indicate left or right)	Batch/ Lot No.	Name of Manufacturer	Expiry Date	Name of Vaccinator	Profession of Vaccinator
Diluent	Date of Reconstitution	Time of Reconstitution	Batch/Lot No.	Expiry Date	Name of Vaccinator				
Vaccination Center/Facility:									
Vaccination Session: <input type="checkbox"/> Routine session <input type="checkbox"/> Clinic <input type="checkbox"/> Mass Campaign <input type="checkbox"/> School – based <input type="checkbox"/> Others, _____									
III. TYPE OF AEFI:									
<input type="checkbox"/> Anaphylactoid reaction (acute hypersensitivity reaction) <input type="checkbox"/> Anaphylaxis <input type="checkbox"/> Brachial neuritis <input type="checkbox"/> Disseminated BCG infection <input type="checkbox"/> Encephalopathy <input type="checkbox"/> Hypotonic-Hyporesponsive Episode (HHE) <input type="checkbox"/> Injection site abscess <input type="checkbox"/> Intussusception <input type="checkbox"/> Lymphadenitis <input type="checkbox"/> Osteitis/ Osteomyelitis <input type="checkbox"/> Persistent (> 3hours) inconsolable crying					<input type="checkbox"/> Seizures ◊ Febrile ◊ Afebrile <input type="checkbox"/> Sepsis <input type="checkbox"/> Severe local reaction ◊ Pain, redness and/or swelling of > 3 days ◊ Swelling beyond the nearest joint <input type="checkbox"/> Thrombocytopenia <input type="checkbox"/> Toxic Shock Syndrome <input type="checkbox"/> Others (specify) _____ _____ _____				

Case Definition:

- Adverse event following immunization** is defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.
- Serious AEFI** is defined as an event that is causing a potential risk to the health/life of a recipient leading to hospitalization.

AEFI Case Investigation Form

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IV. EXAMINATION** DETAILS						
Source of Information	<input type="checkbox"/> Attending physician	<input type="checkbox"/> Nurse	<input type="checkbox"/> Midwife	<input type="checkbox"/> Parent/Guardian	<input type="checkbox"/> Other _____	
Mode of examination	<input type="checkbox"/> Interview	<input type="checkbox"/> Medical records	<input type="checkbox"/> Physical Examination	<input type="checkbox"/> Verbal autopsy	<input type="checkbox"/> Laboratory Result	
	<input type="checkbox"/> Other _____					
If from Verbal autopsy, please mention the source: _____						
Name & Designation of person who first examined the patient:				Date & time:		
Signs & Symptoms in Chronological Order: **Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, lab and autopsy reports) and then complete additional information NOT AVAILABLE in existing documents. If patient has taken medical care - <u>Attach copies of all available documents</u> (including case sheet, discharge summary, <u>laboratory reports and post mortem reports - if available</u>) and <u>write only information unavailable in the attached documents below.</u> If patient has not taken medical care – examine the patient and write down your findings below (use additional sheets if necessary)						
Working/Final Diagnosis:						
Condition at Investigation: <input type="checkbox"/> Alive : <input type="checkbox"/> Recovering <input type="checkbox"/> Fully recovered <input type="checkbox"/> With Permanent Disability, Specify: _____ <input type="checkbox"/> Died, Date: ____/____/____						
V. Relevant patient information prior to immunization			YES/NO	Remarks		
History of allergy						
Pre-existing illness / congenital disorder						
History of hospitalization in last 30 days (indicate the cause)						
Recent history of trauma (indicate date, time and site)						
For adult women • Currently pregnant? (If YES, indicate AOG) • Currently breastfeeding?						
For infants • Natal History • Delivery			<input type="checkbox"/> Full term <input type="checkbox"/> Normal <input type="checkbox"/> Any complication, specify	<input type="checkbox"/> Premature <input type="checkbox"/> Caesarian Section	<input type="checkbox"/> Postdated <input type="checkbox"/> Assisted birth	
Was the patient on any concurrent medication for any illness? (If YES, indicate name of drug, indication, doses & date in the remarks)						
Family History of similar event						
Did the patient receive any previous vaccination and experienced the similar event? <input type="checkbox"/> NO <input type="checkbox"/> YES (If YES, complete the table below)						
Vaccine	Date of Vaccination	Time of Vaccination	Batch/ Lot No.	Name of Manufacturer	Expiry Date	Name of Vaccinator

