# Immunization Safety Surveillance

Guidelines for immunization programme managers
on surveillance of adverse events following immunization

**Second Edition**

World Health Organization
Western Pacific Region

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# Preface

This document aims to assist managers in immunization programme and national regulatory authorities to establish/strengthen immunization safety surveillance system.

The first Regional Immunization Safety Surveillance: Guidelines for Managers of Immunization Programmes on Reporting and Investigating Adverse Events Following Immunization was published in 1999. Over the following decade, significant developments had been made in the field of immunization safety, both in knowledge and practices. In 2012, Expanded Programme on Immunization (EPI), at the WHO Regional Office for the Western Pacific, took initiative for an extensive revision of the guidelines to include all updated information. Dr Ananda Amarasinghe, Dr Md. Shafiqul Hossain, Dr Sato Yoshikuni and Dr Sergey Diorditsa reviewed and revised the guidelines.

The writers acknowledge the support from other team members of EPI unit and EPI focal points at country levels in the Western Pacific Region. They are also grateful for valuable comments and support received from Global Vaccine Safety team members of WHO Headquarters as well as from other partners.

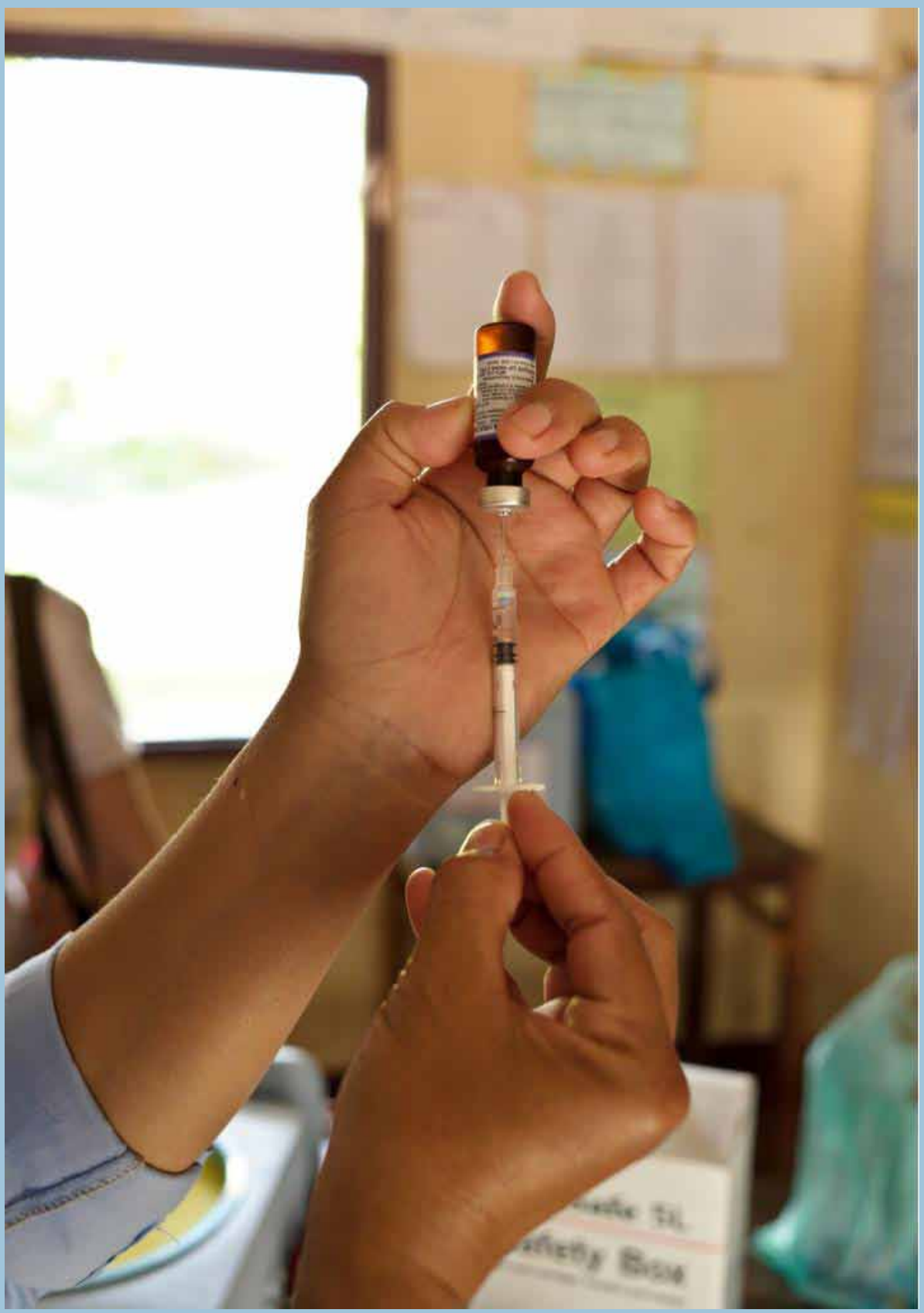
# Glossary

| | |
|---|---|
| Adverse event following immunization (AEFI) | Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. |
| Causal association/link | An AEFI which is caused by administration of a particular vaccine. Causally associated events are also temporally associated (i.e. they occur within a limited time period after vaccine administration), but events which are temporally associated may not necessarily be causally associated. |
| Cluster | Two or more cases of the same or similar events related in time, geography, and/or vaccine administered. National programme managers may decide upon a more precise definition. |
| Coincidental adverse events | A medical event that occurs after immunization, but is not caused by the vaccine. It would have occurred whether or not the individual had received an immunization prior to the event. This occurs due to a chance temporal association. |
| Injection safety | The public health practices and policies dealing with various aspects of the use of injections (including adequate supply, administration and waste disposal) so that the risk of transmission of bloodborne pathogens is minimized. All injections, irrespective of their purpose, are covered by this term (see definition of safe injection practices). |
| Immunization safety | The public health practices and policies dealing with the various aspects of the correct administration of vaccines, focussing on minimizing the risk of transmission of disease with the injection and maximizing the effectiveness of the vaccine. The term encompasses the spectrum of events from proper manufacture to correct administration. |
| Immunization safety surveillance | A system for ensuring immunization safety through detecting, reporting, investigating, and responding to AEFIs. |
| Minor AEFI | An event that is not 'serious' and does not pose a potential risk to the health of the recipient. |
| Safe injection practice | Those public health practices and policies which ensure that the process of injection carries the minimum of risk, regardless of the reason for the injection or the product injected. |
| Serious AEFI | An event that is causing a potential risk to the health/life of a recipient leading to hospitalization, disability/incapacity, congenital abnormalities/birth defects or death. |

| | |
|---|---|
| Surveillance | The continuing, systematic collection of data that are analysed and disseminated to enable decision-making and action to protect the health of populations. |
| Trigger event | A medical incident following immunization that stimulates a response, usually a case investigation. |
| Vaccine | Biological substance that is administered to individuals to elicit immunity (protection) against a specific disease. |
| Vaccine pharmacovigilance | The science and activities relating to the detection, assessment, understanding and communication of AEFIs and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization. |
| Vaccine reaction | An event caused or precipitated by the active component or one of the other components of the vaccine (e.g. adjuvant, preservative or stabilizer). This is due to inherent properties of the vaccine. |
| Vaccination failure | Vaccination failure may be defined on the basis of clinical endpoints or immunological criteria where correlates or surrogate markers for disease protection exist. Primary failure (e.g. lack of seroconversion or seroprotection) needs to be distinguished from secondary failure (waning immunity).<br>Vaccination failure can be due to (i) vaccine failure, or (ii) failure to vaccinate, i.e. an indicated vaccine was not administered appropriately for any reason. |

# Abbreviations

| | |
|---|---|
| AEFI | adverse event following immunization |
| BCG | bacillus Calmette-Guerin vaccine for tuberculosis (TB) |
| CFR | case-fatality rate |
| CIOMS | Council for International Organizations of Medical Sciences |
| CISA | Clinical Immunization Safety Assessment Network |
| CNS | central nervous system |
| CRS | congenital rubella syndrome |
| DT | diphtheria-tetanus vaccine |
| DTP | diphtheria-tetanus-pertussis vaccine |
| DTaP | diphtheria-tetanus-pertussis (acellular) vaccine |
| DTwP | diphtheria-tetanus-pertussis (whole-cell) vaccine |
| EPI | Expanded Programme on Immunization |
| GIT | gastrointestinal tract |
| HCC | hepatocellular carcinoma |
| Hib | Haemophilus influenzae type b vaccine |
| HPV | human papilloma virus |
| ICH | International Conference on Harmonization |
| IPV | injectable polio vaccine |
| MMR | measles-mumps-rubella vaccine |
| MR | measles-rubella vaccine |
| NRA | national regulatory authority |
| NCL | national control laboratory |
| OPV | oral poliomyelitis vaccine |
| PCV | pneumococcal conjugate vaccine |
| PMS | post-marketing surveillance |
| PvV | pentavalent (DTP-HepB-Hib) vaccine |
| SSPE | subacute sclerosing panencephalitis |
| Td | adult tetanus-diphtheria vaccine |
| TSS | toxic shock syndrome |
| VAPP | vaccine-associated paralytic poliomyelitis |
| VPD | vaccine preventable disease |
| WHO | World Health Organization |
| WPR | Western Pacific Region |



# Purpose

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. Some people experience adverse events after immunization ranging from mild side-effects to rare life-threatening illnesses. In the majority of serious cases these events are merely coincidences. In others, they are caused by the vaccine or by an error in the administration or handling of the vaccine. Sometimes there is no causal relationship between the vaccine and the adverse effects. Maintaining public trust in vaccine safety, therefore, is key to the success of all vaccination programmes.

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. Surveillance of AEFIs, i.e. systematic collection of data on events following immunization, provides valuable information to help plan and take necessary actions in order to sustain public confidence and ensure smooth functioning of the programme.

This document provides guidelines for managers of immunization programmes (and others responsible for vaccine safety and quality) on the following:

- strategies and systems for ensuring quality and safety of vaccines,
- new classification of AEFIs and the objectives of immunization safety/AEFIs surveillance,
- understanding vaccine reactions for better decision-making,
- AEFI surveillance system: reporting, investigating, causality assessment and responding processes,
- best use of surveillance data, and
- communication strategy on immunization safety for the public and the media.

As VPDs become less visible through effective immunization programmes, more attention will be given to AEFIs. A good example is poliomyelitis. When there are many cases of poliomyelitis in the community, the very low risk (about 1 in 3 million) of vaccine-associated paralytic poliomyelitis (VAPP) is unlikely to cause a major concern. Western Pacific Region has been free from polio since 2000. In countries where there is no longer any wild poliovirus existent, VAPP have become more visible. As a result, VAPP has become a sufficient concern and these countries have switched from oral (OPV) to injectable poliomyelitis vaccine (IPV).

As technology continues to improve with time, so do the quality, efficacy (level of protection) and effectiveness (disease reduction) of the vaccines. New vaccines are being

added to the programme and the schedule becomes more tight and congested. Instead of triple vaccine (DTP), most countries are now using either tetravalent (DTP-Hib or DTP-HepB) or pentavalent (DTP-HepB-Hib) vaccines. Also with emerging diseases, such as H1N1 influenza, demand for new vaccine has increased. An increase in vaccine use (e.g. mass immunization campaigns) will lead to more vaccine reactions as well as more coincidental events. Immunization errors (previously known as "programme errors") may also increase. Reporting and investigating AEFIs can be used to identify and correct immunization errors-related reactions and may help to distinguish a coincidental event from a true AEFI. Surveillance of AEFIs is an effective means of monitoring immunization safety and it contributes to the credibility of the immunization programme. It allows for proper management of AEFIs and avoids inappropriate responses to reports of AEFIs that can create a sense of crisis in the absence of immunization safety surveillance.

Public alertness regarding vaccine safety has increased through awareness and increased access to information through the internet. Also, the vigilance of health-care providers on vaccine safety has increased due to strengthening of AEFI surveillance. As a result, more concerns on quality and safety of vaccine are highlighted and/or demanded by service providers and the public. With this increasing complexity in the immunization context, to determine whether a vaccine is causally linked to an AEFI or the AEFI is a mere coincidence requires detailed investigation and causality assessment.

In order to maintain and improve public confidence in national immunization programmes, all health-care providers should be comprehensively aware of all aspects of AEFIs and remain prepared to respond to public concerns at 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 programme. After recognizing the need for such a concerted action on vaccine safety, WHO conducted a landscape analysis. The analysis provides an overview of existing structures, activities and needs of vaccine safety stakeholders and initiatives at national and international levels. Based on the landscape analysis, the Global Vaccine Safety Blueprint, a framework aiming to optimize the safety of vaccines through effective use of state of the art pharmacovigilance principles and methods was developed in a collaborative process. The Blueprint suggests three strategic goals that identify three areas of work at different levels. The first goal is to ensure minimal capacity in all countries, the second to provide enhanced capacity for specific circumstances, and the third to establish a global support network.

Countries in the Western Pacific Region represent vast differences in demographic, socio-economic and geographic status. Immunization service functions in the Region too demonstrate a significant variance in capacities. Several vaccines are used, and the capacity for immunization safety surveillance is generally varied. It is hoped that these guidelines will help countries in the Region to either adapt them with necessary modifications or use them as they are to develop a country-specific immunization safety/AEFIs surveillance guideline. The goals of these guidelines are to improve efficiency of surveillance activities of AEFIs and to improve the quality of immunization services at the country and regional levels, and, finally, to ensure immunization safety of all recipients of vaccines leading towards achieving the goals and objectives of the immunization programme globally.

# Principles of immunization and vaccine

## 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.

There are two basic mechanisms for acquiring immunity: active and passive.

### 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 very 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.

Many factors may influence the immune response to vaccination. These include the presence of maternal antibody, nature and dose of antigen, route of administration, and the presence of an adjuvant (e.g. aluminium containing material) added to improve the immunogenicity of the vaccine. Host factors such as age, nutritional factors, genetics and coexisting disease may also affect the response.

### Passive immunity

Passive immunity is the transfer of antibody produced by one human or animal to another. Passive immunity provides protection against some infections, but this protection is temporary. The antibodies degrade over time. The most common form of passive immunity is that which an infant receives from its mother. The antibodies received from the mother protect the infant from certain diseases for up to a year.

### Herd immunity

Herd immunity (or community immunity) describes a type of immunity that occurs when the vaccination of a portion of the population (or herd) provides protection to unprotected

individuals. Herd immunity theory proposes that in diseases passed from individual to individual it is difficult to maintain a chain of infection when large numbers of a population are immune. The higher the number of immune individuals, the lower the likelihood that a susceptible person will come into contact with an infectious agent. From both theoretical and practical perspectives, disease usually disappears before immunization levels reach 100%, as has been seen with smallpox and poliomyelitis. The proportion of immune individuals in a population above which a disease may no longer persist is the herd immunity threshold. Its value varies with the virulence of the disease, the efficacy of the vaccine, and the contact parameter for the population.

### How does immunization work?

There are many types of vaccines, but they all work in the same general way, by preparing the immune system to attack the infection. Basically, vaccine contains components that are more or less similar to the infecting organism, and so the immune system responds as it would to an infection with that organism. The most important consequence of successful vaccination is that it produces long-lived memory lymphocytes that respond more quickly and in a more co-coordinated way to subsequent infections. As a result, the infectious microbe is destroyed more quickly. Protection is not always complete; an infection may not be always prevented but the severity of the illness is usually reduced.

The first exposure to a vaccine stimulates the immune response (known as priming). The immune system takes time to respond to the antigen by producing antibodies and immune cells. Initially, immunoglobulin M (IgM) antibody is produced but this occurs in small amounts and does not bind very strongly to the antigen. After a few days, the immune response begins to make immunoglobulin G (IgG) antibody which is more specific to the microbe and lasts longer than IgM.

Subsequent administration of the same vaccine stimulates the secondary response. The secondary response is much faster than the primary response and produces predominantly IgG rather than IgM. The aim is to generate enough immune cells and antibodies, specific to the infectious microbe, to provide long-lasting protection against the disease.

## Vaccine

Vaccine is a biological product that improves and enhances immunity to a given disease. A vaccine contains a disease-causing microorganism, or portion of it, and is often made from either live-attenuated or inactivated (killed) forms of the microbe, its toxin or one of its surface proteins.

Vaccines may be monovalent or multivalent. A monovalent vaccine contains a single strain of a single antigen (e.g. measles vaccine), whereas a polyvalent vaccine contains two or more strains/serotypes of the same antigen (e.g. OPV).

Combined vaccines contain two or more antigens (e.g. DTwP, DTP-HepB-Hib). Potential advantages of combination vaccines include reducing the cost of stocking and administering separate vaccines, reducing the cost of extra health-care visits, improving timeliness of vaccination, and facilitating the addition of new vaccines into immunization programmes.

**Key point**

No evidence exists that the administration of several antigens in combined vaccines increases the burden on the immune system which is capable of responding to millions of antigens at a time. Combining antigens usually does not increase the risk of adverse reactions and can, in fact, lead to an overall reduction in adverse reactions.

## Classification of vaccines

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

### Live-attenuated vaccines (LAV)

LAV are derived from "wild," or disease-causing, virus or bacteria. These wild viruses or bacteria are attenuated, or weakened, in a laboratory, usually by repeated culturing. The resulting vaccine organism retains the ability to replicate (grow) in the vaccinated person and produce immunity, but usually does not cause illness. The immune response to a LAV is virtually identical to that produced by a natural infection.

