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Global Manual on Surveillance of Adverse Events Following Immunization

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This manual has been developed on the basis of the Guidelines for immunization programme managers on surveillance of adverse events following immunization (second edition) published by the WHO Western Pacific Regional Office in 2012.

Contents

Tables and Figures

Glossary

Adverse event following immunization (AEFI)*	Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.
Causal association	A cause-and-effect relationship between a causative (risk) factor and an outcome. Causally associated events are also temporally associated (i.e. they occur after vaccine administration), but events which are temporally associated may not necessarily be causally associated.
Causality assessment	In the context of AEFI surveillance, causality assessment is a systematic review of data about AEFI case(s) in order to determine the likelihood of a causal association between the event and the vaccine(s) received.
Cluster	Two or more cases of the same or similar events related in time, geography (place), and/or vaccine administered. AEFI clusters are usually associated with a particular supplier/ provider, health facility, and/or a vial of vaccine or a batch of vaccines.
Coincidental events*	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.
Contraindication	A situation where a particular treatment or procedure, such as vaccination with a particular vaccine, must not be administered for safety reasons. Contraindications can be permanent (absolute), such as known severe allergies to a vaccine component, or temporary (relative), such as an acute/severe febrile illness.
Injection safety	The public health practices and policies dealing with various aspects of the use of injections (including adequate supply, administration and waste disposal) so that the provider and recipient are not exposed to avoidable risks of adverse events (e.g. transmission of infective pathogens) and creation of dangerous waste is prevented. All injections, irrespective of their purpose, are covered by this term (see definition of safe injection practices).

Immunity	The ability of the human body to tolerate the presence of material "indigenous" to the human "body" (self) and to eliminate "foreign" (non-self) material. This discriminatory ability provides protection from infectious diseases, since most microbes are identified as foreign by the immune system.
Immunization safety	The process of ensuring the safety of all aspects of immunization, including vaccine quality, adverse events surveillance, vaccine storage and handling, vaccine administration, disposal of sharps and management of waste.
Immunization safety surveillance	A system for ensuring immunization safety through detecting, reporting, investigating and responding to AEFI.
Non-serious AEFI	An event that is not "serious" and does not pose a potential risk to the health of the recipient. Non-serious AEFI should also be carefully monitored because they may signal a potentially larger problem with the vaccine or immunization, or may have an impact on the acceptability of immunization in general.
Safe injection practice	Practices which ensure that the process of injection carries the minimum of risk, regardless of the reason for the injection or the product injected.
Serious AEFI	An event that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/ incapacity, or is a congenital anomaly/birth defect. Any medical event that requires intervention to prevent one of the outcomes above may also be considered as serious.
Signal* (safety signal)	Information (from one or multiple sources) which suggests a new and potentially causal association, or a new aspect of a known association, between an intervention and an adverse event or set of related adverse events, that is judged to be of sufficient likelihood to justify verificatory action.
Surveillance	The continuing, systematic collection of data that 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	A biological preparation that improves immunity to a particular disease. In addition to the antigen, it contains multiple components (excipients) and each component may have unique safety implications.
Vaccine pharmacovigilance*	The science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.
Vaccine product-related reaction*	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product, whether the active component or one of the other components of the vaccine (e.g. adjuvant, preservative or stabilizer).
Vaccine quality defect-related reaction*	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.
Vaccination failure*	Vaccination failure may be defined on the basis of clinical endpoints or immunological criteria where correlates or surrogate markers for disease protection exist. Primary failure (e.g. lack of seroconversion or seroprotection) needs to be distinguished from secondary failure (waning immunity). Vaccination failure can be due to (i) failure to vaccinate (i.e. an indicated vaccine was not administered appropriately for any reason) or (ii) because the vaccine did not produce its intended effect.
Vaccine reaction	An event caused or precipitated by the active component or one of the other components of the vaccine. It may also relate to a vaccine quality defect.
Vaccine safety	The process that maintains the highest efficacy of, and lowest adverse reaction to, a vaccine by addressing its production, storage and handling. Vaccine safety is a part of immunization safety.

*Source: Definition and application of terms for vaccine pharmacovigilance. Report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Geneva: Council for International Organizations of Medical Sciences; 2012 (http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf, accessed 25 July 2014).

Abbreviations

AEFI	Adverse event following immunization
BCG	Bacillus Calmette-Guerin vaccine for tuberculosis (TB)
CIOMS	Council for International Organizations of Medical Sciences
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
HHE	Hypotonic hyporesponsive episode
Hib	Haemophilus influenzae type b vaccine
ICH	International Conference on Harmonization
IPV	Inactivated poliovirus vaccine
LAV	Live attenuated vaccine
MMR	Measles-mumps-rubella vaccine
NRA	National regulatory authority
NCL	National control laboratory
OPV	Oral poliovirus vaccine
PCV	Pneumococcal conjugate vaccine
PvV	Pentavalent (DTP-HepB-Hib) vaccine
TSS	Toxic shock syndrome
VAPP	Vaccine-associated paralytic poliomyelitis
VPD	Vaccine-preventable disease
WHO	World Health Organization

1 Purpose

Immunization is one of the most effective public health interventions for protecting the individual and the public from vaccine-preventable diseases (VPDs). Immunization has saved millions of lives. Modern vaccines are safe and effective. However, like other medicinal products, vaccines are not free from adverse reactions.

Vaccines rarely cause serious adverse reactions, and common reactions are minor and self-limited. We monitor the safety of vaccines by looking for adverse events following immunizations (AEFI). An AEFI may be caused by a vaccine reaction but often, particularly if the event is serious, the event is coincidental to vaccination. Other events may be caused by an error in administration or handling of the vaccine. Irrespective of the specific cause, an AEFI may lead to public suspicions of vaccines and parents may refuse further immunization for their children, making them susceptible to VPDs which are disabling and life-threatening. Vaccine pharmacovigilance, which includes the surveillance of AEFI (i.e. systematic collection of data on medically important events following immunization, which provides information on investigation leading to necessary follow-up action), should be part of all immunization programmes as this helps sustain public confidence in the programme.

This manual provides guidance for the 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;
- the objectives of vaccine and immunization safety surveillance;
- AEFI surveillance system: reporting, investigation, causality assessment and the new classification of cause-specific AEFI;
- understanding vaccine reactions for better decision-making;
- the best use of surveillance data;
- response processes, including a communication strategy on immunization safety for the public and the media.