AEFI Case Investigation Form

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IV. IMMUNIZATION PRACTICES (Fill up this section by asking and observing immunization practices at the place (s) where concerned vaccine was used)		
Syringes and Needles Used	YES/NO/NA*	Remarks
Are auto-disable syringes used for immunization?		
If NO, specify the type: <input type="checkbox"/> Glass <input type="checkbox"/> Disposable <input type="checkbox"/> Recycled disposable <input type="checkbox"/> Pre-filled syringes <input type="checkbox"/> Other _____		
Specific key findings/additional observations and comments:		
Reconstitution procedure (complete only if applicable) * Not applicable		
Same reconstitution syringe used for multiple vials of same vaccine?		
Same reconstitution syringe used for reconstituting different vaccines?		
Separate reconstitution syringe for each vaccine vial?		
Separate reconstitution syringe for each vaccination?		
Are the vaccines and diluents used as recommended by the manufacturer		
Specific key findings/additional observations and comments:		
Injection technique of vaccinator (s): (Observe another session in the same locality –same or different place)		
Correct dose and route?		
Time of reconstitution mentioned on the vial (in case of freeze dried vaccines)?		
Non-touch technique followed?		
Contraindication screened prior to vaccination?		
How many AEFI reported from the center that distributed the vaccine in the last 30 days?		
Training received by the vaccinator: (Title)		If YES, specify date of last training ____/____/____
Specific key findings/additional observations and comments:		
V. COLD CHAIN AND TRANSPORT (Fill up this section by asking and observing practice)		
Last vaccine storage point:	YES/NO	Remarks
Type of vaccine storage: <input type="checkbox"/> Freezer <input type="checkbox"/> Refrigerator <input type="checkbox"/> Dry Store <input type="checkbox"/> Other, specify:		
Temperature: Body of refrigerator _____ °C Freezer: _____ °C		
Correct procedure of storing vaccines, diluents and syringes followed?		
Any other item (other than vaccines and diluents) in the refrigerator or freezer?		
Partially used reconstituted vaccines in the refrigerator?		
Unusable vaccines in the refrigerator?		
If YES, check all that apply: <input type="checkbox"/> expired <input type="checkbox"/> no label <input type="checkbox"/> VVM Stage 3/4 <input type="checkbox"/> Frozen		
Unusable diluents in the storage area?		
If YES, check all that apply: <input type="checkbox"/> expired <input type="checkbox"/> manufacturer not matched <input type="checkbox"/> cracked <input type="checkbox"/> dirty ampule		
Specific key findings/additional observations and comments:		
Vaccine transportation:		
Vaccine carrier used: <input type="checkbox"/> Polyurethane Foam Insulation <input type="checkbox"/> Insulated Plastic Container <input type="checkbox"/> Styrofoam <input type="checkbox"/> Other, specify		
Vaccine carrier sent to the site on the same day of vaccination?		
Vaccination carrier returned from the site on the same day of vaccination?		
Condition of the vaccine carrier: Was ice-pack used?		
Specific key findings/additional observations and comments:		

AEFI Case Investigation Form

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VI. VACCINE DETAILS (Indicate vaccines provided at the site linked to AEFI on the corresponding day)									
Number of recipients immunized for each antigen at the session site. Attach record (s) if available	Vaccine Name								
	Total Doses Given								
NOTE: Provide explanation for each YES answers on the following:									YES/NO/#
a) When was the patient immunized? (Tick box below)									
<input type="checkbox"/> Within the first vaccinations of the session <input type="checkbox"/> Within the last vaccinations of the session <input type="checkbox"/> Unknown									
<input type="checkbox"/> Within the first few doses of the vial administered <input type="checkbox"/> Within the last doses of the vial administered <input type="checkbox"/> Unknown									
b) Was the recommendation for use of this vaccine not followed?									
c) Based on the investigation, does the vaccine (ingredients) administered could have been unsterile?									
d) Based on the investigation, does the vaccine's physical condition (e.g. color, turbidity, foreign substances etc.) was abnormal at the time of administration?									
e) Based on the investigation was there an error in vaccine reconstitution/preparation by the vaccinator (e.g., wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?									
f) Based on the investigation, was there an error in vaccine handling? (e.g. Break in cold chain during transport, storage and/or immunization session etc.)?									
g) Based on the investigation, was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?									
h) Number of OTHER recipients immunized from the concerned vaccine vial/ampule									
i) Number of OTHER recipients immunized with the concerned vaccine in the same session:									
j) Number of OTHER recipients immunized with the concerned vaccine having the same batch number in other locations: _____ Specify locations: _____									
k) Is this case a part of a cluster?									
If yes, how many other cases have been detected in the cluster?									
a. Did all the cases in the cluster receive vaccine from the same vial?									
b. If No, Number of vials used in the cluster (enter details separately)									
VII. COMMUNITY INVESTIGATION									
Any known similar events reported recently in the locality/community? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> UNK									
a. If YES, Describe:									
b. How many events/episodes?									
Of those affected, how many are: Vaccinated _____ Not vaccinated _____ <input type="checkbox"/> Unknown									
Other significant findings in the community									
VIII. CAUSALITY ASSESSMENT									
<input type="checkbox"/> NAEFIC					<input type="checkbox"/> RAEFIC				
<input type="checkbox"/> [A1] Vaccine product-related reaction					<input type="checkbox"/> [A4] Immunization anxiety-related reaction				
<input type="checkbox"/> [A2] Vaccine quality defect-related reaction					<input type="checkbox"/> [B1] Consistent temporal relationship but insufficient evidence				
<input type="checkbox"/> [A3] Immunization error-related reaction					<input type="checkbox"/> [B2] Conflicting trends of consistency and inconsistency with causality				
<input type="checkbox"/> error in vaccine handling					<input type="checkbox"/> [C1] Co-incidental - Underlying emerging condition (s)				
<input type="checkbox"/> error in vaccine prescribing or non-adherence to recommendations for use					or exposure to external factors/something				
<input type="checkbox"/> error in administration					other than vaccine				
<input type="checkbox"/> Other, specify _____					<input type="checkbox"/> [D] Unclassifiable/Inadequate information				