For LAV, the first dose usually provides protection. An additional dose is given to ensure seroconversion. For instance, 95% to 98% of recipients will respond to a single dose of measles vaccine. The second dose is given to assure that nearly 100% of persons are immune (i.e. the second dose is "insurance"). Immunity following live vaccines is long-lasting, and booster doses are not necessary, with the exception of oral polio vaccine, which requires multiple doses. LAV are labile, and can be damaged or destroyed by heat and light. They must be handled and stored carefully. Currently available LAV include measles, mumps, rubella, varicella, yellow fever, oral polio and influenza (intranasal). Live-attenuated bacterial vaccines include BCG and oral typhoid vaccine.

### Inactivated whole-cell vaccines

Inactivated vaccines are produced by growing viruses or bacteria in culture media and then inactivating them with heat or chemicals (usually formalin). Because they are not alive, they cannot grow in a vaccinated individual and, therefore, cannot cause the disease, even in an immunodeficient person. Inactivated vaccines are generally safer than LAV, with no risk of inducing the disease. Unlike live antigens, inactivated antigens are usually not affected by circulating antibody. They are often more stable than LAV.

Growing whole bacteria (e.g. whole-cell pertussis vaccine) or viruses (e.g. inactivated poliomyelitis vaccine) in culture media, then treating them with heat and/or chemicals, produces an inactivated, non-viable vaccine.

Inactivated vaccines always require multiple doses. In general, the first dose does not produce protective immunity, but only "primes" the immune system. A protective immune response is developed after multiple subsequent doses. In contrast to live vaccines, in which the immune response closely resembles natural infection, the immune response to an inactivated vaccine is mostly humoral and little or no cellular immunity results. Antibody

titers against inactivated antigens diminish with time. As a result, some inactivated vaccines may require periodic supplemental doses to increase, or "boost," antibody titers.

### Subunit vaccines

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

#### Protein-based

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

#### Polysaccharide vaccines

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

#### Conjugated vaccines

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

### Toxoid vaccines

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

## Other components in vaccines (excipients)

### Adjuvant

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

### Antibiotics

Antibiotics are used during the manufacturing phase to prevent bacterial contamination of the tissue culture cells in which the viruses are grown. For example, MMR vaccine and IPV each contains less than 25 micrograms of neomycin per dose (less than 0.000025g). 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.

### Preservatives

These are chemicals (e.g. thiomersal, formaldehyde) 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.

### Stabilizers

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

**Key point**

Excipients are added to vaccines for different purposes and some of them are removed in subsequent manufacturing steps. However, minute "trace" amounts may remain in the final product. The amounts present are only of consequence for individuals who are allergic to them.

Note: WHO Uppsala monitoring centre is developing a vaccine dictionary with details of all excipients in vaccines available in immunization practices.

## 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 (Annex C). Most contraindications are temporary, and the vaccination can be administered later. The only contraindication applicable to all vaccines is a history of a severe allergic reaction after a prior dose of 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 (especially if the would be recipient is an immunocompromised or pregnant person. Precautions stated in product labeling can sometimes be inappropriately used as absolute contraindications, resulting in missed opportunities to vaccinate.

## Summary

- Immunity is described as the body's protective ability against disease. There are two basic mechanisms for acquiring immunity: active and passive.
- Active immunity can be either natural, following an infection, and can last a lifetime, or through vaccination, which also lasts for a long period.
- Passive immunity also can be either natural or artificial; both last relatively for a short period.
- Vaccine is a biological product that improves immunity to a given disease and is divided into four types: live-attenuated, inactivated whole cell (killed), subunit and toxoid.
- Excipients (adjuvant, preservatives and other additives) contained in vaccines can cause occasional reactions. Knowledge of them is important in immunization safety surveillance.

# Adverse events following immunization (AEFIs)

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

An AEFI is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. Reported adverse events can either be true adverse events, i.e. really a result of the vaccine or immunization process, or coincidental events that are not due to the vaccine or immunization process but are temporally associated with immunization.

In 2012, the Council for International Organizations of Medical Sciences (CIOMS) and WHO revised the existing classification relevant to cause-specific categorization of AEFIs and a new categorization has been introduced (Table 1).

**Table 1: Cause–specific categorization of AEFIs (CIOMS/WHO 2012)**

| Cause–specific type 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 (formerly "programme error") | 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. |

**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.

## Vaccine reactions

The new cause-specific categorization is important for decision-making on a vaccine product, since it clearly differentiates the two types of possible vaccine reactions. The first, vaccine product-related reaction, is a reaction in an individual's response to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly. The second, vaccine quality defect-related reaction, is the defect in a vaccine that occurred during manufacturing process. Such a defect may have an impact on an individual's response and thus increase the risk of adverse vaccine reactions. In early years of immunization programmes, a few major incidences of vaccine quality defect-related reactions were reported (e.g. Cutter case study). However, due to introduction of improved Good Manufacturing Practices (GMP) since, such defects are now very rare. Vaccine manufacturers follow GMP, and national regulatory authorities (NRA) have been strengthened by being able to avoid or minimize such 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.

**Case Studies**

I. A suspected link between Guillain-Barre Syndrome (GBS) and vaccinations was reported in the US in 1976, during a national campaign to vaccinate people against swine flu virus. Subsequent investigation found that vaccine recipients had a higher risk for GBS than those who were not vaccinated (about 1 additional case occurred per 100 000 people vaccinated). Given this association, and the fact that the swine flu disease was limited, the vaccination programme was stopped.

**Cause:** Vaccine product- related reaction

Note: It is not fully understood why some people develop GBS, but it is believed that the nerve cells are damaged by a person's immune system. Many types of infections, and in very rare cases vaccines, may activate the immune system to cause damage to the nerve cells.

II. In 1955, after administration of the Cutter laboratory manufactured inactivated polio vaccine in the US, 40 000 people developed abortive polio; 51 were permanently paralyzed and 5 died. Investigations revealed that two production pools of 12 000 doses contained live virus.

**Cause:** Vaccine quality defect-related reaction

### 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 likely to be observed with the most commonly used vaccines and their treatments are listed in Table 2.

**Table 2: Common, minor vaccine reactions and treatment**

| Vaccine | Local adverse events (pain, swelling, redness) | Fever (> 380C) | Irritability, malaise and systemic symptoms |
|---|---|---|---|
| BCG[1] | 90–95% | - | - |
| Hepatitis B | Adults up to 15%<br>Children up to 5% | 1–6% | - |
| Hib | 5–15% | 2–10% | - |
| Influenza inactivated | 10–64% | 5-12%[2] | - |
| Influenza live-attenuated | - | 16–31% | 4–23% |
| Japanese encephalitis (JE) inactivated | <4% | - | <1% |
| JE live-attenuated | <1% | - | - |
| Measles/MR/MMR | ~10% | 5–15% | 5% (Rash) |
| OPV | None | Less than 1% | Less than 1%[3] |
| Pertussis (DTwP)[4] | up to 50% | up to 50% | up to 55% |
| †Pnemucoccal conjugate | ~10% | ~20%<br><1% (>39°C) | ~20% |
| Pneumococcal unconjugated | 50% | <1% (>39°C) | |
| Tetanus/DT/aTd | ~ 10%[5] | ~ 10% | ~ 25% |
| Varicella | 7 - 30% | | |
| Treatment | • Cold cloth at injection site<br>• Paracetamol* | • give extra oral fluids<br>• wear cool clothing<br>• tepid sponge or bath<br>• Paracetamol* | |

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

2 Among children 1-15 years

3 Diarrhoea, headache and/or muscle pains

4 When compared with whole-cell pertussis (DTwP) vaccine, acellular pertussis (DTaP) vaccine rates are lower.

5 Rate of local reactions are likely to increase with booster doses, up to 50 -85%

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

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

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 be affected. BCG causes a specific local reaction that starts as a papule (lump) two or more weeks after immunization, which 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 about 10% or less of vaccinees, except for DTwP where the reactions are about half. Other common systemic reactions (e.g. irritability, malaise, 'off-colour', loss of appetite) can also occur after DTwP. For LAV 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. However, 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 15% suffering from joint pains. Systemic reactions from OPV affect less than 1% of vaccinees with diarrhoea, headache and/or muscle pain.

It is important to note that these observed rates are expected as vaccine reactions or response to vaccine antigen. However, in case of any significant increase of these observed rates for any vaccine, an investigation is needed to exclude possible adverse reaction to the given vaccine. (This will be described later under the cluster investigation.)

## Rare, more serious vaccine reactions

'Serious' and 'severe' are often used as interchangeable terms but they are not. An AEFI will be considered serious, if it results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or required intervention to prevent permanent impairment or damage. 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. (For example, 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.) Table 3 details the rare vaccine reactions; case definitions are in Annex B. Most of the rare and more serious vaccine reactions (e.g. seizures, thrombocytopenia, HHEs, 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.

## Table 3: Rare vaccine reactions, onset interval and rates

| Vaccine | Reaction | Onset interval | Rate / doses |
|---|---|---|---|
| BCG | Suppurative lymphadenitis | 2–6 months | $1–10/10^4$ |
| | BCG osteitis | 1–12 months | $1–700/10^6$ |
| | Disseminated BCG infection | 1–12 months | $0.19–1.56/10^6$ |
| Hib | None | | |
| Hepatitis B | Anaphylaxis | 0–1 hour | $1.1/10^6$ |
| Influenza (inactivated) | Anaphylaxis<br>Guillain-Barré syndrome (GBS)<br>Oculo-respiratory syndrome | | $0.7/10^6$<br>$1–2/10^6$<br>$76/10^6$ |
| Influenza (live-attenuated) | Anaphylaxis<br>Wheezing (children 6–11 months age) | - | $2/10^6$<br>14/100 |
| Japanese encephalitis (inactivated) | Neurologic events (encephalitis, encephalopathy§, peripheral neuropathy) | - | $1-2.3/10^6$ |
| Measles/MMR/MR* | Febrile seizures | 6–12 days | $3/10^3$ |
| | Thrombocytopaenia | 15–35 days | $3/10^4$ |
| | Anaphylaxis | 0–1 hour | $\sim 1/10^6$ |
| | Encephalopathy§ | 6–12 days | $< 1/10^6$ |
| Oral poliomyelitis | VAPP | 4–30 days | $2–4\ /10^{6\dagger}$ |
| Pertussis (DTwP) | Persistent (>3 hours) inconsolable screaming | 0–24 hours | <1/100 |
| | Seizures†† | 0–3 days | <1/100 |
| | Hypotonic, hypo responsive episode(HHE) | 0–48 hours | $1-2/10^3$ |
| | Anaphylaxis | 0–1 hour | $20/10^6$ |
| | Encephalopathy§ | 0–2 days | $0-1/10^6$ |
| Pneumococcal | None proven± | | |
| Rota virus | None known** | | |
| Tetanus toxoid, DT | Brachial neuritis | 2–28 days | $5–10/10^6$ |
| | Anaphylaxis | 0–1 hour | $1–6/10^6$ |
| Yellow fever | Vaccine-associated viscerotropic disease *** | | $1/10^6$ |
| Varicella | Febrile seizures | | $4–9\ /\ 10^{4\dagger\dagger}$ |

Notes:

* Reactions (except anaphylaxis) do not occur if already immune (~90% of those receiving a second dose are immune): children over six years unlikely to have febrile seizures.

† VAPP Risk is higher following the first dose (1 in 750 000 compared to 1 in 5.1 million for subsequent doses), and for adults and immunocompromised.

± No proven risk of severe febrile or anaphylactic reactions or neurological disorders (e.g. Guillain–Barré syndrome)

** Post-marketing surveillance of currently available rotavirus vaccines has detected a small increased risk of intussusception (~1-2 cases per 100 000 infants vaccinated) in some settings shortly after the first dose of rotavirus vaccine.

*** Very rare in children

††Seizures are mostly febrile and the risk depends on age, with much lower risk in infants under the age of four months.

§ 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.

Although other serious events have been reported following immunization, it is likely that these events are coincidental, not true reactions.

**Key point**

Comparing the observed rate of an adverse event in a single population with the 'expected rate' of this event for the vaccine used can help identify if an event is related to the immunization or not. WHO has developed vaccine-specific information sheets on observed rates of vaccine reactions that provide observed reaction rates found in literature.

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

### Prevention and treatment of vaccine 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 to a vaccine or its components. **Live vaccines should not be given to immunedeficient children.**

Advice on managing the common reactions should be given to parents, in addition to instructions to return if there are more serious symptoms. Such action will help to reassure parents about immunization and prepare them for common reactions.

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. A feverish child can be cooled with a tepid sponge or bath, and by wearing cool clothing. Extra fluids need to be given to feverish children. For a local reaction, a cold cloth applied to the site may ease the pain.

Practising 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 may also save life.

It is recommended that facilities be available at all clinic setting to provide initial emergency care. All immunization providers need to have skill and competence on managing anaphylaxis. Availability of adrenalin and other basic items in emergency tray is vital. (More details on treatment of vaccine reactions are in Annex B and for anaphylaxis in Annex C.)

## Immunization error–related reactions

"Immunization" as used here 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.

*Note: This AEFI type was earlier categorized as "Programme error" (Table 1)*

Immunization errors-related reactions are preventable and they derail the benefit of the immunization programme (Table 4). The identification and correction of these errors in a timely manner are, therefore, of great importance.

An immunization error-related reaction may 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 errors-related reactions can also affect many vials. For example, freezing vaccine during transport may lead to an increase in local reactions.

**Table 4: 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 diluent) where applicable.<br>Use of a product after the expiry date. | 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.<br>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.<br>Failure to adhere to vaccine indications or prescription (dose or schedule). | Anaphylaxis, disseminated infection with an attenuated live, VAPP.<br>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.<br>Incorrect sterile technique or inappropriate procedure with a multidose vial. | Failure to vaccinate due to incorrect diluent , Reaction due to the inherent properties of whatever was administered other than the intended vaccine or diluent.<br>Infection at the site of injection/ beyond the site of injection. |

In the past, the most common immunization error was an infection (including bloodborne 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 bloodborne virus infection (e.g. HIV, hepatitis B or hepatitis C). However, with the introduction of auto disabled (AD) syringes, infection occurrence has reduced significantly. 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 to 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, diarrhoea, cyanosis and a 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 increase the risk of sterile abscess and of 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).

Ignoring contraindication can lead to serious vaccine reactions and it is considered an immunization error. Immunization team should be clearly aware of absolute and temporary contraindications. Any uncertainty should call for a referral or consultancy from a higher level programme manager or paediatrician or physician. However, it is equally important not to overreact to concerns of false contraindications, which may lead to missed opportunity of vaccination, reduce coverage and, thereby, increase the risk of disease of both individuals and the community.

Also, health-care workers need to have a clear understanding of contraindications and precautions. Precautions are not contraindications, but decision on vaccination requires a case-based assessment. 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 foetus. The presumed risk is mostly theoretical and limited to LAV which have demonstrated evidence of potential risk and harm, particularly in animal models. Vaccine manufacturers instruct pregnancy as a contraindication not due to proven evidence, but as a precautionary measure against litigation.

To avoid immunization error:

- Vaccines must only be reconstituted with the 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 immunization centre.
- Immunization workers must be adequately trained and closely supervised to ensure that proper procedures are being followed.
- Careful epidemiological investigation of an AEFI is needed to pinpoint the cause and to correct immunization practices.
- Adequate attention must be given to possibility of contraindications.

Case studies

- In 1992, one hospital in country A, five neonates collapsed a few minutes following immunization with BCG. Four were resuscitated and one died. Muscle relaxant drugs were found in the refrigerator in which vaccines were also kept.

  **Cause:** Immunization error- related reaction. Use of muscle relaxant instead of diluents.

- In 2008–2009, in country B, during a school-based rubella immunization programme, two 14 year-old girls collapsed within a few minutes following immunization. The incidents occurred in two separate places and at different times. Both girls were hospitalized and later died.

  Investigation revealed that both had informed the immunization teams about past history of allergic reactions to some food products. Also there were no emergency kits to manage anaphylaxis.

  **Causes:** Immunization error-related reaction. Lack of attention on possible contraindication and precautions to manage anaphylaxis.

  Vaccine product-related reaction: Anaphylaxis is a known vaccine reaction to rubella vaccine.

- In 1997, in country C, 21 infants died out of 70 infants supposedly given DTP vaccine. Insulin was stored in similar vials and in the same refrigerator as DTP vaccine.

  **Cause:** Immunization error related reaction: Use of insulin instead of DTP.

## Immunization anxiety-related reactions

Individuals and groups can react in anticipation to and as a result of an injection of any kind. This reaction is unrelated to the content of the vaccine. Fainting 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.

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.

An anxiety reaction to injection can include convulsions in some case. These children do not need to be investigated but should be reassured.

These reactions are not related to the vaccine, but to the injection. Some individuals may be needle-phobic, aggravating such reactions. In a group situation, mass hysteria is possible, especially if a vaccinee is seen to faint or have some other reaction. Clear explanations about the immunization and calm, confident delivery will decrease the level of anxiety about the injections, and thus reduce the likelihood of an occurrence.

It is important to note that faintish attack (syncope) can be misdiagnosed as anaphylaxis. Health workers need to differentiate between the two statuses. (Details are given in Annex B.) 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 just syncope, but it does not harm the vaccinee. To avoid such unnecessary medical emergency interventions, continued training and awareness for health staff is necessary.

**Case studies**

- In 2004, a mass school-based measles-rubella immunization campaign was conducted among 12–19 years in country D. On the first day, 44 children were hospitalized with either hyperventilation or/and vomiting. Investigation concluded that more than 90% were anxiety reactions, and except for two cases all were discharged from hospital the same day.

  **Cause:** Immunization anxiety-related reactions

## Coincidental events

An event may occur coincidentally with immunization and at times may be falsely attributed to be a result of the vaccine. In other words, a chance temporal association (i.e. event happening 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.

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 to encounter many events, including deaths, to be falsely attributed to vaccine through chance association.

For example, sudden infant death syndrome (SIDS or cot death) incidence peaks around the age of early childhood immunization. So, many SIDS cases will be in children who have been recently immunized. However, controlled studies have shown that the association of SIDS and immunization is purely coincidental, not causal (Howson et al, 1991).