As VPDs become less prevalent as a result of effective immunization programmes, more public attention will be given to AEFI. New vaccines are being added to the programmes and the schedule contains more vaccine antigens, with some included in multivalent vaccines. For example, instead of the trivalent vaccines (DTP), most countries

are now using either tetravalent (DTP-Hib or DTP- HepB) or pentavalent (DTP-HepB-Hib) combined vaccines. With emerging diseases such as H1N1 influenza, demand for seasonal and pandemic influenza vaccines has grown. An increase in the number of vaccines given (e.g. in mass immunization campaigns) will lead to more AEFI, with some being associated with vaccines or immunization and others being unrelated to them (i.e. due to coincidental events). Immunization error-related reactions (previously known as "programme error") may also increase. Reporting and investigating AEFI can be used to identify and correct immunization error-related reactions and may help to distinguish an inconsistent coincidental event from a vaccine reaction and other immunization-related events. AEFI surveillance allows for proper management of AEFI and avoids inappropriate responses to reports of AEFI that can create a sense of crisis. For example, without an immunization safety surveillance system a coincidental event may be mistaken for a vaccine reaction and could lead to inappropriate suspension of a vaccine programme.

Public awareness of vaccine safety has grown through increased access to information through the internet, television and other media. In addition, the vigilance of health-care providers with regard to vaccine safety has increased due to the strengthening of AEFI surveillance. As a result, more concerns about the quality and safety of vaccines are highlighted and more information is demanded by the public and service providers. In this increasingly complex situation, 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 aware of AEFI and be prepared to respond to public concerns. 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.

The goals of these guidelines are to improve the efficiency and quality of AEFI surveillance activities – and thus strengthen the quality of immunization programmes at national and regional levels – and to ensure the immunization safety of all recipients of vaccines.

KEY POINTS

Who will use this manual?

This manual will be useful for immunization programme managers, staff of the national regulatory authority (NRA) at national and subnational levels, immunization service providers at institutions and in the field, staff of pharmacovigilance centres and other stakeholders in immunization services.

2 Principles of immunization and understanding vaccines

2.1 Immunity

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

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

2.1.1 Active immunity

Active immunity is the stimulation of the immune system to produce antigen-specific humoral (antibody) and cellular immunity for which the protective function of immunization is associated with cells. Usually this lasts for many years, and often for 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, the memory cells begin to replicate and produce antibody very rapidly to re-establish protection.

A safer 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) that is added to improve the immunogenicity of the vaccine. Host factors such as age, nutritional factors, genetics and coexisting disease may also affect the response.

2.1.2 Passive immunity

Passive immunity is the transfer of antibody produced by a human or animal to another. This may be natural (from mother to infant) or artificial[1] (when high levels of human antibodies specific to a pathogen or toxin are transferred to non-immune individuals) 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. However, maternal antibodies may inhibit successful immunization against live or attenuated live viral vaccines by interfering with vaccine virus growth. For example, vaccination with the live attenuated measles vaccine needs to be given at the appropriate age (usually after 9 months of age) at which time the presence of maternal antibodies (to measles) in the infants has fallen.

Passive artificial immunity provides only temporary protection against infection – as short as 1-6 weeks – because the antibodies degrade over time.

2.1.3 Herd immunity

Herd immunity describes immunity that occurs when the vaccination of a portion of the population (the "herd") provides protection to unprotected individuals.[2] 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 the population are immune. Hence, the higher the proportion of immune individuals in a population, the lower the likelihood that a susceptible person will come into contact with an infectious agent. Both theoretically and practically, disease usually disappears before immunization levels reach 100%, as has been seen with smallpox and is hoped will happen with 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 and transmissibility of the disease, the efficacy and overall coverage of the vaccine, vaccination coverage among the population at risk and the contact parameter for the population.

2.1.4 How does immunization work?

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

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1 The history of vaccines. Philadelphia (PA): The College of Physicians of Philadelphia (http://www.historyofvaccines.org/content/articles/passive-immunization, accessed 1 August 2014).

2 Community immunity («herd Immunity»). Washington (DC): US Department of Health and Human Services (http://www.vaccines.gov/basics/protection, accessed 1 August 2014).

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 immune response, which is much faster than the primary response and produces predominantly IgG rather than IgM. The aim of vaccination is to generate enough immune cells and antibodies specific to that vaccine-preventable microbe in order to provide long-lasting protection against the disease.

2.2 Vaccines

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

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

Combined vaccines contain two or more different antigens (e.g. DTwP, DTPa-HepB-Hib). The potential advantages of combination vaccines include reducing the cost of storing and administering multiple vaccines simultaneously, reducing the cost of extra health-care visits, improving timeliness of vaccination, and facilitating the addition of new vaccines into immunization programmes.

There is no evidence that the administration of several antigens in combined vaccines increases the burden on the immune system, which is capable of responding to millions of antigens at a time.[3] Combining antigens usually does not increase the risk of adverse reactions and can lead to an overall reduction in adverse reactions.[4] For instance, it can decrease the number of anxiety-related reactions and the chances of immunization error-related reactions.

[3] Frequently asked questions about multiple vaccinations and the immune system. Atlanta (GA): Centers for Disease Control and Prevention (http://www.cdc.gov/vaccinesafety/vaccines/multiplevaccines.html, accessed 1 August 2014).

[4] Alberta immunization policy – general guidelines. Edmonton: Government of Alberta; 2014 (http://www.health.alberta.ca/documents/AIP-General-Guidelines.pdf, accessed 1 August 2014).

2.2.1 Classification of vaccines

There are different types of vaccines, such as: live attenuated, inactivated (killed antigen), subunit (purified antigen) and toxoids (inactivated toxic compounds). The characteristics of these vaccines differ, and these characteristics determine how the vaccines work (Table 1).

2.2.1.1 Live attenuated vaccines

Live attenuated vaccines (LAVs) are derived, as are inactivated vaccines, from "wild" or disease-causing viruses or bacteria. These wild viruses or bacteria are attenuated, or weakened, in a laboratory, usually by repeated culturing. Live microorganisms provide continuous antigenic stimulus, giving sufficient time for memory cell production in the vaccinated person, and they are also capable of replicating within the host. The immune response to a LAV is virtually identical to that produced by a natural infection.

Table 1. **Classification of vaccines**

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

There are a few safety and stability concerns for LAVs, including the rare possibility of attenuated pathogens reverting to their original form and causing disease, particularly in individuals with compromised immune systems[5] (e.g. HIV) or in cases of sustained infection (BCG - local lymphadenitis), or immunization errors (reconstitution, cold chain).

The first dose of LAV usually provides protection. For instance, 82-95% of recipients will respond to a single dose of measles vaccine at 9 months.[6] The second dose is given as an additional opportunity to induce immunity in those who did not respond to the first dose, and with the second dose more than 95% of persons will be immune. Immunity following live vaccines is long-lasting and booster doses are not necessary, with the exception of OPV which requires multiple doses for seroconversion. LAVs are labile and can be damaged or destroyed by heat and light. They must be handled and stored carefully. Currently used LAVs include vaccines for influenza (intranasal), measles, mumps, OPV, rotavirus, rubella, varicella and yellow fever. Live attenuated bacterial vaccines include BCG and oral typhoid vaccine.