ANNEX D. Adverse events and treatment

Adverse event	Case definition	Treatment*	Vaccines
Acute flaccid paralysis (Vaccine associated paralytic poliomyelitis)	Acute onset of flaccid paralysis within 4 to 30 days of receipt of oral poliovirus vaccine (OPV), or within 4 to 75 days after contact with a vaccine recipient and neurological deficits remaining 60 days after onset, or death.	No specific treatment available; supportive care.	OPV
Anaphylactoid reaction (acute hypersensitivity reaction)	Exaggerated acute allergic reaction, occurring within 2 hours after immunization, characterized by one or more of the following: <ul style="list-style-type: none"> ▪ wheezing and shortness of breath due to bronchospasm ▪ one or more skin manifestations, e.g. hives, facial oedema, or generalized oedema. Less severe allergic reactions do not need to be reported. ▪ laryngospasm/laryngeal oedema 	Self-limiting; anti-histamines may be helpful.	All
Anaphylaxis	Severe immediate (within 1 hour) allergic reaction leading to circulatory failure with or without bronchospasm and/or laryngospasm/laryngeal oedema (See Annex E).	Epinephrine	All
Arthralgia	Joint pain usually including the small peripheral joints. Persistent if lasting longer than 10 days, transient : if lasting up to 10 days.	Self-limiting; analgesics	Rubella, MMR

Brachial neuritis	Dysfunction of nerves supplying the arm/shoulder without other involvement of nervous system. A deep steady, often severe aching pain in the shoulder and upper arm followed in days or weakness by weakness and wasting in arm/shoulder muscles. Sensory loss may be present, but is less prominent. May present on the same or the opposite side to the injection and sometimes affects both arms.	Symptomatic only; analgesics.	Tetanus
Disseminated BCG infections	Widespread infection occurring within 1 to 12 months after BCG vaccination and confirmed by isolation of <i>Mycobacterium bovis</i> BCG strain. Usually in immunocompromised individuals.	Should be treated with anti-tuberculous regimens including isoniazid and rifampicin.	BCG
Encephalopathy	<p>Acute onset of major illness characterized by any two of the following three conditions:</p> <ul style="list-style-type: none"> ▪ seizures ▪ severe alteration in level of consciousness lasting for one day or more ▪ distinct change in behaviour lasting one day or more. <p>Needs to occur within 48 hours of DTP vaccine or from 7 to 12 days after measles or MMR vaccine, to be related to immunization.</p>	No specific treatment available; supportive care.	Measles, Pertussis

Fever	The fever can be classified (based on rectal temperature) as mild (38 to 38.9°C), high (39 to 40.4°C) and extreme (40.5°C or higher). Fever on its own does not need to be reported.	Symptomatic; Paracetamol.	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: <ul style="list-style-type: none"> ▪ limpness (hypotonic) ▪ reduced responsiveness (hyporesponsive) ▪ pallor or cyanosis – or failure to observe/ recall 	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	Fluctuant or draining fluid-filled lesion at the site of injection. Bacterial if evidence of infection (e.g. purulent, inflammatory signs, fever, culture), sterile abscess if not.	Incise and drain; antibiotics if bacterial.	All
Lymphadenitis (includes suppurative lymphadenitis)	Either at least one lymph nodes 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).	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	Inflammation of the bone with isolation of <i>Mycobacterium bovis</i> BCG strain.	Should be treated with anti-tuberculous regimens including isoniazid and rifampicin.	BCG
Persistent inconsolable screaming	Inconsolable continuous crying lasting 3 hours or longer accompanied by high-pitched screaming.	Settles within a day or so; analgesics may help.	DTP, Pertussis
Seizures	Occurrence of generalized convulsions that are not accompanied by focal neurological signs or symptoms. Febrile seizures: if temperature elevated >38°C (rectal) Afebrile seizures: if temperature normal	Self-limiting; supportive care; paracetamol and cooling if febrile; rarely anticonvulsants.	All, especially Pertussis, Measles
Sepsis	Acute onset of severe generalized illness due to bacterial infection and confirmed (if possible) by positive blood culture. Needs to be reported as possible indicator of program error.	Critical to recognize and treat early. Urgent transfer to hospital for parenteral antibiotics and fluids.	All
Severe local reaction	Redness and/or swelling centred at the site of injection and one or more of the following: <ul style="list-style-type: none"> ▪ swelling beyond the nearest joint ▪ pain, redness, and swelling of more than 3 days duration ▪ requires hospitalization. Local reactions of lesser intensity occur commonly and are trivial and do not need to be reported.	Settles spontaneously within a few days to a week. Symptomatic treatment with analgesics. Antibiotics are inappropriate.	All