**Case studies**

- In response to a severe diphtheria outbreak in country E in 1996, DT was delivered to children in a mass campaign. The death of a seven year-old girl, two to three days following immunization, was reported. The symptoms reported included convulsions that might have been attributable to a vaccine reaction. Upon investigation, it was found that the girl had a history of convulsions and neurological symptoms unrelated to immunization.

  **Cause:** Coincidental event

- In 2010, six infants died within 48 hours following administration of pentavalent (DTP-HepB-Hib) vaccine in country F. Use of vaccine was temporarily suspended. A high-level investigation was warranted, as the deaths had led to a public concern, and health staff were reluctant to use the vaccine.

  **Cause:** Coincidental. Out of six cases, three were confirmed coincidental. One was suffocation and two were due to underlying infections. Among the other three, one was anaphylactic and the other two remained undetermined.

- In 2010, the death of a four-month old infant following DTwP was reported in country G. Within a week, six more cases of severe local reactions were reported with the same batch of DTwP, causing a high public and media attention. Implicated vaccine lot was temporarily suspended and replaced with another lot, and a comprehensive investigation was done including toxicity and sterility testing at national and a WHO-accredited and national laboratories.

  **Cause:** Coincidental. Causality assessment confirmed the death as coincidental, but six reported severe local reactions were most likely due to the immunization errors-related reactions.

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

For example, let us assume that one million 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 eight deaths on the day of the immunization, simply by coincidence. These deaths will be temporally associated with, even though entirely unrelated to, immunization.

A similar calculation is shown in Table 5 for infant (aged under one-year) deaths in selected Western Pacific Regional 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 use statistical analysis to ensure that differences are not simply the result of chance. It is important to also note that the expected number of death calculations presented below may be inflated as it is assumed that children who are near to death will still be immunized.

### Table 5: Estimated coincidental deaths temporally linked to DPT immunization in selected countries in the Western Pacific Region

| Country | Infant mortality rate per 1000 live births (IMR) | Number of births per year | Estimated number of infant death during year in | | |
|---|---|---|---|---|---|
| | | | Month after immunization | Week after immunization | Day after immunization |
| | | | =(IMR*N/12)* nv*ppv | =(IMR*N/52)* nv*ppv | =(IMR*N/365)* nv*ppv |
| Australia | 5 | 267 000 | 300 | 69 | 10 |
| Cambodia | 69 | 361 000 | 5605 | 1293 | 185 |
| China | 18 | 18 134 000 | 73 443 | 16 948 | 2421 |
| Japan | 3 | 1 034 000 | 698 | 161 | 23 |
| The Lao People's Democratic Republic | 48 | 170 000 | 1836 | 424 | 61 |
| New Zealand | 5 | 58 000 | 65 | 15 | 2 |
| The Philippines | 26 | 2 236 000 | 13 081 | 3019 | 431 |

Note: Assumes uniform distribution of deaths and children who are near to death will still be immunized.
Infant mortality and births from 2008 immunization summary, WHO/UNICEF (2010).
IMR= Infant mortality rate per 1000 live birth; IMR/1000
nv = number of immunization doses: assumed here to be three dose schedule; 3.
ppv = proportion of population vaccinated: assumed here to be 90% for each dose; 0.9.

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 programme. Availability of information on background rates reported coincidental event may be helpful in the investigation of an AEFI.

If the same or similar events also affected others in the same age group around the same time but who 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.

With increasing awareness of AEFI surveillance even health staff may report more coincidental events. Also, with introduction of a new vaccine, there is a trend of reporting

many AEFIs, including coincidental events. It is crucial to differentiate these reported coincidental events from potential signals.

**Summary**

- Adverse events may occur due to some inherent properties of the vaccine (vaccine product-related reaction) or due to quality defect (vaccine quality defect-related reaction) or due to immunization errors-related reactions. At times, the event may be unrelated to immunization, but may have a temporal association (coincidental event).
- Immunization anxiety-related reactions are common, resulting from fear or pain of injection rather than the vaccine. In some cases, the cause of the AEFI remains unknown.
- Antigen/vaccine-specific background rates of vaccine reaction are useful to guide decision-making on vaccine related reactions. Minor vaccine reactions are common and do not require special treatments. Rare, serious vaccine reactions need a timely treatment by qualified medical personnel.
- Immunization error-related reactions (previously classified as “programme errors”) are avoidable.

# Establishing immunization safety surveillance

Pharmacovigilance is the practice of detecting, assessing, understanding, responding and preventing adverse drug reactions, including reactions to vaccines. It is now an integral part of the regulation of drug and vaccine safety. While vaccines are considered drugs, they are different and require modified systems to monitor adverse events. Immunization safety is the process of ensuring and monitoring safety of all aspects of immunization, including vaccine quality, adverse events, vaccine storage and handling, vaccine administration, disposal of sharps and management of waste.

Immunization safety surveillance systems exist at national and international levels to ensure effective monitoring and prompt actions in response to AEFIs. Immunization safety surveillance needs to be a collaborative venture between the immunization programme and, when it exists, the NRA, as both parties are responsible for the safety of vaccines. Depending on the country administrative and operational structure, one unit/institution needs to be the focal point for immunization safety surveillance. This can even be delegated to another organization (e.g. a university department), as long as the links with the NRA and the national immunization programme are maintained. The system should build on and mutually strengthen any existing system of reporting information (e.g. immunization coverage reports, disease incidence reports, and adverse drug reaction reports). The best reporting system is the one which achieves the highest compliance and takes timely appropriate action in response to reports.

## Objectives

There are several potential objectives for establishing immunization safety surveillance. Clarifying the most important objective(s) of the system will assist in design and implementation. The relative importance of the objectives will depend on the state of the immunization programme and local circumstances. The objectives may also change over time.

The major goal of immunization safety surveillance is early detection and appropriate and quick response to adverse events in order to lessen the negative impact on the health of the individuals and on the immunization programme. It is an indicator of programme quality. It will also enhance programme credibility and provide actual country and regional data on vaccine safety.

In establishing immunization safety surveillance, the objectives, clearly articulated, should engender the support of health workers to encourage reporting. If resources are limited, prioritizing the objectives is recommended. One option is to have a minimum level of surveillance conducted on the national level to detect immunization errors with a few hospitals/facilities conducting enhanced AEFI surveillance.

It is important for any information obtained through immunization safety surveillance to be immediately assessed and analysed to identify and respond to problems. Response is a critical aspect of immunization safety surveillance.

**Specific objectives of the immunization safety surveillance:**

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

## Steps for establishing a system

When developing an immunization safety surveillance system, countries are advised to consider the following steps:

1. Clarify and agree on roles and responsibilities of both the immunization programme and NRA in immunization safety surveillance. It is important to designate a surveillance implementation body.
2. Develop a protocol with clearly-defined objectives of the immunization safety surveillance: identified strategies, activities to be done, and availability of resources.
3. Clearly identify the role and responsibilities of each staff category involved in immunization safety surveillance.

4. Seek legal provision for vaccine pharmacovigilance and endorsed government commitment.
5. Establish a national (central) expert committee for causality assessment and for highest technical support and decision-making. Large countries may have state/province/regional experts committees for similar purposes and smaller countries, where such experts are not available, can identify a supporting unit from the region.
6. Develop and disseminate a list of events to be reported (and investigated) and their case definitions, standard investigation procedures, and AEFI reporting and investigation forms. (For more information, visit: www.who.int/entity/vaccine_safety.)
7. Train staff on reporting, data analysis, and investigation and report preparation, depending on at what level each function has to be done. Develop training materials and training modules suitable for the country.
8. Make sure the staff are aware that monitoring and evaluation of activities are important and necessary.
9. Develop a communication plan to address issues and information based on immunization and safety surveillance.
10. Consider establishment of a legal framework and a compensation scheme where applicable. Identify also if the legal framework is a government policy.

## Role and responsibility of NRA in immunization safety surveillance

NRAs are responsible for ensuring that every pharmaceutical product - including a vaccine - used within the country is of (i) good quality, (ii) effective, and (iii) safe for the purpose or purposes for which it is proposed. Whereas the first two criteria must be met before any approval of the vaccine's medical use, the issue of safety is more challenging. Strengthening NRA activities leads to ensure vaccine safety. The Global Vaccine Safety Initiative (GVSI), through the WHO-led Vaccine Safety Blueprint Project, has already developed strategies to strengthen NRAs, particularly in low- and low-middle income- countries.

The immunization programme and NRA collectively play specific roles and responsibilities in immunization safety surveillance. WHO considers that in all vaccine-producing countries and in all other countries where an NRA exists, the NRA must be involved in immunization safety surveillance. WHO has defined six functions to be carried out by NRA, as follows:

1. marketing authorization and licensing activities: with clear written instruction for licensing products and manufacturers;
2. pharmacovigilance, including surveillance of AEFI;
3. NRA lot release: system for lot release;
4. laboratory access: use of laboratory when needed;
5. regulatory inspection: regular inspection of manufacturers for GMP compliance; and
6. regulatory oversight of clinical trials: evaluation of clinical performances through authorized clinical trials.

WHO carries out periodical assessment of functions of NRA in all countries, leading to strengthened NRA functions. A WHO manual for assessment of the national regulatory systems for vaccines was published in_2009 (http://www.who.int/immunization/topics/nra_aidememoire_2003.pdf). This assessment is carried out using a tool specifically designed to assess regulatory systems and the above six functions. Performance indicators and sub-indicators have been developed for each function. Some indicators and sub-indicators are marked as 'critical', i.e. mandatory to 'pass' to qualify NRA as fully functioning. For pharmacovigilance surveillance of AEFI, there are seven indicators and of which six are critical (Annex E). Out of the six functions, first two are mandatory for all countries to perform, irrespective of their status as vaccine-producing or not. Furthermore, WHO recommends that all countries which do not actually produce vaccines must still define minimum specifications for the vaccines they use. There should also be a system of post-marketing surveillance to detect if there are problems of vaccine performance in the field. Certain adverse events following vaccination should be monitored, investigated, and reported.

The NRA may have limited knowledge about the immunization programme. It is, therefore, essential that the immunization programme manager be involved in immunization safety surveillance. The respective role of the two key parties needs to be established.

## Role and responsibility of immunization programme (manager) in immunization safety surveillance

An effective immunization safety surveillance system is required involving health workers at all levels in the immunization programme. This section identifies the key role players at different levels of the surveillance system and also outlines their roles and responsibilities in carrying out surveillance activities. However, their roles and responsibilities will depend on the operational levels in different country settings.

It is assumed that a country should have three levels of immunization safety surveillance: national (central), intermediate (state/province/region/district) and service-provider level. In small Pacific islands, however, the surveillance may be limited to only two levels. When a country has three levels, functions and responsibilities among intermediate and national levels are shared by varying degrees, depending on country size and the health-care system.

### Immunization service provider level

In these guidelines, immunization service provider level refers to the lowest administrative level in the country, which provides the immunization service to the public. Among the tasks of immunization service providers are the following:

- **Detection of AEFIs**

  Inquiries should be made at the clinic, hospital or in community, individually regarding any AEFIs experienced after previous vaccination from the recipient or parent/guardian of the recipient.

  If treatment is necessary for a particular condition, the recipient having AEFIs should be referred to the nearest hospital/health facility.

- **Recording of AEFI**

  Supply of necessary forms and registers for immunization safety surveillance should be maintained. All necessary data should be entered into the forms/records/registers.
- **Reporting of AEFI**

  The higher-up administrative/operational level should be immediately informed of all serious events, unusual AEFIs, and deaths.

  Other cases should be reported in a routine way, as instructed by the next administrative/operational level.
- **Investigation of AEFI**

  If the capacity to carry out an investigation exists, it may be done at this level. All investigations required among reported AEFIs, as listed in the national guidelines, need to be done at the earliest possible time. Communication with the staff and the community is essential. Public should be kept informed regarding what is being done during the investigation and, once it is over, the conclusions and results should be shared with other members of the team and the community. Findings of investigation should be disseminative with both service provider and next administrative / operational level authority. If the guidelines instruct, investigation reports need to be submitted to the next administrative/operational level or national level authority.
- **Corrective action**

  Corrective action, particularly related to immunization errors, should be taken immediately. It should be based on the findings of investigation.
- **Analysis of AEFI**

  It is recommended to keep both line listing and detail information separately. Depending on the capacity of staff attached at this level, analysis may be limited to the basic variables.
- **Public education/communication**

  Whenever an opportunity is available, the public should be communicated with and be made aware of what is being done. People should be educated regarding AEFIs.

## Intermediate level

The use of the term "intermediate level" in these guidelines will be varied, depending on the countries' health-care service administration structures. It may refer to one or more administrative levels in a country. Hence, "intermediate level" represents all levels between the national and lowest administrative levels in a specific country.

(For example, country A may have an administrative structure on four levels: national, provincial, district and divisional. The provincial and district levels constitute the intermediate level for the country.)

- **Reporting of AEFI**

  The national level should be informed immediately of serious events, unusual AEFIs and deaths. Other cases should be reported routinely, as stipulated by national level authority. All records on AEFI surveillance should be maintained.
- **Investigation of AEFI**

  All investigations required among reported AEFIs, as listed in national guidelines, need to be done at the earliest possible time. In most settings, capacity to conduct a comprehensive investigation at immunization service provider level does not exist. Therefore, collection of preliminary information of detailed investigations is often the responsibility at this level. Developing capacity to carry out such investigation is necessary and logical. Findings of investigation should be disseminative with both service provider and national level authorities.
- **Corrective action**

  Corrective action should be taken immediately. It should be based on the findings of investigation. In practice, intermediate level has more responsibilities to implement corrective actions both logistically and administratively. For example, if any immunization error-related reactions are observed, strengthening supportive supervision, training and even logistic replacements could be implemented by the authorities at this level.
- **Analysis of AEFI**

  Carrying out data analysis is necessary. Reports need to be produced based on findings of data analyses and investigations.
- **Monitoring and supervision/training**

  Monitoring, supervision and training are key functions at this level. Authorities need to develop the capacity at this level to carry out these functions efficiently and effectively. Whenever necessary, the national level can assist intermediate level for these activities, including providing standard formats for supportive supervision, guidelines and training materials.

## National level

- **Investigation and causality assessment of AEFI**

  Investigations that need national level experts service (e.g. serious cases, deaths, AEFIs with public concerns) need to be done at the earliest possible time. Causality assessment by national expert committee needs to be facilitated. If necessary, further research needs to be conducted to test a hypothesis generated by the surveillance system/investigation.
- **Corrective action**

  Corrective action should be taken immediately. It should be based on the findings of investigation. Vaccine withdrawal or suspension should be taken only if available data are strongly supported by the causative link of the vaccines. Corrective action even can lead to policy or/and programme strategy changes.

- **Analysis and sharing of AEFI data**

  Reports should be produced on findings of data analyses and investigations. AEFI data need to be shared among all stakeholders responsible for country EPI, immunization programme managers, NRA, NCL, academia and, when necessary, manufacturers. Countries are encouraged to share data regionally and globally through the WHO Programme for International Drug Monitoring to generate additional and new information on vaccine safety.
- **Public education/communication**

  Whenever needs arise, conducting public and media awareness is necessary. Developing communication plan is also essential.
- **Monitoring and supervision/training**

  Monitoring and supervision of immunization service is necessary. Guidance and adequate training should be provided to the staff on AEFI surveillance and good quality immunization practices. Whenever necessary, the staff must be re-trained. Developing training materials and getting WHO support, if necessary, should be done.

**Table 6: Programme implementation level, responsibility and purpose of surveillance**

| Programme implementation level | Responsibility | Related reaction |
|---|---|---|
| Local level<br><br>(Immunization provision level) | • Detection of AEFIs<br>• Reporting of AEFIs<br>• Maintaining of records/ registers<br>• Preliminary investigations<br>• Basic analysis of data<br>• Carrying out corrective actions<br>• Communication with patients and community | • Case detection and reporting are the first and founding steps of surveillance.<br>• Establishing a good link with private sector will enhance private sector reporting as well.<br>• Conducting basic analysis of data & preliminary investigation will help to identify corrective actions, particularly of immunization errors, in a timely manner at local level and do the needful corrections.<br>• Good communication at local level is very important as it will lead to limit rumours and negative messages again timely in local settings. National level media get most of negative information from local reporters. Hence, necessity of good communication at the local level is further justifiable. |

| Programme implementation level | Responsibility | Related reaction |
|---|---|---|
| Intermediate level<br><br>(Regional/ province/ district/ town etc.,) | • Verifying reporting data<br>• Looking for additional data (e.g. clusters)<br>• Conducting investigations (and supporting investigations to both local and national teams)<br>• Analysis of data<br>• Feedback (investigation and data analysis)<br>• Guiding and monitoring to carry out corrective actions<br>• Supportive supervision on surveillance activities at local level<br>• Training<br>• Communication with stakeholders | • Verification of data will ensure the quality of data.<br>• Very often clusters and vaccine-related problems are identified at this level.<br>• Conducting investigation by intermediate level will assure quality (availability of resources including experts) and independence of investigation.<br>• At intermediate level, the amount of data is very often sufficient to carry out detailed analysis to identify cause-specific AEFIs. Findings are necessarily needed to be shared with local level, in order to carry out necessary corrective actions in a timely manner. Also guidance and other logistical support need to be provided to the local level.<br>• Supportive supervision and training will lead to ensure smooth functioning of AEFIs surveillance.<br>• Communication with stakeholders, including media, is important to avoid a national level crisis of AEFIs and build confidence on immunization programme. |
| National level | • Conducting investigations (and supporting investigations below levels)<br>• Causality assessment and research<br>• Data analysis/ feed back<br>• Guidance and monitoring to carry out corrective actions<br>• Supportive supervision on surveillance activities<br>• Training<br>• Communication with stakeholders<br>• Sharing information with international agencies (WHO, UNICEF) and manufacturers | • Conducting detailed investigations and causality assessment on cases with national interest.<br>• 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.<br>• National level monitoring of AEFI surveillance will identify gaps and lead strategically lead to changes to be done, in order to get better performances.<br>• Good communication, particularly with the media, will avoid risks and ensure public confidence in the national immunization programme.<br>• Sharing data with WHO is largely to identify vaccine reactions (signals). It also will lead to operational and policy decisions at international level. |

### Private sector

Private sector plays an important role in immunization service either directly providing vaccination or treating cases seeking private sector services. Private sector also functions at different levels. Therefore, to maintain immunization safety surveillance, private sector contribution is important and useful. Countries are strongly advised to actively involve private sector into the immunization safety surveillance.