2.2.1.2 Inactivated (killed) vaccines

Inactivated vaccines are produced by growing viruses (e.g. poliomyelitis vaccine) or bacteria (e.g. whole-cell pertussis vaccine) in a culture medium and then inactivating them with heat or chemicals (usually with formaldehyde). Because they are not alive, these viruses cannot grow in a vaccinated individual and therefore cannot cause the disease, even in an immunodeficient person. Inactivated vaccines are generally safer than LAVs, with no risk of inducing the disease. Unlike LAVs, inactivated vaccines are usually not affected by circulating maternal antibodies and do induce an immune response in an infant. They are often more stable than a LAV.

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 only 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 with little or no cell-mediated immunity. Antibody titres against inactivated antigens diminish with time. As a result, some inactivated vaccines may require periodic supplemental doses to increase, or "boost", antibody titres.

2.2.1.3 Subunit vaccines

The whole organism is grown in culture media and then is further processed to purify only those components to be included in the vaccine. Subunit vaccines are categorized in three groups: protein-based, polysaccharide and conjugate vaccines.

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5 Global Advisory Committee on Vaccine Safety, 3–4 December 2009. Wkly Epidemiol Rec. 2010;85(5):29-36 (http://www.who.int/vaccine_safety/committee/reports/Dec_2009/en/index.html, accessed 1 August 2014).

6 Measles vaccines: WHO position paper. Wkly Epidemiol Rec. 2009;84(35):349–360 (http://www.who.int/wer/2009/wer8435.pdf, accessed 1 August 2014).

Protein-based vaccines

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 antigen is identical to the natural hepatitis B surface antigen but does not contain virus DNA and is unable to replicate and produce infection. Protein-based subunit vaccines present an antigen to the immune system without viral particles.

Another protein-based vaccine is the acellular pertussis (aP) vaccine which contains inactivated pertussis toxin (protein) and may contain one or more other pertussis components. The pertussis toxin is detoxified either by chemical treatment or by molecular genetic techniques.

Polysaccharide vaccines

When infecting humans, some bacteria are protected by a polysaccharide (sugar) capsule that helps the organism to evade the human defence systems, especially in infants and young children. Polysaccharide vaccines provoke an immune response against this capsule; however, they are not very immunogenic and induce only short-term immunity, particularly in infants and young children. Examples of these vaccines are the meningococcal and pneumococcal polysaccharide vaccines which contain the polysaccharide coats, or capsules, of encapsulated bacteria which are purified and non-infectious.

Conjugated vaccines

Infants and young children do not sufficiently respond well to polysaccharide vaccines which produce antibodies through a T-cell independent mechanism. If these polysaccharide antigens are chemically linked (conjugated) to a protein that T-cells recognize, then the conjugated vaccines can elicit strong immune responses and immune memory in young children. Haemophilus influenzae type b (Hib)[7], pneumococcal (PCV-7, PCV-10, PCV-13)[8] and meningococcal A are conjugated vaccines that are widely used provide longer protection, even among young children.

2.2.1.4 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. While they are no longer toxic, the toxoid is still capable of inducing a specific immune response that is protective against the effect of the toxin. To increase immune response, toxoid is combined with an adjuvant (e.g. aluminium salts). Toxoids are not highly immunogenic and require booster doses. They are stable, long-lasting and have a good safety profile.[9]

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[7] WHO position paper on Haemophilus influenzae type b conjugate vaccines. Wkly Epidemiol Rec. 2006;81(47):445—452 (http://www.who.int/immunization/topics/hib/en/, accessed 1 August 2014).

[8] Pneumococcal conjugate vaccine for childhood immunization. WHO position paper. Wkly Epidemiol Rec. 2007;82(12):93–104 (http://www.who.int/wer/2007/wer8212/en/, accessed 1 August 2014).

[9] Tetanus vaccine. WHO position paper. Wkly Epidemiol Rec. 2006;81(20):197–208 (http://www.who.int/wer/2006/wer8120/en/, accessed 1 August 2014).

2.2.2 Other components of vaccines (excipients)

Adjuvants

Sometimes a substance is added to a vaccine to enhance the immune response by degree and/or duration, thus making it possible to reduce the amount of antigen (immunogen) per dose or the total number of doses needed to achieve immunity. An adjuvant helps slow escape of the antigen from the injection site to lengthen the duration of contact between the antigen and the immune system. The commonly-used adjuvant is aluminium salts (aluminium potassium phosphate or aluminium potassium sulfate) which primarily enhance the immune response to protein. They have been shown to be safe over several decades of use. Oil-in-water emulsions (ASO3 and ASO4) have used as adjuvants in some vaccines developed in recent years. Rarely, adjuvants may cause injection site reactions – including subcutaneous nodules, sterile abscess, granulomatous inflammation and contact hypersensitivity – particularly if the administration technique is wrong (e.g. subcutaneous). Adjuvant-containing vaccines should be administered intramuscularly.

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 contain less than 25 micrograms of neomycin per dose (less than 0.000025 g). Persons who are known to be allergic to neomycin should be closely observed after vaccination so that any allergic reaction can be treated at once. Neomycin allergy is very rare.

Preservatives

These are chemicals (e.g. thiomersal, phenol derivatives) that are added to killed or subunit vaccines in order to inactivate viruses, detoxify bacterial toxins, and prevent serious secondary infections in multidose vials as a result of bacterial or fungal contamination. Thiomersal, which contains ethyl-mercury, has been subject to intense public scrutiny but there is no evidence of any toxicity from thiomersal in vaccines.[10]

(Formaldehyde, an inactivating agent, is used during the manufacturing process to inactivate viruses and bacteria and detoxify toxins and is removed almost completely during the purification process.)

Stabilizers

Stabilizers are used to help the vaccine maintain its effectiveness during storage. To confirm product quality (antigenicity) or stability, compounds may be added to vaccines to address problems with acidity, alkalinity (pH), stability and temperature.

Vaccine stability is essential, particularly if the cold chain is unreliable. Instability can cause decreased infectivity of LAVs and loss of vaccine antigenicity. Bacterial vaccines

[10] WHO Global vaccine safety webpage (http://www.who.int/vaccine_safety/committee/topics/thiomersal/en/, accessed 22 August 2014).

can become unstable due to hydrolysis and aggregation of protein and carbohydrate molecules. Stabilizing agents include MgCl2, MgSO4, lactose-sorbitol and sorbitol-gelatine.