Thrombocytopenia	Serum platelet count of less than 50,000/ml leading to bruising and/or bleeding	Usually mild and self-limiting; occasionally may need steroid or platelets.	MMR
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. Needs to be reported as possible indicator of program error.	Critical to recognize and treat early. Urgent transfer to hospital for parenteral antibiotics and fluids.	All

***Brighton collaboration** has developed cases definitions for many vaccines reactions and available at: www.brightoncollaboration.org.

******Attending physician will still be the one to decide the individual patient management based on assessment of the illness.

ANNEX E. Recognition and Treatment of Anaphylaxis

Anaphylaxis is a very rare, unexpected, and occasionally fatal allergic reaction. It is reported even more rarely from developing countries. In addition, misdiagnosis of faints and other common causes of collapse as anaphylaxis, can lead to inappropriate use of epinephrine (dosage). Vaccinators should be able to distinguish anaphylaxis from fainting (vasovagal syncope), anxiety and breath-holding spells, which are common benign reactions.

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 some more time to recover fully.

An anxiety spell can lead to pale, fearful appearance and symptoms of hyperventilation (light-headed, dizziness, tingling in the hands and around the mouth). Breath holding occurs in young children and will lead to facial flushing and cyanosis. It can end in unconsciousness, during which breathing resumes. Anaphylaxis develops over several minutes up to a few hours 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.

Differences between a fainting attack and anaphylaxis		
Clinical features	Fainting	Anaphylaxis
Timing	Before, during or few minutes after injection	A short time, up to a few hours
Skin	Generalized pallor, cold clammy skin	Itching, generalized erythema, urticaria, swelling of lips, face, tingling around lips
Respiratory system	Normal breathing Shallow breathing	Tachypnea, difficulty in breathing, wheezing, stridor, hoarseness, cyanosis, recession of intercostal spaces
Cardiovascular	Bradycardia, weak pulse, carotid pulse felt , hypotension may occur - reversed by supine position	Tachycardia, weak pulse, carotid pulse may be weak, hypotension - not reversed by supine position

GIT	Vomiting	Vomiting, diarrhea, abdominal cramps
CNS	Faintishness, light headedness relieved by supine posture	Anxiety and distress, loss of consciousness not relieved by supine posture
Panic attack - No hypotension, pallor, wheeze, or urticarial rash or swelling. May have flushing or blotchy skin		


Before immunization, check for contraindications to immunization by asking about known allergies and previous adverse reactions to vaccines. In cases of possible serious allergies, check with a specialist before giving the vaccine.

Recognition

Anaphylaxis is a severe reaction of rapid onset, characterized by circulatory collapse. The early signs of anaphylaxis are generalized erythema and urticaria with upper and/or lower respiratory tract obstruction. In more severe cases, limpness, pallor, loss of consciousness and hypotension become evident in addition. Vaccinators should be able to recognize the following signs and symptoms of anaphylaxis:

Diagnostic features of anaphylaxis	
Respiratory	<p>Airway</p> <ul style="list-style-type: none"> • Throat and tongue swelling (pharyngeal/laryngeal edema) - the patient has difficulty in breathing and swallowing and feels that the throat is closing up. • Hoarse voice. • Stridor <p>Breathing</p> <ul style="list-style-type: none"> • Bronchospasm • Respiratory distress—2 or more of the following: <ul style="list-style-type: none"> ○ Tachypnoea ○ Increased use of accessory respiratory muscles ○ Recession ○ Cyanosis • Grunting • Respiratory arrest
Cardiovascular	<ul style="list-style-type: none"> • Hypotension • Clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following: <ul style="list-style-type: none"> ○ Tachycardia ○ Capillary refill time >3 s ○ Reduced central pulse volume ○ Decreased level of consciousness or loss of consciousness • Cardiac arrest • Bradycardia (a slow pulse) is usually a late feature, often preceding cardiac arrest

CNS	<ul style="list-style-type: none"> • Confusion/Agitation • Headache • Loss of consciousness
Dermatologic or mucosal	<ul style="list-style-type: none"> • Tingling of lips • Generalized urticaria or generalized erythema • Angioedema, localized or generalized (angioedema is similar to urticaria but involves swelling of deeper tissues, most commonly in the eyelids and lips, and sometimes in the mouth and throat). • Generalized itching of skin especially hands, forehead and eyes in children <p><i>Note: skin changes alone without life-threatening cardio-respiratory signs do not signify an anaphylactic reaction</i></p>
Gastrointestinal	<ul style="list-style-type: none"> • Diarrhea • Colicky abdominal pain • Vomiting • Incontinence

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

In general, the more severe type of reaction, the more rapid 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.