- Case detection and reporting: Development of health-care service in private sector will lead to opportunities for case detection and reporting. Even individuals receiving vaccines at immunization service in public sector will tend to receive medical care for AEFI in private sector. Developing a link to report AEFI cases from private sector to the public health authority is necessary. Countries have integrated communicable notification system with public and private sectors. It is proposed to adopt a similar system to ensure reporting of AEFI from private sector. Further, it is advised to use a standard reporting form including a minimum set of co-variables recommended by the WHO.
- Investigation of AEFI: Investigation is required for all reported AEFIs, as listed in national guidelines. Private-public sector joint investigation is necessary, when it is either serious or there is an increased public concern. Findings need to be communicated with the staff and the community.
- Analysis of AEFI: Carrying out data analysis is necessary. Staff need to have training on analysis of data and producing reports.
- Corrective action: Corrective action, particularly regarding immunization errors, should be taken immediately as in public sector. It also should be based on the findings of investigation.

**Keypoints**

Immunization safety is the process of ensuring and monitoring the safety of all aspects of immunization, including vaccine quality, adverse events, vaccine storage and handling, vaccine administration, disposal of sharps and management of waste.

## Terms of Reference (TOR) of the National Immunization Safety Expert Committee

Maintaining an actively functioning expert committee is a challenge. It is advised that only the most necessary cases with public or national concern, particularly where causality needs to be assessed, are to be referred to this committee. This will lead to getting the experts' service within a minimum time period; otherwise, the possibility of obtaining their service is remote.

The Immunization Safety Expert Committee plays a critical role in confirming the causality assessments of selected investigations and in determining causality when not established with confidence by the investigator. Expert committee may use the WHO Aide-Memoire

on causality assessment as a resource material, which is available at www.who.int.immunization_safety/en. Also the committee is encouraged to guide comprehensive case definitions developed by the Brighton Collaboration.

The committee should include a wide range of specialists whose expertise may add to the task of reviewing the AEFIs. Areas of expertise would include paediatrics, neurology, general medicine, forensic medicine, pathology, microbiology, immunology and epidemiology. Medical experts in particular areas should be invited for the review of special clinical events. It also needs support from the both EPI and NRA to ensure its functions.

Following generic TOR may be adapted by the committee:

- assessing potential causal links between AEFIs and a vaccine;
- monitoring reported AEFI data for potential signals of previously unrecognized vaccine-related adverse events;
- reviewing all reported serious AEFI presented for expert opinion and making arrangements to investigate further to establish causality and to make necessary recommendations to rectify issues;
- making final decisions on causality assessment of inconclusive investigations and ensuring quality control on immunization surveillance system;
- communicating with other national and international experts when requirements arise in establishing causality and vaccine quality issues;
- advising the national immunization programme (manager) and NRA about AEFI-related issues when requested by these institutions; and
- advising the Ministry of Health about vaccine and immunization safety-related matters when requested by the Ministry.

A few point on expert committee content and function:

- Independence and transparency: Complete independence from government and industry-associated experts may not be possible to achieve as that may result in losing too much of the potential expertise needed. Therefore, it is encouraged that the committee explore what transparency means, i.e. discuss how to declare conflicts of interest/competing interests and decide which conflicts may hinder an individual expert from taking part in causality assessment of a specific event for a given vaccine, etc. and which conflicts may not.
- Role of immunization programme and NRA: Staff of the immunization programme and regulatory authority are critical to the process and should serve the role of a Secretariat to facilitate the committee's review (including preparing the documentation to be reviewed) but should not influence in deciding on the causality. Their role may be advisory.
- No industry participation: It is important to emphasize that employees of the vaccine manufacturing companies cannot sit on these committees. Such a conflict is too flagrant and could undermine the credibility and acceptance of the committee's conclusions.

## Differences between surveillance of AEFIs and of adverse events to drugs

Vaccines are administered to healthy people for the prevention of disease while most drugs are used to treat or control disease in sick people. Thus, a much higher level of risk is acceptable for a drug compared to a vaccine. An involuntary risk is perceived as greater than a voluntarily taken risk. This fact further reduces tolerance of AEFI if there is any element of compulsion in the immunization programme. Also, unlike drugs, vaccines are administered not only for the benefit of the individual, but also for the benefit of the community. Hence, AEFI may be perceived as being the responsibility of the community, as compared to drug reactions.

These differences do not preclude a monitoring system for adverse drug events being used to monitor AEFI. But the system must be sensitive to the specificity of vaccines. Furthermore, in many countries with a single monitoring system, surveillance of AEFI is often overlooked. Different reporting pathways and responses to AEFI need to be built into the existing system of adverse drug event surveillance.

The reporting pathways for the immunization programme may not be part of the usual reporting scheme for drugs and that the most efficient way to collect adverse event reports may be different for vaccines and drugs. The investigation and assessment of causality cannot be done in the same manner for vaccines and drugs. This investigation requires a very different type of expertise and an understanding of immunization programmes. The priority for immunization safety surveillance is to identify and correct immunization errors.

The implication of an adverse event is quite different in scale for a vaccine, which is given to an entire cohort of the population compared with a drug, which is only used in a relatively small number of individuals. Hence, the response and communication about AEFI are likely to be both more important to the health of the population, of greater interest, and more challenging. The wide use of vaccines also leads to the reporting of many coincidental events, which are only temporally related to immunization.

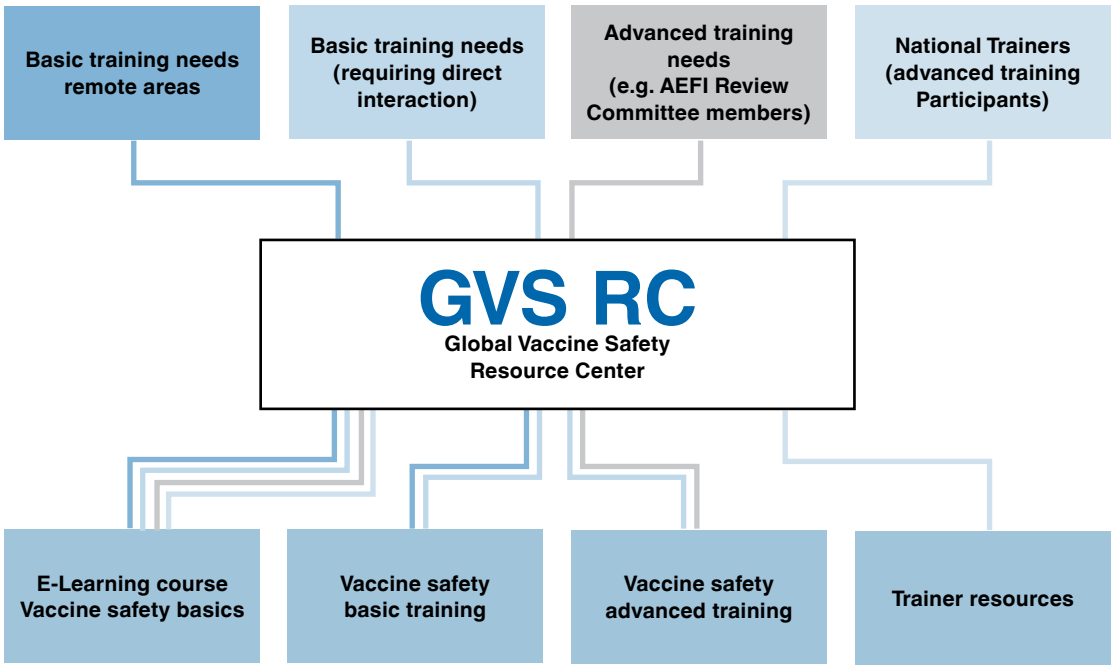
## Training opportunities for vaccine safety

Immunization safety surveillance should include training that will enable appropriate response at all levels in the system. It is also important to learn more about the process and the outcomes in relation to immunization safety from past experience.

To strengthen vaccine safety capacity among staff in countries, WHO has developed the Global Vaccine Safety Resource Centre (GVS RC). This online platform offers training to national public health officials, immunization programme managers, vaccination staff and members of AEFI review committees. (http://www.who.int/entity/vaccine_safety/initiative/tech_support/en/index.html)

The training can be provided in workshops conducted by WHO or online. The figure below shows the concept of how WHO'S GVS RC meets training needs of different target audiences by offering different learning paths (e.g. immunization safety expert committee members can train their skills to assess the causality of adverse events in the vaccine safety advance training).

**Figure 1: Global Vaccine Safety Resource Centre**




## E-learning course on vaccine safety basics

The E-learning course on vaccine safety basics developed by WHO in collaboration with international vaccine safety experts is a flagship course aiming to establish shared understanding of among all staff and officials working on vaccine safety-related issues.

The course comprises six modules, through which the learner can acquire detailed information on immunological vaccine safety aspects, characteristics of AEFIs, vaccine pharmacovigilance components, surveillance systems, national and international vaccine safety institutions and their services. The course also includes a module dealing with communication, including risk communication to vaccinees, their parents and communities, as well as advice on how to communicate effectively with the media.

Programme managers and all who are actively involved in and responsible for immunization services are recommended to use the free online course. As the training course is self-guided and user-friendly, it can be taken at any setting and over any period of time. The E-learning course material is available at www.vaccine-safety-training.org.

## Summary

- Immunization safety surveillance needs to be a collaborative venture between the immunization programme and, when it exists, the national regulatory authority (NRA), as both parties are responsible for the safety of vaccines.
- Setting clear objectives and following each step on establishing the surveillance are important.
- Identifying clear role and responsibilities at different levels by different stakeholders are necessary for functioning immunization safety surveillance in the country.
- To ensure capacity among vaccination staff, immunization officers and immunization safety expert committee, training should be undertaken at the country level, supported by international resources, such as the GVS-RC.

# Reporting AEFIs

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.

A suspicion alone is sufficient for reporting and the primary reporter is not expected to assess causality which is implied when considering the cause-specific definitions. Rapid detection and evaluation of possible vaccine link is essential to ensure the continued safety of vaccines. Thus, in case of suspicion it is preferable to submit a report on a timely basis rather than wait for all aspects of an investigation to be completed. This is particularly true for reports which meet the criteria to be considered serious reports. In many settings the primary reporter submits a report to the immediate reporting authority, which is, in general, a local public health authority. Then it moves up, through the intermediate level to the national level and to the central immunization programme or NRA. The onward reporters may seek to clarify or expand on the information before sending the report on. Depending on country system, this chain of movement may be varied.

To improve the detection capacity, a good knowledge in the primary reporter of AEFIs, its types, and purpose of AEFI surveillance is necessary. Regular training and awareness programmes are necessary to update knowledge and keep the interest among primary reporters.

## Which events should be reported?

Any AEFI that is of concern to the parents or to the health-care worker should be reported.

In particular, health workers must report:

- serious AEFIs,
- signals and events associated with a newly introduced vaccine,
- AEFIs that may have been caused by an immunization error-related reaction,
- significant events of unexplained cause occurring within 30 days after vaccination, and
- events causing significant parental or community concern.

A list of suggested reportable events with case definitions is presented in Table 7 and in Annex B. Reportable events listed in Table 7 only indicate those events that could be considered for inclusion in the AEFI surveillance system. Each country should decide individually which events are appropriate for inclusion in its system.

Reporting all minor AEFIs such as high fever and minor local reactions is optional. These vaccine reactions are expected to occur and, if reported, the volume of reports would

overwhelm the system while contributing information may have limited value. However, monitoring crude numbers is helpful to monitor and compare with background rates that could identify either product quality defect or immunization error or even increased susceptibility of vaccine reaction among the given population.

**Table 7: List of reportable AEFIs**

| Reportable AEFI | Onset time interval* |
|---|---|
| • Anaphylactoid reaction (acute hypersensitivity reaction)<br>• Anaphylaxis<br>• Persistent (more than three hours) inconsolable screaming<br>• HHE<br>• Toxic shock syndrome (TSS) | Within 24 to 48 hours of immunization |
| • Severe local reaction<br>• Sepsis<br>• Injection site abscess (bacterial/sterile) | Within seven days of immunization |
| • Seizures, including febrile seizures (6-12 days for measles/MMR; 0-2 days for DTP)<br>• Encephalopathy (6-12 days for measles/MMR; 0-2 days for DTP) | Within 14 days of immunization |
| • Acute flaccid paralysis (4-30 days for OPV recipient; 4-75 days for contact)<br>• Brachial neuritis (2-28 days after tetanus containing vaccine)<br>• Intussusception (commonly within 21 days after rota vaccines)<br>• Thrombocytopaenia (15-35 days after measles/MMR) | Within three months of immunization |
| • Lymphadenitis<br>• Disseminated BCG infection<br>• Osteitis /Osteomyelitis | Between 1 and 12 months after BCG immunization |
| • Death<br>• Hospitalization<br>• Disability<br>• 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 will depend on the antigen and adverse reaction. For detailed antigen or adverse reaction specific 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/vaccinfosheets/en/index.html).

Local reactions occurring at increased frequency, even if not severe, should also be reported. They can be markers for immunization errors or for problems with specific vaccine lots. If all cases received vaccines from the same health worker/facility and there are no other cases, an immunization error is likely. If all cases received the same vaccine or lot, and there are no similar cases in the community, a problem with the vaccine is likely. If the event is a known vaccine reaction but occurring at an increased rate, an immunization error or a

vaccine problem are likely causes. Finally, if cases include people from the same area in the same age group who were not immunized, then the adverse event was probably coincidental (refer to Figure 2 on page 47).

## When to report?

*Immediately.* A report always needs to be made as quickly as possible so that an immediate decision on the need for action and investigation can be made. In incidents with many cases or a high level of community concern, an urgent phone call/fax to the decision-making administrative/operational level should be made.

## How to report?

Reports should be made on a standard AEFI Report Form (see Annex F). This is the responsibility of immunization service provision unit. The report should be kept simple to ensure that health workers can input the essential information.

It is important that minimum information should be entered into the reporting form, as this is the basis for decisions of further investigation. Also, countries are strongly encouraged to maintain minimum required information, so the data can be shared with regional and global partners through the WHO Programme for International Drug Monitoring.

For the purpose of signal detection, data collection tools should remain as simple as possible. However, after signals are detected or in a serious case, additional data are critical to determine the association of the AEFI case with vaccines as well as to assess the need for further investigation. WHO recommended 22 core variables with 10 identified as critical (basic information) that should be collected for any AEFI surveillance (Table 8) and an additional 33 variables of interest for a more detailed case review (see Annex F1). Basic information collected needs to be prioritized because the AEFI data collection, collation, transmission, analysis and feedback systems in different countries are heterogeneous. Also quantitative and qualitative aspects of data need to be considered. It is proposed that the reporting tool includes the WHO-Adverse Reaction Terminology (WHO-ART) dictionary in order to standardize the terminology used to record signs, symptoms or a diagnosis as well as a vaccine dictionary which will include pertaining to all of the vaccines suspected.

**Keypoints**

- Any AEFI that is of concern to the parents or to the health-care worker should be reported.
- Collection of harmonized data on AEFI allows for better comparison and pooled analysis with findings from vaccine safety surveillance systems. Therefore, countries are recommended to incorporate a minimum set of 22 core variables in their reporting form, making the form useful both in the country and globally.

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

| Core variables | Onset time interval* |
|---|---|
| Identity | Date AEFI report first received at national centre |
| | Country where the AEFI was 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 the 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 programme, it is of utmost importance to ensure AEFI reporting for two reasons:

1. Mass immunization and special immunization programmes cover 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. The rate of events remains unchanged, but the increased number of events tends to be noticed by both staff and the public, particularly when injectable vaccines are used and at a time of intensive social mobilization. Unless an event is properly investigated or analysed, it can cause concern among the public and also may affect the immunization programme.
2. During special immunization programmes, a new vaccine may be 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 programmes. For example, there were cases of narcolepsy reported following H1N1 influenza mass vaccination in Finland in 2009–2010.

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

It is worth emphasizing that, unless immunization service units at field level appropriately process reports, an adequate immunization safety surveillance system will not exist. Staff must be encouraged to report adverse events without fear of penalty. The aim is to improve systems or provide further training and not to blame individuals.

Positive feedback to health workers is essential. The feedback should include the outcome of investigations or causality assessment when these are carried out and recommendations on the management of child/recipient especially concerning the need for future vaccination.

There must be an adequate supply of forms to support reporting. Pre-addressed and postage-paid forms may improve reporting in some countries, especially for private physicians.

## Private sector reporting

As in government institutions, all private sector medical institutions handling immunization services and treating AEFI cases should report all AEFIs to the respective immunization safety surveillance focal points. Reporting from the private sector is encouraged for two reasons:

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

To maintain uniformity of reporting data, it is encouraged that AEFI reporting forms used in the AEFI surveillance system are made available at private sector as well.

**Summary**

- Availability of a list of AEFIs to be reported is necessary.
- Case definition (e.g. by Brighton Collaboration) for each reportable event should be made available.
- AEFI reporting should be made on standardized reporting form using a minimal set of core variables to enable global evaluation of signals that will benefit countries in their evaluation of AEFI.
- Private sector reporting is encouraged.
- Sharing reports with the Western Pacific Region and globally (WHO Programme for International Drug Monitoring /UMC) is encouraged.
- Identifying barriers to report and taking appropriate action will improve the reporting process.