KEY POINTS

Other components (excipients) are added to vaccines for different purposes and some are removed in subsequent manufacturing steps. However, minute traces may remain in the final product. The amounts present are of consequence only to individuals who are allergic to them.

2.3 Contraindications and precautions

A contraindication to vaccination is a rare characteristic in a recipient that increases the risk of a serious adverse reaction. Ignoring contraindications can lead to avoidable vaccine reactions. One of the most serious reactions following vaccination is anaphylaxis which is the only contraindication applicable to subsequent doses of the same vaccine. Most contraindications such as severe acute illnesses (e.g. acute respiratory tract infection) or treatment with steroids are temporary and the vaccination can be administered later. These are called temporary or relative contraindications.

Precautions are not contraindications, but are events or conditions that should be considered in determining if the benefits of the vaccine outweigh the risks (especially if the would-be recipient is immunocompromised or pregnant). Precautions stated in the product labelling may sometimes be inappropriately interpreted as contraindications, resulting in missed opportunities to vaccinate.

No evidence exists of risk to the foetus from vaccinating pregnant women with inactivated virus, bacterial vaccines or toxoids. LAVs administered to a pregnant woman pose a theoretical risk to the fetus. However, the benefits of vaccinating pregnant women usually outweigh potential risks when the likelihood of disease exposure is high, when infection would pose a risk to the mother or fetus, and when the vaccine is unlikely to cause harm.[11]

The safety and effectiveness of vaccines in immunocompromised persons are determined by the type of immunodeficiency and degree of immunosuppression. Each immunocompromised person is different and presents unique considerations with regard to immunization. There is a potential for serious illness and death if immunocompromised persons are under-immunized, and every effort should be made

[11] See: Immunization during pregnancy. Geneva: World Health Organization (http://www.who.int/vaccine_safety/committee/topics/influenza/pregnancy/Jun_2013/en/index.html, accessed 1 August 2014);
Guidelines for vaccinating pregnant women. Atlanta (GA): Centers for Disease Control and Prevention (http://www.cdc.gov/vaccines/pubs/preg-guide.htm).

to ensure adequate protection through immunization. However, inappropriate use of LAV can cause serious adverse events in some immunocompromised persons as a result of uncontrolled replication of the vaccine virus or bacterium.[12]

Summary

Immunity is the body's innate ability to protect itself 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 it can be caused through vaccination and also lasts for a long period.
- Passive immunity can also be either natural or artificial. Both last for a relatively short period.
- Vaccine is a biological product that improves immunity to a given disease and is divided into four types: live attenuated, inactivated (killed), subunit and toxoid vaccines.
- Excipients (antibiotics, and stabilizers) contained in vaccines can very rarely cause reactions.
- Knowledge of what a vaccine contains is important in safety surveillance.

Bibliography:

Plotkin S, Orenstein W, Offit P. Vaccines, sixth edition. Edinburgh: Elsevier/Saunders; 2013.

WHO has developed position papers for vaccines which are periodically reviewed and updated. These position papers provide details of vaccines, including their safety profiles. See: http://www.who.int/immunization/documents/positionpapers/en/index.html, accessed 1 August 2014.

[12] Canadian immunization guide. Vaccination of specific populations. Ottawa: Public Health Agency of Canada (http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-07-eng.php, accessed 1 August 2014).

3 Adverse events following immunization

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

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. resulting from the vaccine or immunization process – or coincidental events that are not due to the vaccine or immunization process but are temporally associated with immunization.

In 2012, the existing classification regarding cause-specific categorization of AEFI was revised by the Council for International Organizations of Medical Sciences (CIOMS) and WHO and a new categorization was introduced (Table 2).

Table 2. Cause-specific categorization of AEFI (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")	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization.
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety, but a temporal association with immunization exists. and anxiety.

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

3.1 Vaccine reactions

Based specifically on 1) cause and on 2) seriousness and frequency, vaccine reactions may be grouped into two broad categories:

1. Cause-specific vaccine reactions:
   - vaccine product-related reaction;
   - vaccine quality defect-related reaction;
2. Vaccine reactions by seriousness and frequency:
   - common or minor reactions;
   - rare or serious reactions.

3.1.1 Cause-specific vaccine reactions

The new cause-specific categorization is important for decision-making about a vaccine product since it clearly differentiates the types of possible reactions related to the components of a vaccine.

The first, a vaccine product-related reaction, is an individual's reaction to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly. Most often the exact mechanism of a vaccine product-related reaction is poorly understood. The reaction may be due to an idiosyncratic immune mediate reaction (e.g. anaphylaxis) or to replication of the vaccine-associated microbial agent (e.g. vaccine-associated poliomyelitis following OPV which contains attenuated live virus). However, it is important to note that, among certain high-risk individuals, there is a higher probability of these rare vaccine product-related reactions which do not occur in the majority of vaccinees.

The second reaction, a vaccine quality defect-related reaction, is a due to a defect in a vaccine (or its administration device) that occurred during the manufacturing process. Such a defect may have an impact on an individual's response and thus increase the risk of adverse vaccine reactions. Insufficient inactivation of wild-type vaccine agent (e.g. wild polio virus) during the manufacturing process or contamination introduced during the manufacturing process could cause the vaccine quality defect-related reactions. In the early years of immunization programmes, some major vaccine quality defect-related reaction incidents were reported. However, since the introduction of good manufacturing practice (GMP) manufacturing defects are now very rare. Since vaccine manufacturers have started following GMP, and NRAs have been strengthened, the potential risk of such quality defects is now rare.

CASE STUDY

In 1955, after administration of inactivated polio vaccine manufactured by Cutter Laboratories in the USA, 40 000 people developed abortive polio, 200 were permanently paralysed and 10 died. Investigations revealed that two production pools of 12 000 doses contained live virus.

Cause: Vaccine quality defect-related reaction

See: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1383764/.

3.1.2 Vaccine reactions by seriousness and frequency

Most vaccine reactions are minor and subside on their own. Serious reactions are very rare and, in general, do not result in death or long-term disability (Table 3).

Table 3. **Frequency of occurrence of reported adverse reactions**

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

3.1.2.1 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 antigens. Local site reaction, fever and systemic symptoms can result as part of the immune response. In addition, some of the vaccine's components (e.g. adjuvant, stabilizers or preservatives) can lead to reactions. An effective and safe vaccine produces the best possible immunity and reduces these reactions to a minimum. The proportions of reaction occurrences likely to be observed with the most commonly used vaccines are listed in Annex 1.

The occurrence of local reactions such as pain, swelling and/or redness at the injection site varies by the type of antigen. For example, these local reactions are reported very commonly (>10%) with whole-cell DTP, whereas for acellular DTP it is only a common reaction with a frequency of 1-10%. BCG causes a specific local reaction which starts as a papule (lump) two or more weeks after immunization, then becomes ulcerated and heals after several months, leaving a scar. Keloid (thickened scar tissue) from the BCG lesion is more common among African and Asian populations.