Treatment

Epinephrine: Stimulates the heart and reverses the spasm in the blood vessels and the lung passages, reduces oedema and urticaria, thus countering the anaphylaxis. But this very potent agent can cause irregular heartbeat, heart failure, severe hypertension, and tissue necrosis if used in inappropriate doses and routes, but not in anaphylaxis.

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. Epinephrine that has a brown tinge must be discarded.

Recommended minimum items for an emergency tray	
<u>Evaluation equipment</u> <ul style="list-style-type: none"> • Sphygmomanometer <ul style="list-style-type: none"> ○ adult and child cuffs) • Stethoscope 	<u>Drug (local)</u> <ul style="list-style-type: none"> • Clearly labeled adrenaline (Epinephrine) vials • Hydrocortisone vials • Chlorphenamine vials • Oxygen
<u>Treatment equipment</u> <ul style="list-style-type: none"> • Tourniquet • Disposable syringes • Alcohol swabs • IV solutions (LR, 0.9% Sodium chloride) 	<u>Resuscitation equipment</u> <ul style="list-style-type: none"> • Pocket mask with –way valve • Airways (small, medium, and large) • Ambu bag • Tongue depressors • ET tubes
Other materials: Laminated copy of updated protocol, Event record sheet/Pen/Pen torch	

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

- Place the unconscious recipient in the recovery position and ensure the airway is clear.
- Assess breathing and pulse (if strong carotid pulse is not anaphylaxis).
- If appropriate begin cardiopulmonary resuscitation.
- Give adrenaline (see below for dosage) by deep intramuscular injection.
- If the recipient is conscious after the adrenaline is given, place the head lower than the feet and keep the recipient warm.
- Give oxygen by facemask, if available
- 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.
- If there is no improvement in the recipient's condition 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.

Note: Hydrocortisone and anti-histamine may be used as adjunctive medication. Nebulized salbutamol is helpful for bronchospasm and nebulized adrenaline for laryngeal oedema.

Adrenaline in the <i>initial</i> management of acute anaphylaxis			
Drug, site and route of administration	Frequency of administration	Dose (adult)	Dose (child) *
Adrenaline (epinephrine) 1:1000, IM to the midpoint of the anterolateral aspect of the middle third of the thigh immediately	Repeat in every 5–15 min as needed until there is resolution of the anaphylaxis. <i>Note: Persisting or worsening cough associated with pulmonary oedema is an important sign of adrenaline overdose and toxicity.</i>	0.5 mL	According to age; <1years: 0.05mL 2-6 years: 0.15 mL 6-12 years: 0.3 mL Children > 12 years: 0.5ml

*Note: The needle used for injection needs to be sufficiently long to ensure that the adrenaline is injected into muscle. This treatment guide is optional and countries may practise their own country-specific protocols for treatment of anaphylaxis with drugs of choice, steps to be followed and etc..

ANNEX F. Checklist for Immunization Safety Surveillance

CHECK LIST FOR IMMUNIZATION SAFETY SURVEILLANCE SYSTEM

1. Be prepared

- Clarify respective roles of the national regulatory authority and EPI, and agree on the overall goal and specific objectives for the system.
- Identify the resources available and needed and establish political commitment to immunization safety surveillance.
- Appoint or designate regional/national assessors for immunization safety.
- Establish expert regional/national Immunization Safety Committee.
- Develop and disseminate a list of events to be reported and their case definition; a standard investigation procedure; and AEFI report and investigation forms.
- Designate and train staff to make reports (At lowest level: local public health authority), complete report forms and investigate AEFI.
- Inform all health workers/clinicians of the need to report immediately an AEFI, and which ones should be reported.
- Consider establishment of a compensation scheme for specified AEFI.

2. Receive a report (Investigating authority)

- Decide if the report is a genuine AEFI according to your definition, and whether it needs investigating and/or advising to the public/media.
- Travel to the location of the AEFI, or delegate responsibility to another trained person or team to do this.
- Decide if need to communicate with community and/or media to alleviate concern.

3. Investigate and collect data

- Ask about the patient, the event, and the vaccine.
- Ask about immunization service and observe it in action (emphasise that aim is to find system error not to blame individual).
- Formulate a working hypothesis as to what was the cause of the AEFI.
- If appropriate, collect and dispatch specimens to the laboratory.