# Investigating AEFIs

## Why reports should be investigated?

The ultimate goal of a case investigation is to find the cause of an AEFI or clustering of AEFIs and prevent the occurrence of 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 event was due to some other reason than immunization, the fact that the staff had investigated the incident itself will increase public confidence towards immunizations.

The purposes of investigating an AEFI case are the following:

- 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, it identifies any vaccine-related link to the given AEFI.
- To examine the operational aspects of the programme. 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:

- appears to be a serious event of known or unknown cause,
- belongs to a cluster of minor AEFI,
- demonstrates signals and events associated with a newly introduced vaccine,
- may have been caused by immunization error,
- appears on the list of events defined for AEFI surveillance, and
- causes a significant parental or public concern.

Improved reporting can lead to more AEFI reports without a real increase in reaction rate. The investigator needs to determine if there is a real increase in reaction rate as well as identify the cause of the increase. For example, a change in vaccine manufacturer or in vaccine lot can lead to a change in reaction rate.

Criteria should be established to define the type of AEFI that requires investigation. The intermediate and national units responsible for AEFI surveillance need to ensure that all reports requiring investigation have been adequately investigated.

## Who should investigate?

Carrying out the investigation will depend on the operational structure of the AEFI surveillance system in the country. In most settings, the lowest level does not have the capacity to conduct an investigation. Large and developed countries such as Australia, China, Japan, and Korea will have a capacity to conduct an investigation even by the lowest level team. However, small island countries (e.g. small Pacific island countries) will not have different levels within the system. Therefore, an investigator at any level, likely with minimum capacity, may carry out an investigation. In some other countries, it may be the intermediate (state/regional/provincial/district) level that will carry out the investigation. Expert support from national to local levels and close communication among all levels are necessary and important.

## When to investigate?

The urgency of the investigation will depend on the situation. However, if it is determined that an investigation is needed, it should be initiated as soon as possible. It may be useful to include a "timeliness" criterion in the evaluation of the system. (For example, an investigation should commence within two working days for urgent investigations and five working days for less urgent ones). The criteria that make an investigation urgent (e.g. continuing problem, high community concern) should be specified in advance.

## How to investigate?

An AEFI investigation follows standard epidemiological investigation principles (Table 9).

It is important to investigate suspected adverse events promptly and completely. The investigator 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 on an AEFI Investigation Form (Annex G).

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.

**Keypoints**

Not all reported AEFIs require investigation. Core variables listed by WHO for reporting are not enough for the purpose of comprehensive investigation and countries are encouraged to use separately designed data collection forms for the investigation.

Investigator(s) may use WHO Aide-Memoire on AEFI investigation as a resource material (http://www.who.int/vaccines-documents/DocsPDF05/792.pdf). It provides key definitions, guidance to prepare for an investigation, as well as a checklist providing useful information for each step of an investigation.

Clear case definitions, from the guidelines on reporting or defined during the investigation, are essential. The investigation needs to identify all cases in the community and find out the outcomes for all who received the suspect vaccine. The risk of disease should be compared for those who received the vaccine versus those who did not. A working hypothesis should be established as soon as there is sufficient information. The working hypothesis may change during the course of the investigation. The focus of the investigation should then be to seek to confirm the working hypothesis. No action should be taken based on the hypothesis until it is confirmed with reasonable certainty.

An AEFI Investigation Form (Annex G) should be completed at the end of the investigation.

## Laboratory testing: vaccine

Laboratory testing may sometimes confirm or rule out the suspected cause. The vaccine may be tested for sterility, toxicity and content (e.g. aluminium content); the diluent for sterility and chemical composition; and the needles and syringe for sterility. Testing should be requested on a clear suspicion and not as routine, and never before the working hypothesis has been formulated. Laboratory testing is always costly. Determining which samples to send, if any, depends on the working hypothesis for the cause of the event (Table 10). The WHO guideline on nonclinical evaluation of vaccines is available at http://www.who.int/biologicals/publications/nonclinical_evaluation_vaccines_nov_2003.pdf.

## 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 the intermediate level (state, region/province/district) institutions, sending samples to national laboratory or an accredited laboratory abroad should be considered.

Date and time of collection and type of each sample collected should be recorded and clinical investigations and medical records related to the incident such as microbiology, biochemistry, immunology, histopathology, haematology, radiology etc. should be documented.

It is necessary to obtain a detailed history which includes past medical history, drug history,

immunization history, history of allergies and findings of medical records etc. It is advised to consult clinician(s) treating to make a decision on samples to be tested (see Table 11).

**Table 9: Steps in an AEFI investigation**

| Step | | Actions |
|---|---|---|
| 1 | Confirm information in report | • Obtain patient's medical file (or other clinical record)<br>• Check details about patient and event from medical file and document information<br>• Obtain any details missing from the AEFI Reporting Form<br>• Identify any other cases that need to be included in the investigation |
| 2 | Investigate and collect data about the patient | • Immunization history<br>• Previous medical history, including prior history of similar reaction or other allergies<br>• Family history of similar events |
| | About the event | • History, clinical description, any relevant laboratory results about the AEFI and diagnosis of the event<br>• Treatment, whether hospitalized, and outcome |
| | About the suspected vaccine(s) | • Conditions under which the vaccine was shipped, its present storage condition, state of vaccine vial monitor, and temperature record of refrigerator<br>• Storage of vaccine before it arrived at health facility, where it has come from (movement up the cold chain), vaccine monitor card |
| | About other people: | • Whether others received the same vaccine and developed illness<br>• Whether others had similar illness (may need case definition); if so, exposure of cases to suspect vaccine(s)<br>• Investigate the local immunization service |
| 3 | Assess the service by asking about | • Vaccine storage (including open vials), distribution, and disposal<br>• Diluents storage and distribution<br>• Reconstitution(process and time kept)<br>• Use and sterilization of syringes and needles<br>• Details of training in immunization practice, supervision and vaccinator(s)<br>• Number of immunizations greater than normal? |
| | Observing the service in action | • Refrigerator – what else is stored (note: if similar containers stored next to vaccine vials which could be confused); which vaccines/diluents stored with other drugs; whether any vials have lost their label<br>• Immunization procedures (reconstitution, drawing up vaccine, injection technique, safety of needles and syringes; disposal of opened vials)<br>• Do any open vials look contaminated? |

| Step | | Actions |
|---|---|---|
| 4 | Formulate a working hypothesis | • The likely/possible cause(s) of the event |
| 5 | Test working hypothesis | • Does case distribution match working hypothesis?<br>• Occasionally, laboratory tests may help (see text). |
| 6 | Conclude investigation | • Reach a conclusion on the cause<br>• Complete AEFI Investigation Form (Annex F)<br>• Take corrective action, and recommend further action (Chapter 9). |

### 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 | Composition (for frozen vaccine) |
| Reconstitution error | Vaccine vial and/or diluent | Sterility or composition (chemical) |
| Non-sterile injection | Needle, syringe, vaccine vial and diluent | Sterility |
| Vaccine problem | Vaccine vial | Composition, toxicity |

### Table 11: Guide to specimen samples obtained following selected AEFIs

| Event | Specimen from the patient |
|---|---|
| Severe local reaction | Blood |
| Abscess | Swab, blood |
| Lymphadenitis | Blood |
| CNS symptoms with no paralysis | Cerebrospinal fluid, blood |
| CNS symptoms with paralysis | Stools |
| Anaphylaxis | Blood |
| Toxic shock syndrome | Blood, blood culture |
| Death | Postmortem tissue specimen |

## Investigating AEFI clusters

A cluster of AEFI is defined as two or more cases of the same adverse event related in time, place or vaccine administration. Apart from checking on these three factors (e.g. checking vaccine batch), the investigator should look for AEFIs occurring in similar age groups and populations with genetic predisposition or disease.

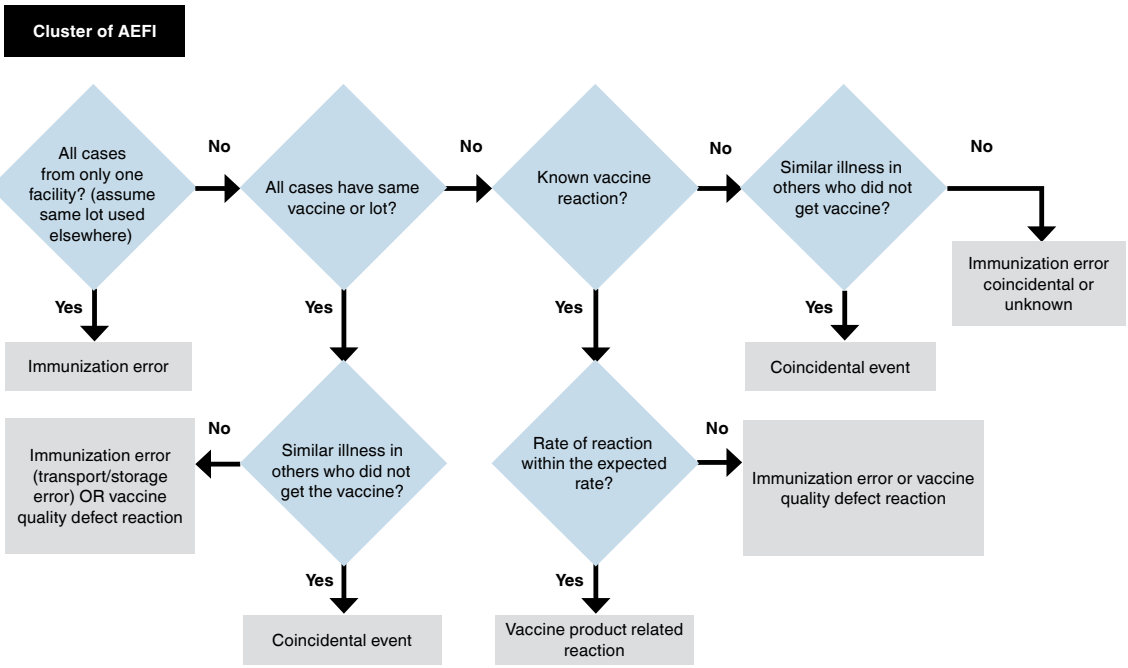
Cluster investigation begins by establishing the case definition and identifying all cases that meet the case definition. The immunization programme manager should then take two actions (Figure 2).

1. Identify the common cases ( the cluster cases) including details of when, where and which vaccines were given, by collecting and recording:
   - detailed data on each patient,
   - programme-related data (storage and handling, etc.), and
   - immunization practices and the associated health workers' 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 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 used in new target populations, a cluster may represent a previously unrecognized vaccine product-related reaction. Knowledge of the background incidence of events which may occur in causal relationship with a vaccine is, therefore, essential for assessing a cluster in terms of the strength of the signal it may provide.

| Cause–specific AEFI | Cluster characteristics |
|---|---|
| Vaccine reaction (product-related or quality defect-related) | • If all cases received the same vaccine or lot, and there are no similar cases in the community.<br>• If an increased frequency of events is reported from multiple settings. |
| Immunization error-related | • If all cases received vaccines from the same health worker/facility and there are no other cases. |
| Coincidental | • If cases include people from the same area in the same age group who were not immunized. |
| Immunization anxiety-related reaction | • Clusters of fainting after immunization are well-recognized immunization anxiety-related reactions during immunization programmes targeting adolescent girls. |

**Figure 2: Identifying cause of AEFI cluster**




## Investigation of deaths

A field investigation of a death following immunization has to be conducted without any delay as it can cause a general panic. The death should be notified to all administrative levels, including the national immunization programme. It is recommended that death investigation be carried out by a team comprising clinical, laboratory and forensic experts. Programme managers' contribution is necessary, but should not be unduly defensive.

A postmortem is preferred and recommended following all deaths suspected to cause by vaccine / immunization. However, decision of conducting postmortem should be within the religious, cultural acceptance and legal framework of the country.

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 necessary.

**Summary**

- Investigation should be timely, comprehensive and methodical.
- Laboratory investigation(s) is (are) important, but should not be routine. To be conducted if only indicated and necessary.
- Autopsy investigations are encouraged.

# Analysis of AEFI data

Immunization safety surveillance should include structured systematic and permanent data collection on the impact of vaccines used in the country immunization programme. In addition, surveillance should include epidemiological analysis of data as well as dissemination of findings to advice programme managers, NRA and other stakeholders including manufacturers.

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 more information, please refer to: http://www.who.int/entity/vaccine_safety/initiative/tools/Guide_Vaccine_rates_information_sheet_.pdf

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

- Completeness of submitted AEFI forms.
- Verification and reassurance of data accuracy.
- Identifying health institutions where AEFIs are not reported. Determination of whether it is due to failure of reporting or whether there are no AEFIs to be reported. Checking on "zero reporting" or "nil reporting".
- Assessing AEFI reports received during stipulated time period.
- Assessing number of events and rate for 1000 or 10 000 or 100 000 doses of vaccine used.
- Categorization of the type of AEFI.
- Analysing each type of immunization errors by number and rates per 100 or 1000 doses of relevant vaccines used.
- Comparison of the rates with available or known vaccine reaction and background rates.

## Who should analyse the data?

Data analysis could be carried out at different levels in the immunization safety surveillance system: programme implementation level, intermediate level 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. The analysis that is repetitive at different levels may necessarily vary by the extent of the analysis.

## How should the data be analysed and interpreted?

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

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

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

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

The numerator for this vaccine reaction (febrile seizures) is 20.

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

**Options for selecting a denominator**

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

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

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

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

Multiplier: Use of proper multiplier is important as it must vary by purpose and level of analysis. At local level, percentage (%) is the best choice, whereas intermediate and national levels may use 1000, 100 000 or million as multiplier.

For common, minor vaccine reactions, percentage is recommended (refer to Table 2) and for rare serious reactions, 10 000 (104), 100 000 (105) or 1 000 000 (106 million) can be used (Table 3).

The WHO Regional Office for the Western Pacific has developed a calculator to estimate reported AEFIs, separately for both minor and serious events (Figure 3).

**Figure 3: WPRO calculator for expected vaccine reaction rates**

Expected annual rate of common minor vaccine reactions
SAMPLE PROVINCE, SAMPLE COUNTRY

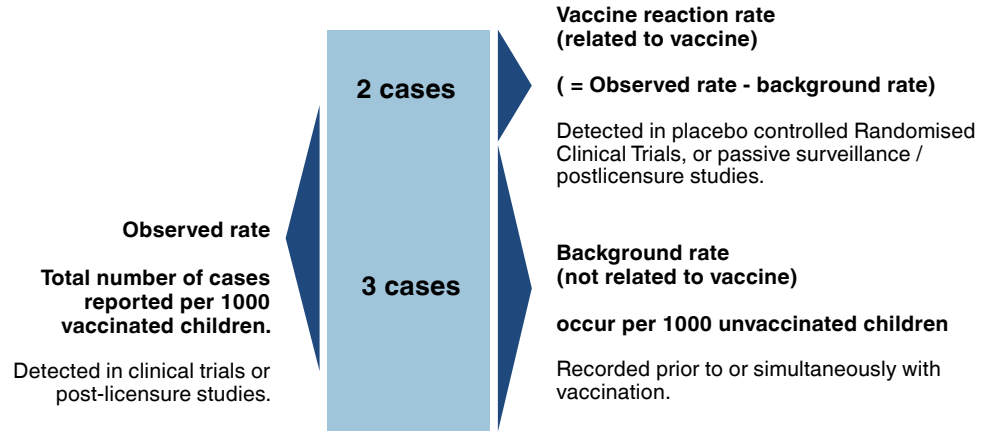
| Vaccine | Symptoms | Rate per 100 doses | | # of vaccines administered each year | Expect number of cases per year | | Notes |
|---|---|---|---|---|---|---|---|
| | | lower rate | upper rate | | lower rate | higher rate | |
| HB | Local reaction, pain swelling redness | 5 | 15 | 1000 | 50 | 150 | |
| HB | Fever | 2 | 10 | 100 | 2 | 10 | |
| HepB children | Local reaction, pain swelling redness | | 5 | 1 000 000 | | 50 000 | |
| HepB adults | Local reaction, pain swelling redness | | 30 | 20 000 | | 6 000 | |
| Measles/ MMR | Local reaction, pain swelling redness | | 10 | 1 526 530 | | 152 653 | |
| Measles/ MMR | Fever | | 5 | 1 526 530 | | 76 327 | |
| Measles/ MMR | Irritability, malaise, non-specific symptoms | | 5 | 1 526 530 | | 76 327 | |
| OPV | Fever | 1 | | 20 000 | 200 | | |
| OPV | Irritability, malaise, non-specific symptoms | 1 | | 20 000 | 200 | | Diarrhoea, headache, muscle pain |
| Tetanus/ DT | Local reaction, pain, swelling, redness | | 10 | 20 000 | | 2 000 | Rate of local reactions like to increase with booster doses up to 50–85% |
| Tetanus/ DT | Fever | | 10 | 20 000 | | 2 000 | |
| Tetanus/ DT | Irritability, malaise, non-specific symptoms | | 25 | 20 000 | | 5 000 | |
| DTP | Local reaction, pain, swelling, redness | | 50 | 4 500 000 | | 2 250 000 | With whole cell pertussis vaccine. Acellular pertussis vaccine rates are lower. |
| DTP | Fever | | 50 | 4 500 000 | | 2 250 000 | With whole cell pertussis vaccine. Acellular pertussis vaccine rates are lower. |
| DTP | Local reaction, pain, swelling, redness | | 60 | 4 500 000 | | 2 700 000 | With whole cell pertussis vaccine. Acellular pertussis vaccine rates are lower. |

To calculate the expected annual number of AEFI by vaccine, just enter the number of vaccines administered annually

**Step 4: Comparison and interpretation of rates.** Available expected vaccine reaction rates for each type of AEFI for an antigen (Tables 2 & 3) present a guide to making 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.