The occurrence of systemic reactions also varies by the type of antigen. Fever is a very common (>10%) systemic reaction reported for most antigens. Other common systemic reactions (e.g. irritability, malaise, loss of appetite) can also occur after many antigens, and DTwP has more reports of these systemic reactions than DTaP. For LAVs such as measles/MMR and OPV, the systemic reactions can occur from vaccine virus infection. Measles vaccine can cause fever, rash and/or conjunctivitis but this is very mild compared to "wild" measles. However, it can be serious, and even fatal, for severely immunocompromised individuals. Vaccine reactions for mumps vaccine (parotitis, swollen parotid gland) and rubella vaccine (joint pains and swollen lymph nodes) are uncommon and affect less than 1% of children. Rubella vaccine commonly causes symptoms in adults, with 15% suffering from joint pains. Systemic reactions from OPV are uncommon and affect less than 1% of vaccinees with diarrhoea, headache and/or muscle pain.

It is important to note that these vaccine reaction rates are an expected response to the vaccine antigen. However, if the observed vaccine reaction rate is significantly higher than the expected vaccine reaction rate for any vaccine, an investigation is needed to explain this. (This is described later in chapters 6 and 7.)

3.1.2.2 Rare, more serious vaccine reactions

"Serious" and "severe" are often used as interchangeable terms but they are different. 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 requires 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 and relatively minor medical event but, according to its severity, it may be graded as mild fever or moderate fever. Anaphylaxis, on the other hand, is always a serious event and life-threatening. Most of the rare and more serious vaccine reactions (e.g. seizures, thrombocytopenia, hypotonic-hyporesponsive episodes (HHEs), persistent inconsolable screaming) do not lead to long-term problems. Anaphylaxis, while potentially fatal, is treatable. Although encephalopathy is included as a rare reaction to measles or DTP vaccine, it is not certain that these vaccines in fact cause encephalopathy.[13]

3.1.3 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, a vaccine is contraindicated if there is a history of anaphylaxis to a given vaccine or its components in previous vaccinations.

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

Antipyretic medicines, in a recommended dosage and schedule, can be given as recommended by the prescriber (or manufacturer). For an example, paracetamol, at a dose of up to 15 mg per kg every 6-8 hours with a maximum of four doses in 24 hours, is useful for common minor reactions; it eases pain and reduces fever. However, it is important to advise against overuse of paracetamol or any other antipyretic medicine as overdosing may harm the vaccinee. A febrile child can be cooled with a tepid sponging or bath, and by wearing light cool clothing. Extra fluids need to be given to children with fever. For a local reaction, a cold cloth applied to the site may ease the pain.

[13] Ray P, Hayward J, Michelson D, Lewis E, Schwalbe J, Black S et al. Encephalopathy after whole-cell pertussis or measles vaccination. Lack of evidence for a causal association in a retrospective case–control study. The Pediatric Infectious Disease Journal. 2006;25(9) (http://www.rima.org/web/medline_pdf/EncephalopathyAfterVaccination.pdf, accessed 1 August 2014).

Using local remedies for any serious vaccine reaction can risk the health and life of the vaccinee and is strongly discouraged. Early medical care by a qualified clinician will minimize any unwanted outcome and ensure early recovery, and may also save lives.

Vaccine anaphylaxis is very rare. However, it is recommended that preparedness to provide emergency treatment for anaphylaxis is necessary in all clinic settings. All immunization providers need to be trained and develop competence in recognizing and managing anaphylaxis. (See Section 9 for details.)

3.2 Immunization error-related reactions[14]

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

Immunization error-related reactions are preventable and they divert attention from 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 sometimes lead to a cluster of events associated with immunization. These clusters are usually linked to a particular provider or health facility, or even to single or multiple vials of vaccine that have been contaminated or inappropriately prepared. For instance, freezing vaccine during transport may lead to an increase in local reactions.

In the past, the most common immunization error was an infection as a result of a non-sterile injection because of contamination of the vaccine or diluent vial or the injecting device (syringe and/or needle). The infection could manifest as a local reaction (e.g. suppuration, abscess) or a severe systemic reaction (e.g. sepsis, toxic shock syndrome). In addition, there was the perception of a risk linking immunization with bloodborne infections. With the introduction of auto-disable (AD) syringes, such occurrences have reduced significantly. Nevertheless, infection can occur in cases of mass vaccination or in disaster situations, particularly if there is a shortage of supplies or problems with logistics. This can be avoided by proper planning and preparedness of programme managers.

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

[14] Note: This AEFI type was earlier categorized as "programme error" (see Table 2)

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

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 abscesses and local reactions. Contamination of vaccine or injection equipment can also lead to a bacterial abscess. For BCG vaccine, injection abscess can result from improper technique of injection (subcutaneous rather than intradermal injection).

Ignoring contraindications can lead to serious vaccine reactions and is considered an immunization error. The immunization team should be clearly aware of absolute and relative contraindications. Any uncertainty should be referred to a higher level – a programme manager, paediatrician or physician. However, it is equally important not to overreact to concerns of false contraindications as this may lead to missed opportunities for vaccination, reducing coverage and thereby increasing the risk of disease in both individuals and the community.

Health-care workers also need a clear understanding of contraindications and precautions. Precautions are not contraindications, but a decision on whether to vaccinate requires a case-based assessment where the risk of the vaccine is balanced against the potential benefits. The use of live vaccines in pregnancy is a good example of this. The vaccines that are recommended in pregnancy will benefit and protect both mother and newborn.

However, the limited use of vaccination in pregnancy is largely due to the potential risk of harm to the foetus. This risk is limited to LAVs which carry a theoretical risk of infecting the foetus. Vaccine manufacturers mention pregnancy as a contraindication on the package inserts not because of proven evidence of harm but as a precautionary measure because there are few licensure studies of vaccination of pregnant women and there is limited information on proven safety or harm to the foetus.

To avoid/minimize immunization error, the following should be noted:

- It is both important and necessary to maintain the cold chain at all levels.
- Vaccines must be reconstituted only with the diluents supplied by the manufacturer.
- Reconstituted vaccine should be used within six hours after reconstitution; it must be discarded at the end of each immunization session and should never be retained.
- Other than vaccines, no other medicines or substances should be stored in the refrigerator of the immunization centre.
- Immunization workers must be adequately trained and closely supervised to ensure that proper procedures are followed.
- Careful epidemiological investigation of an AEFI is needed to pinpoint the cause and to correct immunization practices.
- Prior to immunization, adequate attention must be given to contraindications.