4. Analyze the data

- Review on-site investigation, clinical findings, and laboratory results (if sent).
- Review epidemiological findings e.g. clustering of cases in time or space or by vaccine manufacturer or lot.
- Summarise findings and complete Investigation Form.

5. Take action

- Communicate with health staff (e.g. treatment, information).
- Communicate findings and action to the parents and public (and media).
- Correct problem (based on the cause) by improving training, supervision, and/or distribution of vaccines/injection equipment (see Table 12).

ANNEX G. VACCINE PREVENTABLE DISEASES RISKS

Disease	Disease Risk
Diphtheria	
<p>Diphtheria is a potentially acute disease caused by exotoxin-producing <i>Corynebacterium diphtheriae</i>. Morbidity and mortality result from the bacterial toxin that may cause obstructive Pseudo-membranes in the upper respiratory tract (croup) or damage to myocardium and other tissues. Devastating diphtheria epidemics affecting mainly children have been described from many countries throughout history. Diphtheria toxoid is one of the oldest vaccines in current use.</p> <p>Largely eliminated from the WPR through successful immunization.</p>	<p><u>Complication</u></p> <p>Heart 10%-25%</p> <p>CNS 20%</p> <p><u>Mortality</u> 2%-10%</p>
Haemophilus influenzae type b (Hib)	
<p><i>Haemophilus influenzae b (Hib)</i> is a common cause of bacterial meningitis, pneumonia and septicemia in children. In industrialized countries and some parts of the developing world, immunization has greatly reduced the incidence of Hib disease.</p> <p>Risk peaks in the second six months of life, then decreasing to become very rare after the fifth birthday.</p>	<p><u>Disability</u></p> <p>Neurological Impairment 15%-30%</p> <p><u>Mortality</u> 5%</p> <p>Hib infection may manifest in a variety of systems leading most often to meningitis, pneumonia, epiglottitis. Also causes septicaemia, cellulitis (often facial), septic arthritis, osteomyelitis</p>
Hepatitis B	
<p>Caused by hepatitis B virus (HBV), is a major cause of acute and chronic hepatitis in the world. The rate of progression from acute to chronic hep B is primarily determined by the age of infection, the rate being approximately 80-90% for those infected during the first year of life, 30-50% for infections between the age of 1-4 years, and 5-10% for adult-acquired infection. An estimated 350 million people worldwide have chronic HBV infection.</p>	<p><u>Mortality</u></p> <p>Acute hepatitis B <1%</p> <p>Chronic hepatitis B 2%</p> <p><u>Complications</u></p> <p>Cirrhosis 5%</p> <p>Hepatocellular carcinoma (HCC)* 5%</p> <p>Lifetime risk of infection up to</p>

Carrier prevalence of HBV differs in different parts of the world, and within country too. HBV, though similar to HIV in its primary routes of transmission, is hundred times more infectious than HIV.	50% (or even higher) in some countries of Western Pacific compared to about 5% in Europeans.
Human Papilloma Virus infections	
Human papilloma virus (HPV) comprise of many genotypes which are associated with a diverse spectrum of clinical manifestations. In the genital tract, HPV infections are the commonest sexually transmitted viral infections leading to cervical cancer. Globally, cervical cancer is the second highest cause of cancer deaths in women and in many developing countries it remains the leading cause. Prophylactic vaccines available are not therapeutic to combat existing infection.	5%-10% of infected women will progress persistent infection leading to precancerous lesions. HPV caused 70% of cervical cancer. <u>Morbidity</u> Around 0.5million/year <u>Mortality</u> Around 0.25 million/year
Influenza	
Human influenza viruses comprise three serologically distinct types: A, B and C. Type A infection occurs more frequently and is responsible for most amounts of mortality and morbidity associated with epidemics and pandemics. The capacity of Influenza A and B viruses to undergo gradual antigenic change in their surface antigens complicates vaccination against the disease. It also necessitates annual changes in influenza vaccine strains and annual administration of the vaccine.	<u>Morbidity</u> 1918 Pandemic- 500million cases <u>Mortality</u> 1918 Pandemic – 50-100 million 2009 Pandemic – 18,000
Japanese Encephalitis	
Japanese encephalitis (JE), caused by a mosquito borne flavi virus, transmitted in Asia to North Australia. Children are highly susceptible to JE.	<u>Morbidity</u> 30,000-50,000 cases/year <u>Disability</u> Residual neurological psychiatric sequale 25%-40% <u>Mortality</u> Up to 0.3%-60%