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).

## Vaccine reaction rate = Observed (reported) rates – Background rates




**Example: Fever following vaccination**

Source:http://vaccsafetytraining.fillmann.net/rates-of-adverse-vaccine-reactions.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

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

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

**Vaccine dose**
The same vaccine given as a 'primary dose' may have a different reactogenicity profile than when it is given as a 'booster dose'. For example, the DTaP vaccine given as a primary dose is less likely to result in extensive limb swelling when compared with the same vaccine given as a booster dose.

**Case definition**
Adverse event may be defined differently in 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).

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

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

Source: http://vaccsafetytraining.fillmann.net/rates-of-adverse-vaccine-reactions.html

In the scenario presented here, compare the observed rate of 0.44% of febrile seizers reported in country A with the expected rate of febrile seizure following measles containing vaccines: it is 0.03% (Table 3). This concludes that the observed (reported) rate of 0.44% is greater than the expected vaccine reaction rate of 0.03%. This warrants investigation. Is the case definition correct? Does the onset interval tally with reported febrile seizures or any other reasons? Or is there anything wrong with the vaccine product? In any vaccine adverse event analysis, confounders or sources of bias to be considered include (but are not limited to) age, gender, race/ethnicity, season (e.g. for influenza vaccines), calendar time and country/ region.

## Purpose of analysis at different levels

| Programme implementation level | What data to analyse | Purpose of data analysis at given level |
|---|---|---|
| Local level (Immunization provision level) | • Number of reports by clinics, hospitals, villages by a given time<br>• Reported AEFIs by place (clinics, hospitals), persons & time<br>• Reported AEFIs by antigen | • These are programme operation indicators (timeliness, completeness).<br>• Identification of immunization errors will lead to corrective action.<br>• Will identify vaccine reactions and coincidence. |
| Intermediate level (Regional/ province/ district/ town) | • Number of reports by local levels<br>• Reported AEFIs by place (clinics, hospitals), persons & time<br>• Cluster analysis<br>• Reported AEFIs by antigen | • These are programme operation indicators (timeliness, completeness) at local level.<br>• Identification of immunization errors will lead to corrective action.<br>• Cluster analysis leads to identify immunization errors, coincidence and vaccine reactions.<br>• Will identify vaccine reactions and coincidence. |
| National level | • Number of reports by intermediate levels<br>• Reported AEFIs by place (clinics, hospitals), persons & time<br>• Cluster analysis<br>• Reported AEFIs by antigen | • These are programme operation indicators (timeliness, completeness) at intermediate level.<br>• Cluster analysis leads to identify immunization errors, coincidence and vaccine reactions.<br>• Will identify vaccine reactions, including signals detection.<br>• Leads to taking operational and policy decisions in the country. |

Purpose at international level data analysis is mainly to identify the signals and compare pre- and post-licensure safety data, and, thus, share the findings with countries to support decision-making. It also helps manufacturers to ensure vaccine safety during the production process of vaccines.

## 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 analyse the data, assign a cause and classify it 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 that the risk in vaccinated individuals is greater than that in the non-vaccinated, provided the effects of confounders and bias are ruled out. Estimating relative risk and attributable risk is necessary, and retrospective or prospective analysis of available data or designing epidemiological studies (case series, case-control, cohort or ecological studies) will lead to confirm the causality.

**Summary**

- 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 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.

# Causality assessment of AEFI

Causality assessment is the systematic review of data about an AEFI case to determine the likelihood of a causal association between the adverse 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. It is a critical part of AEFI monitoring and enhances confidence in the national immunization programme. Whether an AEFI is attributable or not to the vaccine or the immunization programme 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, and
- validation of pre-licensure safety data with comparison of post-marketing surveillance safety data.

The quality of the causality assessment depends on three factors:

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

## Levels of AEFI causality assessment and their scientific basis

Causality assessment of AEFI should be performed in three situations. At the population level, to test if there is a causal association between the usage of a vaccine and a particular AEFI; at the level of the individual AEFI case report, to determine from previous evidence and logical deduction if an AEFI in a specific individual is causally related to the usage of the vaccine; and in the context of the investigation of signals.

1. **Individual AEFI case report:** in order to estimate the probability that the occurrence of a reported AEFI in a specific individual is causally related to the usage of the vaccine. It is usually not possible to establish a definite causal relationship between a particular AEFI and a particular vaccine on the basis of a single AEFI case report.

2. **Population level:** using surveillance data and an appropriate statistical methodology in order to test the hypothesis that there is a causal association between the usage of a vaccine and a particular AEFI. This may sometimes be combined with causality assessment at the individual level (of AEFIs collected within that system) whereby some or all of the cases of interest could undergo individual case review and causality assessment before inclusion in a group analysis.
3. **Investigation of signals:** The assessment of whether a particular vaccine is likely to cause a particular AEFI takes into account all evidence: individual AEFI cases, surveillance data and, where applicable, cluster investigations as well as nonclinical data.

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

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

## 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 be done for the following:

- Serious AEFIs, as per definition ( i.e. events which are life-threatening or leading to death, hospitalization, significant disability or congenital anomaly).
- Clusters of events above expected rate or severity.
- Signals: 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), and
  - events causing significant parental or community concern (e.g. HHE, febrile seizures).

## Prerequisites for AEFI causality assessment

There are three prerequisites that every AEFI report should fulfil before causality assessment:

1. The AEFI case investigation should have been completed. Premature assessments with inadequate information could mislead the classification of the event.
2. All details of the case should be available at the time of assessment. They should include documents pertaining to the investigation as well as laboratory and autopsy findings as appropriate.
3. There must be a "valid diagnosis" (explained below) for the unfavourable or unintended sign, abnormal laboratory finding, symptom or disease in question.

## Causality assessment method

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

The revised process envisages the causality assessment of an individual AEFI case to a particular vaccine. In the event of multiple vaccines being given simultaneously, the assessor will have to conduct a causality assessment separately for each suspected vaccine. There are four steps in causality assessment. The steps and their purpose are outlined below:

- **Step 1: Eligibility:** to determine if the AEFI case satisfies the minimum criteria for causality assessment as outlined below.
- **Step 2: Checklist:** to systematically review the relevant and available information to address possible causal aspects of the AEFI (Annex I).
- **Step 3: Algorithm:** to obtain a direction as to the causality with the information gathered in the checklist.
- **Step 4: Classification:** to categorize the AEFI's association to the vaccine / vaccination based on the direction determined in the algorithm.

## Step 1: Eligibility

To proceed with causality assessment, it is necessary to first confirm that the vaccine was administered before the event occurred. This can be ascertained by eliciting a very detailed and careful history with the relevant stakeholders. It is also essential to have a "valid diagnosis" of the reported AEFI. The valid diagnosis could be an unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. The diagnosis should meet a standard case definition. If available, it is best to adopt the Brighton Collaboration case definition. However, if this is not possible, case definitions can be adapted from standard medical literature, national guidelines or practised 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 4: Causality assessment: Eligibility**

| Name of the patient | Name of one or more victims before this event | What is the valid diagnosis? | Does the diagnosis meet a case definition? |
|---|---|---|---|
| | | | |

**Create your question on causality here**

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

## Step 2: Checklist

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

1. Is there strong evidence for other causes?
2. Is there a known association with the vaccine / vaccination?
   a. vaccine products
   b. immunization error
   c. immunization anxiety

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

3. Is there any 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 5: Causality assessment: Checklist (main subdivisions)**

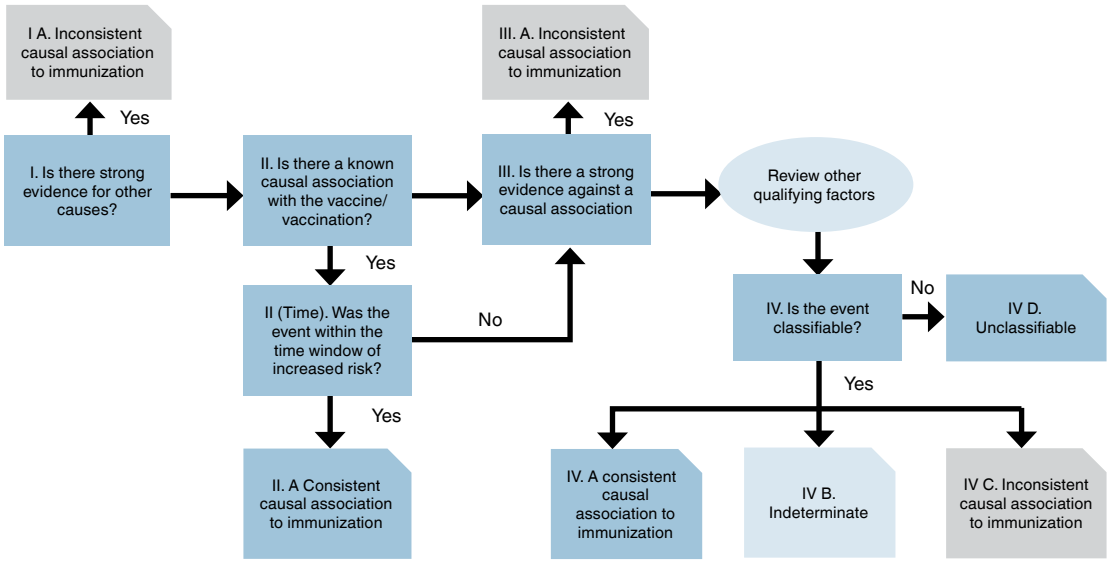
| |
|---|
| I. Is there strong evidence for other causes? |
| II. Is there a known causal association with the vaccine/vaccination? |
| Vaccine product (s) |
| Immunization error |
| Immunization anxiety |
| II (Time). If "yes" to any question in II, was the event within the time window of increased risk? |
| III. Is there strong evidence against a causal association? |
| IV. Other qualifying factors for classification |

For the detailed checklist, see Annex I.

## Step 3: Algorithm

The algorithm is based on the key questions on the checklist. Stepwise approach in algorithm helps determine if the AEFI could be consistent or inconsistent with an association to immunization, indeterminate or unclassifiable.

**Figure 6: Causality assessment: Algorithm**




## Step 4: Classification

The final classification is based on the availability of adequate information.

### I. A Case with adequate information for causality conclusion can be classified as follows:

**A. Consistent causal association to immunization**

A1: vaccine product- related reaction or

A2: vaccine quality defect-related reaction or

A3: immunization error-related reaction or

A4: immunization anxiety-related reaction.

**B. Indeterminate**

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

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

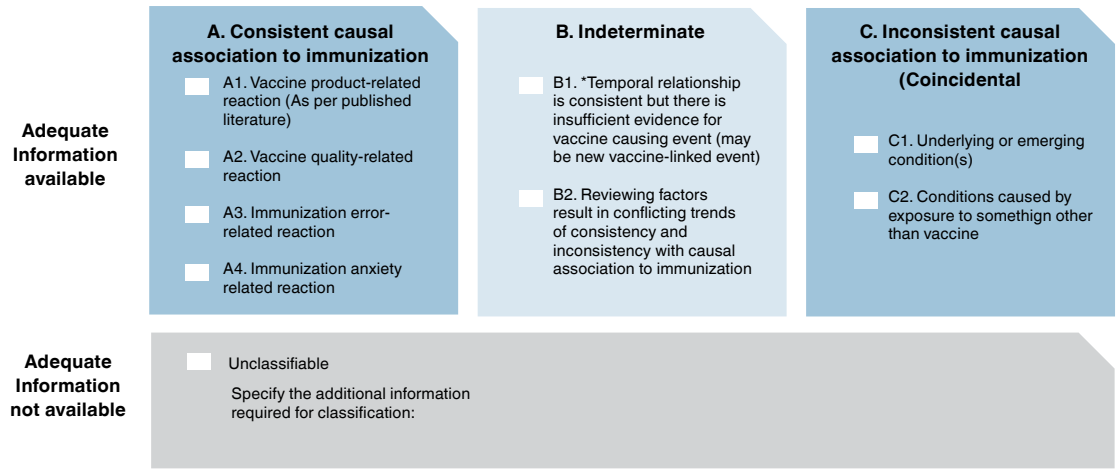
**C. Inconsistent causal association to immunization (coincidental)**

C1. underlying or emerging condition(s), or

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

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

**Figure 7: Causality assessment: Classification**




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

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

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

**Figure 8: Causality assessment of an individual case vs. a cluster/signal**

**Individual case**

- Proving causality is hard unless AEFI already known to be related.
- May be possible to prove the immunization error related
- Unclassifiable is common because of insufficient data
- The critical factor is determining the "indeterminate" and "coincidental".
- Can impact population

**Cluster**

- May be able to prove causality
- Need to determine rate
- Extremely important for detecting immunization errors, but
- Often clusters are not true clusters, rather concurrent events, unrelated to each other.

When clusters are investigated, each case in the cluster shoud be investigated separately. The data should be linelisted to see if there is a pattern. If a new pattern is identified, a signal should be suspected.

**Summary**

- Causality assessment is the systematic review of individual or population data about an AEFI case to determine the likelihood of a causal association between the event and the vaccine/s received.
- The quality of the causality assessment depends on factors such as the effectiveness of the reporting system and the quality of the causality review process.
- Whether an AEFI is attributable or not to the vaccine or the vaccination programme, causality assessment determines what steps need to be taken to address the event.

# Actions and follow-up to AEFIs

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

## Corrective actions

### Patient care

Treatment must be the first response to an AEFI. Mild symptoms such as mild fever and pain are likely to be of short duration and can be managed by assuring and educating parents during immunization. Health workers need to know how to recognize, treat, and report AEFI immediately, if serious. It is of utmost importance to ensure that proper and early treatment is received by affected vaccinees (patients). The treatment of vaccine reactions is similar to other illnesses and is outlined in Annexes B and C.

### 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 programme while awaiting the completion of the investigation.

**Table 12: Actions to safeguard the public during an investigation**

| Stage of investigation | Actions |
|---|---|
| Incident detected | • Assess and investigate with appropriate degree of urgency.<br>• Possibly quarantine suspect vaccines.<br>• Start communicate with all concerned parties. |
| Investigation starts | • Ensure that investigator has adequate resources, provide more if needed (see Chapter 6).<br>• Increase surveillance to identify similar cases in and out of area: some time it requires enhanced or active surveillance to gather more information/data.<br>• Define any suspect vaccine.<br>• Keep continue communication with all concerned parties on process of investigation: do not suggest any hypothesis. |

| Stage of investigation | Actions |
|---|---|
| Investigator develops working hypothesis | • Do not communicate working hypothesis until confirmed. If 'immunization related errors' is the hypothesis, correct them. If 'vaccine problem' is suspected, quarantine suspect vaccines. |
| Investigator confirms working hypothesis | • Advise community of cause, and of planned response.<br>• Communicate with all concerned parties on findings. |

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

**Table 13: Actions to be taken upon completion of the investigation**

| Type of AEFI | Follow up action |
|---|---|
| Vaccine-related reaction | 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:<br>• withdrawal of the lot,<br>• changing manufacturing specifications or quality control, and<br>• obtaining vaccine from a different manufacturer. |
| Immunization errors | Correcting the cause of the error. This may mean one or more of the following:<br>• change in logistics for supplying vaccine,<br>• change in procedures at the health facility,<br>• training of health workers, and<br>• intensified supervision.<br>Whatever action is taken, it is important to review it at a later date to check that the errors have been corrected. |
| Coincidental | Main task is communication to ensure that people are persuaded that the link is coincidental. This communication can be challenging when there is widespread belief that the event was caused by immunization.<br>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 programme through false attribution is immense. |

## Logistics

Immunization supply chain, injection safety and waste management are part of immunization safety surveillance. Countries are encouraged to improve supply chain system and ensure safe injection practices as, generally, the governments act positively to the request by the immunization programme and NRA in such situations.

**Keypoints**

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 with the vaccine manufacturer and WHO is advisable before making any decision.

## Training and awareness

AEFI offers an opportunity for training and awareness for staff. Irrespective of type or outcome of AEFI, it can be used to update knowledge and develop skills and confidence among the staff.

Awareness can expand to involving all stakeholders' link to the immunization programme. The stakeholders include academia, teachers, volunteers, NGOs, policy makers, politicians and the media.

WHO has developed a training programme (basic and advanced courses) targeting different levels of immunization service providers. The training modules are routinely updated and guidelines for both facilitators and trainees are available in both printed and electronic forms. WHO is supporting countries to conduct both basic training and advanced causality assessment training programmes. Also, WHO training programmes are continuing and in 2012 an E-learning course was developed by WHO for those who are engaged in immunization safety surveillance activities. (See more at www.vaccine-safety-training.org)

**Summary**

- The response and follow-up for the AEFI will depend on the findings of the investigation.
- It is worth disseminating the results of the investigation so that others can learn from the experience. The investigation can also make a useful teaching resource in training investigators in the future.
- Immunization errors will need to be corrected. There should be a checking mechanism to ensure that they do not re-appear.
- For coincidental events, the main task is communication to avoid false attribution of blame.

# Communication

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 (programme error), 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.

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 (see Tables 12 and 13).

## 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 EPI 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 EPI 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 programmme 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:

- the ministry of health
- NRA /NCL
- politicians
- professionals / academia
- international agencies: WHO, UNICEF, and
- 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.

### Understanding the media perspective

The media are interested in stories that will attract attention and boost their audience and readership profile. One technique that they sometimes use is dramatizing and personalizing events. It is easy for media stories to create a sense of panic about events which are either unrelated to immunization (coincidental) or a localized immunization error. In addition, the media like statistics and tend to report on numbers of events, ignoring the context of the very small rate of occurrence. One other important fact is the media want early responses to their questions.