Follow-up and corrective actions following immunization error-related reactions should be based on the findings of the investigation. Depending on the nature of the immunization error, these actions can be both general (e.g. training and awareness) and specific (e.g. strengthening cold chain maintenance if the problem found to be related to cold chain issues). Continued monitoring and supportive supervision can help to minimize these adverse events.

CASE STUDIES

- In 1992, in a hospital in country A, five neonates collapsed a few minutes after immunization with BCG. Four were resuscitated and one died. Muscle-relaxant drugs were found in the refrigerator in which the vaccines were kept.
- Cause: Immunization error-related reaction. Use of muscle-relaxant instead of diluent.
- In 2008–2009, in country B, during a school-based rubella immunization programme, two 14 year-old girls collapsed within 15 minutes of immunization. Prior to collapsing they developed generalized rash (urticaria or hives) and a persistent cough with wheeze.The incidents occurred in two separate places and at different times. Both girls were hospitalized and later died. Investigation revealed that both children had informed the immunization teams about their past history of allergic reactions to some animal food products, but the immunization teams ignored the history. Also there was no preparedness to manage anaphylaxis.
- Cause: Immunization error-related reaction. Lack of attention on a contraindication and lack of preparedness to manage anaphylaxis.
- Vaccine product-related reaction. Anaphylaxis is a known reaction to rubella vaccine. (Rubella vaccine used in this country has contained gelatine, and the link between gelatine and red meat, leading to severe allergic reactions, is documented in medical literature)
- 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 the DTP vaccine.

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

3.3 Immunization anxiety-related reactions

Individuals and groups can become stressed and may react in anticipation to, and as a result of, any kind of injection. This reaction is unrelated to the content of the vaccine. Fainting (vasovagal syncope or syncope) is relatively common, particularly in children over five years of age and among adolescents. Fainting does not require any clinical management beyond placing the patient in a recumbent position. Some children who faint may have a syncopal hypoxic convulsion. This is a short-lived generalized tonic-clonic seizure. The management is to keep the child lying down and secure the airway by placing the child in the "coma" position. The seizure will end spontaneously but, if prolonged or focal, further investigations may be required. The likelihood of fainting should be anticipated when immunizing older children. It can be reduced by minimizing stress among those awaiting injection, through short waiting times, comfortable room temperatures, preparation of the vaccine outside the recipient's line of vision, and privacy during the procedure.

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

Younger children tend to react differently, with vomiting a common symptom of anxiety. Breath-holding may also occur and can result in a brief period of unconsciousness during which breathing resumes. Young children may also scream or run away to avoid the injection.

These reactions are not related to the vaccine, but to the injection. Some individuals may have needle-phobia, aggravating such reactions. In group immunization, mass hysteria is possible, especially if a vaccinee is seen to faint or have some other reaction such as itching, weakness of limbs and so on. Sometime, these cases may even require hospitalization and can cause public concern. Clear explanations about the immunization and a calm, confident delivery will decrease the level of anxiety about the injections and thus reduce the likelihood of an occurrence.

It is important to note that a fainting episode can be misdiagnosed as anaphylaxis. Health workers need to be able to differentiate between the two conditions. Careful observation and clinical judgement is necessary. However, if by mistake a health-care worker administers a single dose of adrenaline (intramuscularly) to a vaccinee with only syncope, this does not harm the vaccinee. Therefore it is necessary to promote training and awareness to enable health staff to identify and manage medical emergencies appropriately (more details are outlined in Chapter 9).

CASE STUDY

Case studyIn 2004, a school-based mass measles-rubella immunization campaign was conducted among young persons aged 12–19 years in country D. On the first day, 44 children were hospitalized with hyperventilation or/and vomiting. An investigation concluded that more than 90% of the cases were anxiety reactions and all but two cases were discharged from hospital the same day.

Cause: Immunization anxiety-related reactions.

3.4 Coincidental events

An event may occur coincidentally with immunization and sometimes be falsely attributed to the vaccine. In other words, a chance temporal association (i.e. an event happening after immunization) is falsely considered to be caused by immunization. Such temporal associations are inevitable given the large number of vaccine doses administered, especially in a mass immunization campaign.

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

For instance, incidence of sudden infant death syndrome (SIDS or "cot death") peaks around the age of early childhood immunization. Consequently, many SIDS cases will occur in children who have recently been immunized. However, several well designed studies[15] have shown that the association of SIDS and immunization is coincidental and not causal.

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

A similar calculation is shown in Table 5 for deaths of infants (aged under one year) in selected countries for the number of deaths temporally associated with routine DTP or pentavalent vaccine (PVV) 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, number of immunization episodes and 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. In general, coincidental events which are clearly unrelated may still require investigation because certain serious events may be blamed on the vaccine by parents, public or media due to the close temporal association with immunization, especially if the child was previously healthy. Such cases need to be investigated in order 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 of reported coincidental events may be helpful in the investigation of an AEFI.

[15] For current issues and SIDS, see the website of the American SIDS Institute (Naples, FL) at: http://sids.org/category/news/ (accessed 1 August 2014). Also:

– Kuhnert R, Schlaud M, Poethko-Müller C, Vennemann M, Fleming P, Blair PS et al. Reanalyses of case-control studies examining the temporal association between sudden infant death syndrome and vaccination. Vaccine. 2012;30(13):2349-56 (http://www.ncbi.nlm.nih.gov/pubmed/22289512, accessed 1 August 2014).

– Matturri L, Del Corno G, Lavezzi AM. Sudden infant death following hexavalent vaccination: a neuropathologic study. Curr Med Chem. 2014;21(7):941-6 (http://www.ncbi.nlm.nih.gov/pubmed/24083600, accessed 1 August 2014).

CASE STUDIES

- In response to a severe diphtheria outbreak in country E in 1996, diphtheria-tetanus vaccine was provided to children in a mass campaign. The death of a seven-year-old girl, 2-3 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 and it was a coincidental event.
- In 2010, six infants died within 48 hours following administration of pentavalent (DTP-HepB-Hib) vaccine in country F. Use of the vaccine was temporarily suspended. A high-level investigation was carried out as the deaths had led to public concern and health staff were reluctant to use the vaccine. Investigation and assessment revealed that, out of six cases, three were confirmed as coincidental. One was suffocation and two were due to underlying infections. Of the other three cases, one was diagnosed as anaphylaxis and the other two were inconclusive.
- In 2010, the death of a four-month old infant following DTwP vaccination was reported in country G. Within a week, six more cases of severe local reactions were reported with the same batch of DTwP, causing high public and media attention. The implicated vaccine lot was temporarily suspended and replaced with another lot, and a comprehensive investigation was carried out, including toxicity and sterility-testing at national and WHO-accredited laboratories. Causality assessment confirmed the death as coincidental, but six reported severe local reactions were most likely due to immunization error-related reactions.