Meningococcal disease	
<p>Bacteria called <i>Neisseria meningitidis</i> (meningococcus) is a leading cause of meningitis and fulminant septicaemia and a significant public health problem in most countries. In temperate regions the number of cases increases in winter and spring. The largest burden of meningococcal disease occurs in an area of sub-Saharan Africa known as the meningitis belt.</p>	<p><u>Morbidity</u></p> <p>Developed countries 1-5/100,000</p> <p>Developing countries 10-25/100,000</p> <p><u>Mortality:</u></p> <p>Meningococcal meningitis 5% - 10%</p> <p>Fulminant septicaemia 15% - 20%</p> <p><u>Disability</u></p> <p>Meningococcal meningitis 5% - 10%</p>
Measles	
<p>Measles is an acute viral illness which is caused by a virus of the paramyxovirus family. It is the complications of measles that kill, rather than the disease itself. Complications of the disease are more common in children under the age of 5 years.</p> <p>It is high infectivity and can be a threat in situations of natural disasters and war, if preventative measures are not taken.</p> <p>Vaccination for measles has made a major impact on the morbidity and mortality in WPR/globally.</p>	<p>Otitis media 7%-9%</p> <p>Pneumonia 1%-6%</p> <p>Diarrhoea 6%</p> <p>Encephalitis 0.05%-1% (of these 15% die and 25% subsequently brain damaged)</p> <p>Subacute sclerosing Panencephalitis (SSPE) 0.001%</p> <p>Mortality 0.01-0.1%</p>
Mumps	
<p>Mumps is an acute viral illness caused by an RNA virus in the Paramyxoviridae family transmitted by respiratory droplets. Usually a disease affecting primary school and pre-school children and 85% of adults have evidence of past infection.</p>	<p>Aseptic meningitis 10%</p> <p>Pancreatitis (usually mild) 4%</p> <p>Encephalitis 0.06% -0.3%</p> <p>Deafness (Unilateral sensory) 0.007%</p> <p>Orchitis in postpubertal males up to 38% (little evidence that this leads to sterility)</p> <p>Oophoritis in post pubertal females 5%</p>

	<p><u>Mortality</u> 0.02%</p> <p>Mumps during the first trimester of pregnancy is associated with an increased incidence of spontaneous abortions. Nevertheless, no evidence has suggested any congenital malformations.</p>
Pertussis	
<p>Pertussis (whooping cough) caused by <i>Bordetella pertussis</i> is an important public health concern even in countries with high vaccination coverage. The clinical outcome of pertussis depends on factors such as age and vaccination status. Although most cases of clinically recognizable pertussis occur in older children, adolescents and adults, pertussis is often unrecognized because of its frequent atypical course. However, older age groups represent an important source of infection for susceptible infants. The main aim of pertussis vaccination is to reduce the risk of severe pertussis in infancy.</p>	<p><u>Complications</u></p> <p>Convulsions 1 - 3%</p> <p>CNS complications 0.1 to 0.3%</p> <p>Mortality (<1 year) 0.5%</p>
Pneumococcal Infections	
<p>Pneumococcal disease is recognized as the world's leading vaccine preventable child killer. The introduction of pneumococcal conjugate vaccine (PCV) has changed significantly the epidemiology of pneumococcal infections, including invasive pneumococcal diseases. Furthermore herd immunity has significantly reduced the incidence of such infections in the over 65 year age group, as well as in older children. Although there has been some increase in the incidence of pneumococcal infections caused by serotypes not covered by PCV, the overall incidence of pneumococcal disease has been significantly reduced.</p>	<p><u>Complications in invasive infection</u></p> <p>Hearing impairment Septicaemia Septic arthritis Osteomyelitis Pneumonia Meningitis</p> <p><u>Mortality</u> 1.4 million /year (<5 years)</p>

Poliomyelitis	
Although the global eradication program is rapidly clearing poliomyelitis from many parts of the world, the threat of reintroduction remains. Most infections were asymptomatic or non-specific febrile illness.	Aseptic meningitis ~ 1% Paralytic illness 1% <u>Mortality</u> 2%-10% <i>(for paralytic case, increase with age)</i>
Rubella	
Generally mild illness but can rarely cause more serious illness, similar to measles with encephalitis. If infected in first eight weeks of pregnancy up to 85% of infants will be affected with one or more defects, including deafness, blindness, brain damage and heart problems	Encephalitis 0.02% <u>Mortality</u> Neonatal deaths 0.02% Other death 0.0005% Fetal loss 0.005% <u>Congenital Rubella Syndrome (CRS):</u> Deaf children 0.06% Deaf-blind children 0.03% Mentally retarded children 0.014% Total CRS 0.16%
Tetanus	
Tetanus is an infectious bacterial disease caused by <i>Clostridium tetani</i> . Under favorable anaerobic conditions it may produce tetanospasmin, an extremely potent neurotoxin. The disease may affect any age group and protection against tetanus is antibody-dependent and can be achieved only through active (tetanus vaccine) or passive (tetanus-specific immunoglobulin) immunization. The immunized mother passes antitoxin via the placenta to her fetus, thereby preventing neonatal tetanus.	<u>Mortality</u> Neonatal tetanus (without treatment) 95% Neonatal tetanus (with treatment) 20-90%
Typhoid	
Typhoid fever is a life-threatening illness caused by the bacterium <i>Salmonella</i> Typhi. Typhoid can be prevented and can usually be treated with antibiotics. A person may become an asymptomatic carrier of typhoid fever, suffering no symptoms, but capable of infecting others. Approximately 5% of people who contract typhoid continue to carry the disease after they recover.	<u>Morbidity</u> With an estimated 16–33 million cases/year; an average 21 million cases/year. Its incidence is highest in children and young adults between 5 and 19 years old