However, the media can be leveraged positively for the benefit of immunization. Health topics are popular among the public and, therefore, the media like to report about them. The media can be helpful allies in communicating public health messages. They can be helpful allies in reminding the public of the risk benefits of immunization. Building a personal relationship with key health reporters will help them to understand the public health perspective.

## 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:

**Media plan**

| | |
|---|---|
| A database of journalists | • A list of print and electronic media journalists covering health (local, national, international) with contact information.<br>• Use of a database where updating can be done immediately.<br>• Updating regularly any changes in the media list. |
| Information packages | An information package may contain the following documents both in hard copy and e-copies:<br>• Frequently Asked Questions (FAQs) on immunization in general, for specific disease, and AEFIs.<br>• A factsheet or a technical brief on a specific vaccine preventable disease.<br>• Recent updates: statistics, progress made in country, the Western Pacific Region, globally.<br>• Contact addresses of spokespersons (experts) in the ministry.<br>This information package needs regular updating. |
| The draft media release | Must specifically answer the six Ws for journalists:<br>• Who is affected/or responsible?<br>• What happened? What is being done?<br>• Where did it happen?<br>• When did it happen?<br>• Why did it happen?<br>• Will it happen again? |
| Information specific to media characteristics | • Local media: read and believed by more people in the community than national media.<br>• National media: has a wider reach and influences national agendas.<br>• International media: can influence national agendas. |

| | |
|---|---|
| A spokesperson system | • Identify in advance an appropriate spokesperson (or several spokespersons in the different agencies).<br>• Share contact details of spokesperson(s) with all concerned focal points at different levels of programme implementation.<br>• Ensure spokesperson(s) has experience or some training in dealing with the media. |

## Media conference

A media conference, media statements and dissemination of information through a range of channels are all useful tools for responding to public concern. A media conference gives all reporters access to the same information (i.e. no exclusive coverage). Thus, they may be less likely to sensationalize the events.

Media interest is usually greatest initially when relatively little is known. In this environment, rumours can flourish and the potential for harm is huge. It is wise to call a media conference early, even if there is only very limited information to give. This will prevent the circulation of rumours and build a relationship with the reporters. At the end of the press conference, advise that a further conference will be held within a day or so, at which time full details of the event and the investigation will be provided.

Professional organizations and other stakeholder parties may have greater credibility than the government, particularly in a crisis situation. A conference provides an opportunity for their unified support for immunization and the approach being taken to handle/investigate the problem.

Media conferences need to be used judiciously, as there are also dangers, especially if inadequately prepared and facing a hostile pack. Press conferences are hard work, and require careful preparation management, especially if different stakeholders will be present.

The following steps should be considered when preparing for a media conference:

- Who facilitates the press conference? One useful option is a senior expert committee member to take the responsibility.
- If there are several members on the panel, agree beforehand on the key message(s) in response to the AEFI.
- Agree on roles of each panel member beforehand, including the type of questions (media, political etc. each panel member may best handle).
- Panel members must avoid contradicting each other in the press conference unless it is critical to clarify something incorrect that has been said.
- Have a media kit ready and share it with journalists. The media kit may consist of a media release, supplementary background information (e.g. on the benefits of immunization) and a set of FAQs about immunization.

## Preparing key messages

Messages need to be as simple as possible. Use simple words and short sentences. It is helpful to tell a story, if possible. Create a 'word picture' to get the message across. The key messages should be kept to a minimum and should include some of these facts:

- The benefit of immunization in preventing certain diseases is well proven.
- It is very risky not to immunize (risk of disease and complications).
- VPDs caused millions of death and/or disability before the introduction of vaccines, and that situation would return without continued use of vaccines.
- Vaccines may/do cause reactions, but these are rarely serious and hardly ever cause long-term problems.
- Immunization safety is of paramount importance.
- Any suspicion of a problem is investigated (an advantage of well established immunization safety surveillance).
- The AEFI is currently being investigated, but is likely to be coincidental/due to a local problem (depending on type of event), and the immunization programme must continue to keep the population safe from disease.

## Preparing a press statement

All the information to be conveyed in a media conference should be prepared in advance and included in a press statement.

**An effective press release should include:**

- A complete account of the event, framed in its context (e.g. an isolated event or a cluster of AEFI, or a coincidental event). The media release must specifically answer the six Ws.
- No technical jargon.
- An outline of actions taken or planned (such as the AEFI investigation).
- A description of the possible cause of the event.
- An assurance that corrective action has been taken or will be taken.
- Reference to any relevant publication or web site.
- Sender's name and spokesperson's details.
- A one page (400-500 words maximum) account written in short sentences.
- Quotes from key officials may be used after seeking their permission. (The quotes must be positive and carry the key messages.)
- Repetition of key message.

### Follow-up actions with media

**Keeping promises to the media:** If it has been promised that the media will be kept updated about the investigation findings, make sure the media are updated by the promised date. If the findings have been delayed, ensure the media have been informed of the delay because they would be expecting answers.

**Providing answers to unanswered questions:** During media conferences, if a question could not be answered for any reason, get back to the media with the answers as soon as possible.

**Keeping media informed about subsequent developments:** If any decision or action is taken at the highest levels following AEFI investigations or during the investigations and the public must know about it, keep the media informed though a press release or hard copy document.

### Some practical advice on style and techniques for dealing with media

- Be sincere: do not equivocate.
- Be responsible: do not be defensive or find fault with others.
- Be positive: respond in a positive way.
- Be understanding: demonstrate firmness and confidence.
- Be clear.
- Be prepared: do homework in advance.
- Be calm: do not display or express emotion, but be sensitive to the issue.
- Be nice and polite, but stay serious and focussed. (Do not make jokes!)
- Be dynamic and maintain control over the interview.
- Be aware of own vulnerability: do homework in advance.

## 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.

**Summary**

- Communication with parents, community, staff, other stakeholders and the media is necessary and important.
- During communication make sure to build confidence on immunization programme. Be aware of risk-benefits of immunization and the progress and findings of the investigation.
- Communication needs assurance from one in authority, with knowledge and expertise in the subject.
- It is recommended to prepare a communication plan in advance, as it will minimize negative impact of AEFI-related matters.

# Evaluation of the immunization safety surveillance system

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

**Criteria should include:**

- 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.

(Please refer to Training for Mid-Level Managers: Disease Surveillance WHO/IVB/08.08)

- 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.
- Audit of corrective action:

o review by regional/national assessor to check that corrective action recommended has been checked, and adequacy of change in practice to prevent future programme error (programmatic errors).

The progress in immunization safety surveillance can also be monitored from the annual data reported to the national level.

## Annual data reports should include:

- number of AEFI reports, categorized by type of reaction and vaccine(s) and causality assessment (with denominator data on the number of doses of vaccine given);
- rate of each adverse event by vaccine (and lot number) nationally and by region;
- unusual or unusually severe events or large clusters; and
- summary of other important/unusual investigations.

Making the annual report available to health workers encourages and provides positive feedback for their reporting. Publication of the data also allows international comparisons to be made.

**Summary**

- There are three criteria to evaluate the immunization safety surveillance programme performances: (i) timeliness, completeness and accuracy of AEFI reporting, (ii) timelines and completeness of investigation performed, and (iii) audit of corrective actions.
- The safety surveillance can also be monitored by annual data reported to the national level.

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# Annex A

## Websites on vaccine safety

| | |
|---|---|
| Brighton Collaboration | www.brightoncollaboration.org |
| Centers for Disease Control and Prevention (CDC), USA | www.cdc.gov/nip/vacsafe<br>www.cdc.gov/vaccinesafety/Activities/VSD.html<br>http://www.cdc.gov/vaccines/recs/acip/default.htm |
| Chinese Centre For Disease Control And Prevention | http://www.chinacdc.cn/en/ |
| Council for International Organizations of Medical Sciences (CIOMS) | http://www.cioms.ch/ |
| Department of Health, UK | http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/ |
| Korean Centers 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, Department of Health, South Australia | www.health.sa.gov.au/pehs |
| Therapeutic Goods Administration, Australia | http://www.tga.gov.au/ |
| The International Conference on Harmonisation (ICH) | http://www.ich.org |
| World Health Organization | www.who.int/gpv-safety<br>www.who.int/immunization/sage/en<br>http://www.who.int/vaccine_safety/en/<br>http://www.wpro.who.int/health_topics/immunization/ |
| WHO Global Vaccine Safety Resource Centre (GVS RC) | http://www.who.int/entity/vaccine_safety/initiative/tech_support/en/index.html |
| WHO E-learning course on Vaccine Safety Basics | www.vaccine-safety-training.org |
| Aide-memoire on investigation causality assessment | http://www.who.int/vaccine_safety/en/ |
| WHO vaccine reaction rates information sheets | http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/index.html |

# Annex B

## AEFI case definitions and treatment

| Adverse event | Case definition | Treatment | Vaccines |
|---|---|---|---|
| Acute flaccid paralysis (VAPP) | Acute onset of flaccid paralysis within 4 to 30 days of receipt of 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:<br>• wheezing and shortness of breath due to bronchospasm<br>• one or more skin manifestations, e.g. hives, facial oedema, or generalized oedema. Less severe allergic reactions do not need to be reported<br>• 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 | Adrenaline injection | 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 |

| Adverse event | Case definition | Treatment | Vaccines |
|---|---|---|---|
| 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 Mycobacterium bovis BCG strain. Usually in immunocompromised individuals. | Should be treated with anti-tuberculous regimens including isoniazid and rifampicin. | BCG |
| Encephalopathy | Acute onset of major illness characterized by any two of the following three conditions:<br>• seizures<br>• severe alteration in level of consciousness lasting for one day or more<br>• distinct change in behaviour lasting one day or more.<br>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. | 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 |

| Adverse event | Case definition | Treatment | Vaccines |
|---|---|---|---|
| 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:<br>• limpness (hypotonic)<br>• reduced responsiveness (hyporesponsive)<br>• 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 Mycobacterium bovis 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 |

| Adverse event | Case definition | Treatment | Vaccines |
|---|---|---|---|
| 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 programme 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:<br>• swelling beyond the nearest joint<br>• pain, redness, and swelling of more than 3 days duration<br>• requires hospitalization.<br>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 |
| Thrombocytopaenia | 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 programme error. | Critical to recognize and treat early. Urgent transfer to hospital for parenteral antibiotics and fluids. | All |

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

# Annex C

## 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 adrenaline. 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-headedness, 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<br>Shallow breathing | Tachypnoea, 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, diarrhoea, 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. | | |

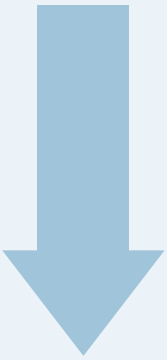
Before immunization, check for contraindications to immunization by asking about known allergies and previous adverse reactions to vaccines. In cases of possible serious allergies, check with a specialist before giving the vaccine.

## 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 may also become evident. Vaccinators should be able to recognize the following signs and symptoms of anaphylaxis:

| Diagnostic features of anaphylaxis | |
|---|---|
| Respiratory | **Airway**<br>• Throat and tongue swelling (pharyngeal/laryngeal oedema) - the patient has difficulty in breathing and swallowing and feels that the throat is closing up.<br>• Hoarse voice.<br>• Stridor<br>**Breathing**<br>• Bronchospasm<br>• Respiratory distress—2 or more of the following:<br>- Tachypnoea<br>- Increased use of accessory respiratory muscles<br>- Recession<br>- Cyanosis<br>• Grunting<br>• Respiratory arrest |
| Cardiovascular | • Hypotension<br>• Clinical diagnosis of uncompensated shock, indicated by the combination of at least three of the following:<br>- Tachycardia<br>- Capillary refill time >3 s<br>- Reduced central pulse volume<br>- Decreased level of consciousness or loss of consciousness<br>• Cardiac arrest<br>• Bradycardia (a slow pulse) is usually a late feature, often preceding cardiac arrest |
| CNS | • Confusion/Agitation<br>• Headache<br>• Loss of consciousness |

| Diagnostic features of anaphylaxis | |
|---|---|
| Dermatologic or mucosal | • Tingling of lips<br>• Generalized urticaria or generalized erythema<br>• 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).<br>• Generalized itching of skin especially hands, forehead and eyes in children<br>Note: Skin changes alone without life-threatening cardio-respiratory signs do not signify an anaphylactic reaction |
| Gastrointestinal | • Diarrhoea<br>• Colicky abdominal pain<br>• Vomiting<br>• Incontinence |

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

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

Symptoms limited to only one system can occur, leading to delay in diagnosis. Biphasic reactions where symptoms recur 8 to 12 hours after onset of the original attack and prolonged attacks lasting up to 48 hours have been described.

## Treatment

Adrenaline (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. Adrenaline that has a brown tinge must be discarded.

| Recommended minimum items for an emergency tray | |
|---|---|
| Evaluation equipment<br>• Sphygmomanometer<br>• adult and child cuffs<br>• Stethoscope | Drug<br>• Clearly labeled adrenaline (Epinephrine) vials<br>• Hydrocortisone vials<br>• Chlorphenamine vials<br>• Oxygen |
| Treatment equipment<br>• Tourniquet<br>• Disposable syringes<br>• Alcohol swabs<br>• IV solutions (LR, 0.9% Sodium chloride) | Resuscitation equipment<br>• Pocket mask with way valve<br>• Airways (small, medium, and large)<br>• Ambu bag<br>• Tongue depressors<br>• 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, 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 an anti-histamine may be used as adjunctive medication. Nebulized salbutamol is helpful for bronchospasm and nebulized adrenaline for laryngeal oedema.

| Adrenaline in the initial 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.<br><br>Note: Persisting or worsening cough associated with pulmonary oedema is an important sign of adrenaline overdose and toxicity. | 0.5 mL | According to age;<br><1years: 0.05mL<br>2-6 years: 0.15 mL<br>6-12 years: 0.3 mL<br>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 D

## Vaccine preventable diseases (VPD) risks

| Disease | Disease risk | |
|---|---|---|
| **Diphtheria** | | |
| Diphtheria is a potentially acute disease caused by exotoxin-producing *Corynebacterium diphtheriae*. 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.<br><br>Largely eliminated from the Western Pacific Region through successful immunization. | **Complication**<br>Heart<br>CNS<br><br>Mortality | <br>10%–25%<br>20%<br><br>2%–10% |
| **Haemophilus influenzae type b (Hib)** | | |
| *Haemophilus influenzae b (Hib)* 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.<br><br>Risk peaks in the second six months of life, then decreasing to become very rare after the fifth birthday. | **Disability**<br>Neurological impairment<br><br>Mortality | <br>15%–30%<br><br>5% |
| | Hib infection may manifest in a variety of systems leading most often to meningitis, pneumonia, epiglottis. Also causes septicaemia, cellulitis (often facial), septic arthritis, osteomyelitis | |
| **Hepatitis B** | | |
| 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. Carrier prevalence of HBV differs in different parts of the world, and within countries too. HBV, though similar to HIV in its primary routes of transmission, is hundreds of times more infectious than HIV. | **Mortality**<br>Acute hepatitis B<br>Chronic hepatitis B<br><br>**Complications**<br>Cirrhosis<br>Hepatocellular carcinoma (HCC)* | <br><1%<br>2%<br><br><br>5%<br>5% |
| | Lifetime risk of infection up to 50% (or even higher) in some countries of the Western Pacific Region compared to about 5% in Europeans. | |

| Human papilloma virus infections | | |
|---|---|---|
| Human papilloma virus (HPV) comprises 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; in many developing countries it remains the leading cause.<br><br>Prophylactic vaccines available are not therapeutic to combat existing infection. | 5–10% of infected women will progress persistent infection leading to precancerous lesions.<br>HPV caused 70% of cervical cancer.<br><br>**Morbidity**<br>Around 0.5million/year<br><br>**Mortality**<br>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 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. | **Morbidity**<br>1918 Pandemic- 500 million cases<br><br>**Mortality**<br>1918 Pandemic – 50–100 million<br>2009 Pandemic – 18 000 | |
| **JE** | | |
| JE is caused by a mosquito borne flavivirus, transmitted in Asia to North Australia. Children are highly susceptible to JE. | **Morbidity**<br>30 000–50 000 cases/year<br><br>**Disability**<br>Residual neurological psychiatric sequela 25–40%<br><br>**Mortality** Up to 0.3–60% | |
| **Meningococcal disease** | | |
| Bacteria called *Neisseria meningitidis* (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. | **Morbidity**<br>Developed counties<br>Developing countries<br><br>**Mortality**<br>Meningococcal meningitis<br>Fulminant septicaemia<br><br>**Disability**<br>Meningococcal meningitis | <br>1-5/100 000<br>10-25/100 000<br><br><br>5–10%<br>15–20%<br><br>5–10% |

| Measles | | |
|---|---|---|
| Measles is an acute viral illness 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.<br>It is highly infective and can be a threat in situations of natural disasters and war, if preventative measures are not taken.<br>Vaccination for measles has made a major impact on the morbidity and mortality in the Western Pacific Region and globally. | Otitis media<br>Pneumonia<br>Diarrhoea<br>Encephalitis<br><br><br><br>Subacute sclerosing panencephalitis (SSPE)<br><br><br>Mortality | 7-9%<br>1-6%<br>6%<br>0.05 -1%<br>(of these 15% die and 25% subsequently brain damaged)<br><br>0.001%<br><br><br>0.01- 0.1% |
| **Mumps** | | |
| Mumps is an acute viral illness caused by an RNA virus in the Paramyxoviridae family transmitted by respiratory droplets. Usually, it is a disease affecting primary school and pre-school children and 85% of adults show evidence of past infection. | Aseptic meningitis<br>Pancreatitis (usually mild)<br>Encephalitis<br>Deafness (Unilateral sensory) | 10%<br>4%<br>0.06 -0.3%<br>0.007% |
| | Orchitis in post pubertal males up to 38% (little evidence that this leads to sterility)<br>Oophoritis in post pubertal females 5% | |
| | Mortality | 0.02% |
| | Mumps during the first trimester of pregnancy is associated with an increased incidence of spontaneous abortions. Nevertheless, no evidence has suggested any congenital malformations. | |
| **Pertussis** | | |
| Pertussis (whooping cough) caused by *Bordetella pertussis* 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. | **Complications**<br>Convulsions<br>CNS complications<br><br>Mortality (<1 year) | <br>1 - 3%<br>0.1 to 0.3%<br><br>0.5% |