Table 5. Estimated number of coincidental infant deaths that could be temporally linked to immunization (e.g. with DPT/PVV) in the month, week and day after immunization in selected countries

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

Note: Assumes uniform distribution of deaths and immunization over the time period.

Source: Infant mortality and births from 2011 immunization summary. New York (NY) and Geneva: United Nations Children's Fund and World Health Organization; 2013 (http://www.unicef.org/videoaudio/PDFs/EN-ImmSumm-2013.pdf, accessed 7 December 2013).

*The assumption here is a three-dose schedule for either DTP or PVV, with 90% coverage for each dose,

If the same or similar events affect others in the same age group around the same time but those others 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 the introduction of a new vaccine, there is a tendency to report any AEFI, including coincidental events. It is crucial to differentiate these reported coincidental events from potential signals.

Summary

- Vaccine adverse reactions may occur due to some inherent properties of the vaccine (vaccine product-related reactions) or due to quality defects (vaccine quality defect-related reactions) or due to immunization error-related reactions.
- At times, the event may be unrelated to immunization but may have a temporal association with it (coincidental event).
- Immunization anxiety-related reactions are commoner, resulting from fear of, or pain due to, injection rather than from the vaccine itself. In some cases, the cause of the AEFI remains unknown.
- Immunization error-related reactions (previously classified as "programme errors") are avoidable.
- Antigen/vaccine-specific rates of vaccine reactions are useful to guide decision-making on vaccine-related reactions

  (http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/index.html).
- Minor vaccine reactions are common and do not require special treatment. Rare, serious vaccine reactions need timely treatment by qualified medical personnel.

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- WHO has developed vaccine reaction information sheets for selected vaccines. They comprise details of mild and severe adverse reactions (local and systemic) following immunization. See: http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/index.html (accessed 1 August 2014). Expected rates of vaccine reactions have been included, if available, in published literature.

4 Immunization safety surveillance system

Pharmacovigilance is the practice of detecting, assessing, understanding, responding to and preventing adverse drug reactions, including reactions to vaccines.[16] Pharmacovigilance is now an integral part of the regulation of drug and vaccine safety. While regulatory and public health agency pharmacovigilance activities are equally robust for medicines and vaccines, AEFI surveillance often relies on different systems and procedures. Immunization safety is the process of ensuring and monitoring the safety of all aspects of immunization, including the detection and investigation of adverse events, vaccine quality, vaccine storage and handling, vaccine administration, disposal of sharps and management of waste.

4.1 Objectives

There are several potential objectives for establishing immunization safety surveillance. Clearly stating and documenting the most important objective(s) of the system at the time of establishing it will assist in designing both the system and its implementation. The relative importance of the objectives will depend on the state of the immunization programme and local circumstances. The objectives may change over time.

The major goal of immunization safety surveillance is early detection and analysis of adverse events and appropriate and quick response in order to decrease the negative impact on the health of individuals and the immunization programme.

In establishing immunization safety surveillance, the clear articulation of objectives should generate the support of health workers and encourage them to report AEFI. If resources are limited, prioritizing the objectives is recommended.

It is important that any information obtained through immunization safety surveillance is rapidly assessed and analysed in order to identify problems and respond to them. Response is a critical aspect of immunization safety surveillance.

[16] Definition and application of terms for vaccine pharmacovigilance. Report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Geneva: Council for International Organizations of Medical Sciences; 2012 (http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf, accessed 1 August 2014).

Specific objectives of immunization safety surveillance

The specific objectives of immunization safety surveillance are:

- to detect and identify problems with vaccines which could be due to the inherent properties of a vaccine or to defects in quality, and to detect, correct and prevent immunization error-related reactions;
- to determine the observed vaccine reaction rate and relate this to the expected vaccine reaction rates in the population by country, by region and globally;
- to ensure that coincidental events are not mistaken for vaccine reactions and thus negatively affect the immunization programme;
- to ensure and facilitate causality assessment of individual AEFI reports (cases);
- to identify clustering or unusually high rates of AEFI, even if they are considered mild;
- to identify events which may indicate a previously unknown and potential vaccine reaction (i.e. a signal) and to generate new hypotheses about the causal relationship between the event and the vaccine (this will then require further investigations to support or refute the hypothesis);
- to maintain the confidence of the community and health staff in the immunization programme by appropriate and timely responses to their concerns about immunization safety;
- to create awareness on immunization safety among parents, community, the media and other stakeholders without jeopardizing the immunization programme;
- to collaborate and share information with the regulatory authorities in order to ensure vaccine safety;
- to ensure that channels of communication on AEFI between the NRA and the immunization programme are clear and that information is provided regularly by the unit responsible for immunization safety surveillance;
- to collaborate and share information with the WHO regional offices and globally in order to generate additional information on vaccine safety.

4.2 Types of immunization safety surveillance

Passive surveillance: This encompasses all spontaneous AEFI reporting from immunization service providers/hospitals/patients to the first administrative level (e.g. divisional, municipality, township) in the surveillance system. From there, reports are sent to the next reporting subnational level(s), ending at the national-level unit and global institutions responsible for AEFI surveillance. Passive surveillance systems theoretically allow anyone in a country to report, and due to their broad coverage they can provide the first indication of an unexpected AEFI. Therefore, the main strength of passive surveillance is to detect early the unknown serious AEFI (signals). However, passive surveillance has many limitations, including underreporting. Thus, passive surveillance is often not useful for determining whether the rate of an adverse event has increased. Thus, newly introduced vaccines and/or special immunization campaigns should have

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

Active surveillance: This is primarily used for characterization of the AEFI profile, rates and risk factors, but logistical and resource constraints limit its wide application. Countries may carry out active AEFI surveillance only for selected AEFI at selected institutions (sentinel sites). Active surveillance can also be carried out in the community setting (e.g. cohort event monitoring).

Ad hoc studies: Epidemiological studies (e.g. cohort study, case-control study, case series studies) may be conducted in order to further expand immunization safety surveillance activities. These studies are focused on selected vaccine safety concerns (e.g. testing causality hypotheses).

In this manual, the focus is on routine Immunization safety i.e. passive surveillance systems at subnational, national and international levels to ensure effective monitoring and prompt action in response to AEFI. However, within or parallel to the spontaneous reporting of a passive system, an active surveillance system can be established with specific objectives for a specified time period. 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's administrative and operational structure, one unit/institution needs to be the focal point for immunization safety surveillance. As the unit's independence is important, the task can be delegated to another organization or pharmacovigilance centre (e.g. a university department) as long as the links with the NRA and the national immunization programme are maintained. It is important to note that maintaining high levels of transparency and independence are key factors which are necessary for building and maintaining public trust in the AEFI surveillance system.