Large scale vaccine trials provide supportive evidence that mass vaccination strategies are resulted in significant protection against typhoid fever.	<u>Mortality</u> CFR 1-4% and 20,000 – 600,000 deaths in endemic areas/year
Tuberculosis	
<p>Tuberculosis is a chronic disease caused by <i>Mycobacterium tuberculosis</i>. Primary infection often goes unnoticed clinically; tuberculin sensitivity appears within few weeks and lesions commonly become inactive. It may progress to pulmonary tuberculosis, military tuberculosis or meningitis. The only vaccine available for the prevention of tuberculosis is BCG (Bacillus Calmette Guerin), which was first developed in 1920s.</p> <p>Infants, young children, older people and the immuno-compromised are more likely to progress rapidly to severe generalized infection with a poorer outcome</p>	<u>Morbidity</u> 8.8million cases/year (2010) The risk of infection is variable. 95% of those infected enter a latent phase from which there is a lifelong risk of reactivation. <u>Complication</u> The other 5% progress directly to pulmonary tuberculosis or by lympho-haematogenous dissemination of bacilli to miliary, meningeal or other extrapulmonary involvement. Extra pulmonary manifestations occur in 15% of adults and 25% of children <u>Mortality</u> 1.45 million/year (2010)
Varicella Infection (Chicken Pox)	
<p>Varicella is an acute infectious disease caused by Varicella Zoster virus (VZV). Varicella, the primary infection, is also called as Chickenpox. The secondary or recurrent infection is caused reactivated VZV associated with Herpes Zoster, also known as ‘Shingles’.</p> <p>Is primarily a disease of children under 10 years of age in most parts of the world, particularly in temperate region? Now it has even more frequently reported in adult and in subtropics it is equally distributed between children and adults. It is a highly contagious disease with an attack rate of up to 90% following exposure of susceptible individuals.</p>	<u>Complications</u> pneumonia aseptic meningitis/ encephalitis transverse myelitis GBS, Myocarditis, arthritis, orchitis, uveitis, iritis and hepatitis

ANNEX H. Method of Causality Assessment Checklist

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

*Y- Yes, N- No, U-Unknown, NA- Not Applicable

ANNEX I. Websites on vaccine safety

Brighton Collaboration	www.brightoncollaboration.org
Centre for Disease Control (CDC), USA	www.cdc.gov/nip/vacsafe www.cdc.gov/vaccinesafety/Activities/VSD.html http://www.cdc.gov/vaccines/recs/acip/default.htm
Centre For Disease Control And Prevention	http://www.chinacdc.cn/en/
Council for International Organizations of Medical Sciences (CIOMS)	http://www.cioms.ch/
Dept of Health, UK	http://www.dh.gov.uk/en/Publicationsandstatistics/ Publications/
<i>Korea</i> Centre For Disease Control And Prevention	http://www.cdc.go.kr/
Public Health Agency of Canada	http://www.phac-aspc.gc.ca/im/index-eng.php
Public Health, Depart of Health, South Australia	www.health.sa.gov.au/pehs
Therapeutic Goods Administration, Australia	http://www.tga.gov.au/ http://www.ich.org
The international Conference on Harmonization	
World Health Organization	www.who.int/gpv-safety www.who.int/immunization/sage/en http://www.who.int/vaccine_safety/en/ http://www.wpro.who.int/health_topics/immunization/
Aide memoires on investigation causality assessment	http://www.who.int/vaccine_safety/en/
Vaccine information sheet	http://www.who.int/vaccine_safety/initiative/tools/ vaccinfosheets/en/index.html

Annex J. References

1. Immunization Safety Surveillance:
Guidelines for Managers of Immunization Programmes
on Reporting and Investigating Adverse Events Following Immunization
World Health Organization,
Western Pacific Regional Office (WPRO)
<http://www.who.org.ph>
2. Causality assessment of an adverse event following immunization (AEFI):
User manual for the revised classification. March 2013
<http://www.who-umc.org/index2.html>
3. Verbal autopsy standards:
Ascertaining and attributing cause of death.
Geneva: World Health Organization; 2007,
<http://www.int/healthinfo/statistics/verbalautopsystandards/en/index1>
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