<table>
<tr><th colspan="3">Pneumococcal infections</th></tr>
<tr><td>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.</td><td colspan="2">Complications in invasive infection<br>Hearing impairment<br>Septicaemia<br>Septic arthritis<br>Osteomyelitis<br>Pneumonia<br>Meningitis<br><br>Mortality<br>1.4 million /year (<5 years)</td></tr>
<tr><th colspan="3">Poliomyelitis</th></tr>
<tr><td>Although the global eradication programme is rapidly clearing poliomyelitis from many parts of the world, the threat of reintroduction remains. Most infections were asymptomatic or non-specific febrile illness.</td><td>Aseptic meningitis<br>Paralytic illness<br><br>Mortality<br>(for paralytic case, increase with age)</td><td>~ 1%<br>1%<br><br>2%-10%</td></tr>
<tr><th colspan="3">Rubella</th></tr>
<tr><td rowspan="2">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.</td><td>Encephalitis<br>Mortality<br>Neonatal deaths<br>Other death<br>Fetal loss</td><td>0.02%<br><br>0.02%<br>0.0005%<br>0.005%</td></tr>
<tr><td>Congenital rubella syndrome (CRS):<br>Deaf children<br>Deaf-blind children<br>Mentally retarded children<br>Total CRS</td><td><br>0.06%<br>0.03%<br>0.014%<br>0.16%</td></tr>
<tr><th colspan="3">Tetanus</th></tr>
<tr><td>Tetanus is an infectious bacterial disease caused by Clostridium tetani. Under favourable 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 foetus, thereby preventing neonatal tetanus.</td><td colspan="2">Mortality<br>Neonatal tetanus (without treatment) 95%<br>Neonatal tetanus (with treatment) 20–90%</td></tr>
</table>

| Typhoid | |
|---|---|
| Typhoid fever is a life-threatening illness caused by the bacterium *Salmonella 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.<br><br>Large scale vaccine trails provide supportive evidence that mass vaccination strategies result in significant protection against typhoid fever. | **Morbidity**<br>With an estimated 16–33 million cases/ year; an average 21 million cases/year.<br>Its incidence is highest in children and young adults between 5 and 19 years old.<br><br>**Mortality**<br>CFR 1–4% and 20 000–600 000 deaths in endemic areas per year. |
| **Tuberculosis** | |
| Tuberculosis is a chronic disease caused by *Mycobacterium tuberculosis*. 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, which was first developed in 1920s.<br>Infants, young children, older people and the immunocompromised are more likely to progress rapidly to severe generalized infection with a poorer outcome. | **Morbidity**<br>8.8million cases/year (2010)<br>The risk of infection is variable. 95% of those infected enter a latent phase from which there is a lifelong risk of reactivation.<br><br>**Complications**<br>The other 5% progress directly to pulmonary tuberculosis or by lympho-haematogenous dissemination of bacilli to miliary, meningeal or other extrapulmonary involvement.<br>Extrapulmonary manifestations occur in 15% of adults and 25% of children<br><br>**Mortality**<br>1.45 million/year (2010) |
| **Varicella infection (chicken pox)** | |
| Varicella is an acute infectious disease caused by *Varicella zoster* virus (VZV). Varicella, the primary infection, is also called "chicken pox". The secondary or recurrent infection is caused by reactivated VZV associated with *Herpes zoster*, also known as 'shingles'.<br>It is primarily a disease of children under 10 years of age in most parts of the world, particularly in temperate region. It has also been frequently reported in adults. In subtropical regions 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. | **Complications**<br>Pneumonia<br>Aseptic meningitis/ encephalitis<br>Transverse myelitis GBS,<br>Myocarditis, arthritis, orchitis, uveitis, iritis and hepatitis |

# Annex E

## NRA indicators assessing pharmacovigilance including AEFI surveillance

| | Indicator | Critical Status |
|---|---|---|
| PV01 | Institutional regulations and guidelines for the monitoring and management of AEFI | Critical |
| | **PV01.01:** Legal provisions for pharmacovigilance exist in the public and or private sectors as appropriate. | Critical |
| | **PV01.02:** Guidelines exist, published and accessible, distributed or and available when needed to all staff involved in AEFI surveillance and are actively used. | Critical |
| | **PV01.03:** Provisions for the NRA to require the marketing authorization holder to perform a specific study of safety in the post-marketing period as necessary. | Critical |
| | **PV01.04:** Requirements exist for manufacturer to inform NRA of any new safety signal or marketing / regulatory decisions taken in other countries based on safety and is enforced by NRA. | Critical |
| PV02 | Quality Management system for pharmacovigilance activities | Critical |
| | **PV02.02:** Defined organizational chart & responsibilities to implement the quality management system. | Critical |
| | **PV02.02:** Management system to ensure traceability of actions. | Critical |
| | **PV02.03:** Auditing system documented & implemented (external & internal). | Not critical |
| PV03 | Human resource management | Critical |
| | **PV03.01:** Adequate qualified staff (number education, training, skills and experience) to perform pharmacovigilance activities. | Critical |
| | **PV03.02:** Staff training plan developed and implemented. | Not critical |
| | **PV03.03:** Monitoring of acquired skills and/or competencies of the staff after training. | Not critical |

| | Indicator | Critical Status |
|---|---|---|
| PV04 | Routine and functional system for regular review of safety and efficacy of the vaccine product for regulatory action | Critical |
| | **PV04.01:** AEFI data compiled and analysed/interpreted on regular (e.g. monthly) basis. | Critical |
| | **PV04.02:** Information on serious cases and AEFI clusters and investigation reports shared between NRA, NCL, national immunization program, and disease surveillance and pharmacovigilance staff. | Critical |
| | **PV04.03:** Formal/official communication and regular meetings among above-mentioned key players when dealing with AEFI. | Not critical |
| | **PV04.04:** Availability of expert committee to review serious AEFI cases and performance of the national PV system. | Critical |
| | **PV04.05:** Manufacturers are notified of significant safety and efficacy issues and kept up to date or/and at upon request. | Not critical |
| | **PV04.06:** Process to review/assess AEFI and initiate appropriate action including at the sub-national level, when needed. | Not critical |
| | **PV04.07:** Inclusion of "zero" events in routine periodic reports. | Not critical |
| PV05 | Capacity to detect and investigate significant vaccine safety issues | Critical |
| | **PV05.01:** Demonstrated capacity of the reporting system (active or passive, sentinel or countrywide/ statewide) with satisfactory sensitivity | Critical |
| | **PV05.02:** Documented evidence of appropriate investigations or sufficient elements indicative of capacity to investigate. | Critical |
| | **PV05.03:** Evidence of timely reporting and investigations is documented. | Critical |
| | **PV05.04:** A national database or system for collating, managing and retrieving AEFI reports exists. | Critical |

| | Indicator | Critical Status |
|---|---|---|
| PV06 | Regulatory action regarding vaccine performance | Critical |
| | **PV06.01:** Evidence that appropriate regulatory action consistent with NRA guideline is taken in case of serious AEFI cases. | Critical |
| | **PV06.02:** NRA regularly informed of data relevant to on-going assessment of vaccine performance. | Critical |
| PV07 | Communication system is in place to periodically inform stakeholders about AEFI information. | Not critical |
| | **PV07.01:** Periodic (quarterly or yearly) feedback on AEFI including summary and specific investigation reports. | Not critical |
| | **PV07.02:** Process is established for feedback down to health facility level. | Not critical |
| | **PV07.03:** Process is established for feedback to public/ community/patients/parents. | Not critical |

# Annex F

## Reporting Form for Adverse Events Following Immunization (AEFI)

| * Patient name or initials: | Sex<br>M ☐ F ☐ | AEFI reporting ID number: |
|---|---|---|

*Patient Address: Telephone No. (if available):

Locality/Village/Town/City: Province (State)/District:

| *Date of birth (DD/MM/YYYY)<br>☐☐/☐☐/☐☐☐☐ | OR<br>Age at onset<br>☐☐Years ☐☐Months ☐☐ ☐ Days | OR<br>Age Group<br>☐< 1 Year ☐ 1 to 5 years ☐ >5 Years |
|---|---|---|

*Reporter's Name:*

*Institution/Designation & Department:*

*Address:*

*Telephone & e-mail:*

*Health facility (or vaccination centre):*

| Vaccine | Name of vaccine given | Date of vaccination | *Time vaccinated | Dose number (Eg 1st, 2nd 3rd, 4th, 5th) | *Batch/Lot number of vaccine | Expiry date of vaccine |
|---|---|---|---|---|---|---|
| *Primary suspect | | | | | | |
| (Other)1 | | | | | | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |

*Date & Time AEFI started: Date of first reporting:

*Tick box(es) and describe adverse event(s): Describe AEFI: (Signs and symptoms):

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

☐ Abscess ☐ sterile ☐ bacterial

☐ Seizures ☐ febrile ☐ Afebrile

☐ Sepsis
☐ Encephalopathy
☐ Toxic shock syndrome
☐ Thrombocytopenia
☐ Anaphylaxis
☐ Other (specify) .....

*Outcome
☐ Recovered fully Date Recovery (DD/MM/YYYY) ☐☐ / ☐☐ / ☐☐☐☐
☐ Recovered partially
☐ Died If died, date of death ☐☐ / ☐☐ / ☐☐☐☐ Autopsy Yes ☐ No ☐
☐ Unknown

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

First decision making level to complete:

Investigation (preliminary) needed? ☐ Yes ☐ No If yes, date investigation planned: ☐☐ / ☐☐ / ☐☐☐☐

National level to complete:

Date report received at national level: ☐☐ / ☐☐ / ☐☐☐☐ AEFI worldwide unique ID (If available):

Comments:

*Compulsary field
The completed form should be sent to the first decision making level and a copy sent to the National level

# Annex F1:

## Proposed detailed core variables required reporting in AEFI surveillance

| ICH | Core variables |
|---|---|
| Identity | Date AEFI first aware by health system |
| | Type of report |
| | Country where the AEFI occurred |
| Case | Body weight (kg) |
| | Body height (cm) |
| | Birth weight (gram) |
| | Gestational age |
| | Mother vaccinated |
| | Details about pregnancy |
| | Concomitant medication |
| Vaccine | Route of administration of this particular vaccine in this vaccinee |
| | Dose (quantity) of this particular vaccine in this vaccinee (e.g. in ml or drops etc.) |
| | Vaccine presentation |
| | Vaccine(s) name (trade name) |
| | Vaccine expiry date |
| | Site of administration of this particular vaccine in this vaccinee |
| | Diluent batch number |
| | Vaccination session |
| | Tests done on vaccine logistics after AEFI |
| Event | Was the AEFI medically confirmed? |
| | Date of hospitalization |
| | AEFI treatment details |
| | Date of discharge |
| | Tests done on Patient |
| | Date and time of AEFI termination |
| | Duration |
| | Death date |
| | Death cause |
| | Was an autopsy performed? |
| | Details of autopsy |
| | AEFI category |
| Details | AEFI as described by the first reporter |
| | Additional information |

# Annex G

## Adverse Events Following Immunization
## Case Investigation Form

Necessary data should be obtained from the parents / patient / physicians / hospital records and patient medical record

| Family Name | First Name | AEFI Reporting ID | AEFI Investigation ID |
|---|---|---|---|
| Date Investigation Started (DD/MM/YY) ☐☐ / ☐☐ / ☐☐☐☐ | | Date Investigation Completed (DD/MM/YY) ☐☐ / ☐☐ / ☐☐☐☐ | |

**Immunization History (trigger event)**

Type and dose of vaccine: .....

Date & time vaccinated:..... Date & time onset of AEFI/present illness:.....

Reporting AEFI (Describe).....

.....

Any issue with vaccine storage, preparation and administration:.....

.....

**Community Investigation**

| *Any history of similar events reported among those vaccinated* | *Yes* | *No* | *Unknown* | If yes (specify) |
|---|---|---|---|---|
| - At the same clinic session | ☐ | ☐ | ☐ | ..... |
| - Using same vaccine at previous clinic sessions at the same clinic centre | ☐ | ☐ | ☐ | ..... |
| - Using same vaccine at the other clinic centers | ☐ | ☐ | ☐ | ..... |
| - History of similar events reported among those unimmunized | ☐ | ☐ | ☐ | ..... |

**Past Medical History & Family medical history**

| | Yes | No | Unknown | If yes (specify) |
|---|---|---|---|---|
| - Existing congenital disorders | ☐ | ☐ | ☐ | ..... |
| - Persisting underlying disease | ☐ | ☐ | ☐ | ..... |
| - Previous history of significant illnesses | ☐ | ☐ | ☐ | ..... |
| - Family history of similar event | ☐ | ☐ | ☐ | ..... |
| - Previous history of similar event | ☐ | ☐ | ☐ | ..... |

Any significant other information:.....

.....

**Clinical & Laboratory investigation findings**

**Autopsy Findings** *(only for death)*

**Diagnosis**

**Conclusion as to the cause of AEFI** *(Tick category and rank if more than one)*

| ☐ **Immunization Error related reaction** | ☐ **Vaccine Reaction** | ☐ **Coincidence** | ☐ **Immunization Anxiety related reaction** |
|---|---|---|---|
| ☐ Non sterile injection | ☐ Vaccine quality defect | ☐ Similar event in unimmunized | ☐ Syncope |
| ☐ Vaccine prepared incorrectly | ☐ vaccine product-related | ☐ Illness not relevant to vaccine | ☐ Hyperventilation |
| ☐ Incorrect technique/site dose | ☐ known vaccine reaction | ☐ Underline disease is obvious | ☐ Hysteria |
| ☐ Transportation/storage issue | ☐ Other..... | ☐ Other..... | ☐ Other..... |
| ☐ Other..... | | | |

Reason(s) for conclusion:

**Corrective Action**

**Recommendations**

**Name of Investigator :** **Designation :**

**Signature:** **Date:**

# Annex H

## AEFI line listing

**ANNEX H**

**AEFI line listing**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | Name/ID |
| | | | | | | | | | | | | | Village/Town/District |
| | | | | | | | | | | | | | Date of birth(dd/mm/yyyy) and Age |
| | | | | | | | | | | | | | Date of immunisation(dd/mm/yyyy) |
| | | | | | | | | | | | | | Reaction type (code) [1] Minor [2]Severe/Serious |
| | | | | | | | | | | | | | Outcome(Recovered disability/Died) |
| | | | | | | | | | | | | | Suspect vaccine(name and dose, e.g. Penta-2) |
| | | | | | | | | | | | | | Vaccine batch/Lot number |
| | | | | | | | | | | | | | Diluent batch number |
| | | | | | | | | | | | | | Onset time interval (hours, days, weeks) |
| | | | | | | | | | | | | | Date reporting (dd/mm/yyyy) |
| | | | | | | | | | | | | | Investigated?(If yes, date) |
| | | | | | | | | | | | | | Cause (code) |

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

Coding for cause of AEFI:

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

# Annex I

## AEFI Causality Assessment – Step 2: Event checklist

| | Y N UK NA | Remarks |
|---|---|---|
| **I. Is there strong evidence for other causes?** | | |
| Does a clinical examination or laboratory tests on the patient confirm another cause? | ☐☐☐☐ | |
| **II. Is there a known causal association with the Vaccine / Vaccination?** | | |
| ***Vaccine Product(s)*** | | |
| Is there evidence in literature that this vaccine (s) may cause the reported event, even if administered correctly? | ☐☐☐☐ | |
| Did a specific test demonstrate the causal role of the vaccine or any of the ingredients? | ☐☐☐☐ | |
| ***Immunization Error*** | | |
| Was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. usage beyond expiry date, wrong recipient etc.)? | ☐☐☐☐ | |
| Was the vaccine (ingredients) administered unsterile? | ☐☐☐☐ | |
| Was the vaccine's physical condition (e.g. colour, turbidity, 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. break in cold chain during transport, storage and/or immunization session, etc.)? | ☐☐☐☐ | |
| Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)? | ☐☐☐☐ | |
| ***Immunization Anxiety*** | | |
| Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)? | ☐☐☐☐ | |
| **II (Time). If "yes" to any question in II, was the event within the time window of increased risk?** | | |
| Did the event occur within an appropriate time window after vaccine administration | ☐☐☐☐ | |
| **III. Is there strong evidence against a causal association?** | | |
| Is there strong evidence against a causal association? | ☐☐☐☐ | |
| **IV. Other qualifying factors for classification** | | |
| Could the event occur independent 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 / toxin prior to the event? | ☐☐☐☐ | |
| Was there acute illness prior to the event? | ☐☐☐☐ | |
| Did the event occur in the past independent 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 UK: Unknown NA: Not applicable**

# Annex J

## Checklist for immunization safety surveillance system

**1. Be prepared**

- Clarify respective roles of the NRA and EPI. Agree on the overall goal and specific objectives for the system.
- Identify the resources available and needed. 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,their case definitions, 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 of an AEFI, and which ones should be reported.
- Consider establishment of a compensation scheme for specified AEFI.

**2. Receiving a report (investigating authority)**

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

**3. Investigating and collecting data**

- Ask about the patient, the event and the vaccine.
- Ask about immunization service and observe it in action. (Emphasize that the 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. Analyse the data**

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

**5. Take action**

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