Immunization safety reporting systems 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 AEFI reporting system is the one which encourages a high level of appropriate reporting and takes timely action in response to reports.

4.3 Steps for establishing an immunization safety surveillance 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 the NRA in immunization safety surveillance. It is important to designate an institute to implement immunization safety surveillance. The roles and responsibilities of the different categories of staff involved in immunization safety surveillance should

be clearly identified. In countries where a pharmacovigilance centre is functioning, the centre's role and responsibilities in the immunization safety surveillance need to be defined.

2. Develop a protocol with clearly defined objectives for immunization safety surveillance, including strategies, structure, activities and resources.
3. Obtain legal provision for vaccine pharmacovigilance and government commitment.
4. Establish a national (central) expert committee for causality assessment and for high-level technical support and decision-making. Large countries may have state or provincial regional expert committees for similar purposes. Smaller countries where such experts are not available can identify a supporting unit within the same region.
5. Develop and disseminate a list of events or criteria (see section 5.1) to be reported (and investigated), their case definitions, standard investigation procedures and AEFI reporting and investigation forms.
6. Ensure that staff are aware that monitoring and evaluation of activities are both important and necessary. Train staff in reporting, data analysis, and investigation and report preparation, according to the level at which each function is carried out.
7. Develop training materials and training modules suitable for the country's immunization and safety surveillance programme.
8. Develop a feedback system to update regularly the AEFI surveillance system (including statistics, investigation findings, new developments).
9. Develop a communication plan to address concerns about, and information on, immunization and safety surveillance.
10. Consider establishing a legal framework for a compensation scheme or social support scheme, where applicable. If a legal framework is developed, ensure that it is within the government's health and/or social welfare policy.

Once the decisions about the safety surveillance system have been made, it is essential to describe the structure of the system and the mechanisms for reporting. The system will normally consist of the immunization service providers (in the public and private sectors) who will provide reports on AEFI to the local health authority. Other than the immunization service or health service provider at the periphery of the health system, who may be in the private sector, all other key staff and structures for collation of data, management of AEFI, and corrective action and feedback will usually be from government bodies. Depending on a country's administrative structure for health care, there will normally be one or more intermediate levels between the immunization service providers and the national immunization safety surveillance organization. The intermediate levels report to the national level and the links between the NRA and the immunization programme are usually at national level.

It is important to highlight that the functions described below for each stakeholder, or stakeholder level, are only examples. Countries need to adopt their own modalities, defining functions and respective responsibilities for each stakeholder or stakeholder level.

4.4 Roles and responsibilities of the NRA in immunization safety surveillance

NRAs are responsible for ensuring that any pharmaceutical product, including vaccines, used within the country is (i) of good quality, (ii) effective, and (iii) safe for the purpose or purposes for which it is proposed. While the first two criteria must be met before approval of the vaccine's medical use, the issue of safety is more challenging. Strengthening NRA activities is necessary to ensure safe vaccine use and the monitoring of safety events in the pre-licensure and post-marketing phases.

The immunization programme and NRA have a collective responsibility and play specific roles in immunization safety surveillance. WHO has recommended 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 that should be carried out by the NRA, as follows:

- marketing authorization and licensing activities, with clear written instructions for licensing products and manufacturers;
- pharmacovigilance, including surveillance of AEFI;
- NRA lot release, with a system for lot release of vaccines;
- laboratory access, with use of laboratory when needed;
- regulatory inspection, with regular inspection of manufacturers for GMP compliance; and
- regulatory oversight of clinical trials, with evaluation of clinical performance through authorized clinical trials.

All countries should have some level of functioning NRA, but countries that produce vaccines must exercise these six critical control functions (Table 6). The control functions must be exercised in a transparent, technically competent and independent manner with accountability and with the power to enforce changes that are considered necessary. WHO carries out periodic assessment of the functions of NRAs in all countries, leading to strengthened NRA functions over time. WHO has also published a manual for assessment of the functions of national regulatory systems for vaccines.[17] This assessment is carried out by means of a tool specifically designed to assess regulatory systems in general and the above six functions in particular. Performance indicators and sub-indicators have been developed for each function. Some indicators and sub-indicators are "critical" (i.e. it is mandatory for the NRA to achieve these indicators in order to qualify as being fully functional. For pharmacovigilance surveillance of AEFI, there are seven indicators, of which six are critical. Of the six functions, the licensure, marketing authorization and vaccine pharmacovigilance functions are mandatory for all countries, irrespective of whether they produce vaccines or not. Furthermore, WHO recommends that all countries which do not produce vaccines must nevertheless define minimum specifications for the vaccines they use. There should also be a system of post-marketing surveillance in place

[17] Regulation and quality control of vaccines. Geneva: World Health Organization http://www.who.int/biologicals/vaccines/regulation_and_quality_control_vaccines/en/, accessed 1 August 2014).

to detect problems of vaccine performance. In all countries, AEFI should be monitored, reported and investigated.

Table 6. Critical control functions of country NRA by vaccine source

Vaccine source for country	NRA functions					
	Marketing authorization and licensing	Pharamacovigilance including surveillance	Lot release	Laboratory access	Regulatory and GMP inspection	Clinical evaluation
United Nations agency	X	X				
Procured	X	X	X	X		
Produced	X	X	X	X	X	X

The NRA's contribution to, and responsibility for, investigation and appropriate follow-up are part of the AEFI surveillance system in the country. For this purpose, there should be close and clear communication and information-sharing between the NRA and the immunization programme. The roles and modes of functioning of the two key players need to be defined at the national level. Large countries, where NRA functions are expanded to subnational levels, should clearly define the NRA roles and functions at these levels.

4.5 Roles and responsibilities of the immunization programme in immunization safety surveillance

An effective immunization safety surveillance system requires the involvement of health workers at all levels of the immunization programme. This section identifies the key players at different levels of the surveillance system and outlines their roles and responsibilities in surveillance activities. These 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), subnational or intermediate (state/province/region/district) and service-provider level. In small countries, however, the surveillance may be limited to two levels. When a country has three levels, functions and responsibilities are shared to varying degrees between intermediate and national levels, depending on the country's size and the structure of its health-care system.

4.5.1 Roles and responsibilities at the level of the immunization service provider

In these guidelines, the immunization service-provider level refers to the lowest administrative level at which immunization services are provided to the public. Among the tasks of immunization service providers are the following:

Detection of AEFI

Reporting of AEFI by the recipient, or by the parent or guardian of the recipient, should be encouraged by clinics and hospitals. It is the responsibility of the clinic and hospital staff to detect and report cases of AEFI. If treatment is necessary for a particular condition, the child with an AEFI should be referred to the nearest hospital or health facility.

Recording of AEFI

The forms and registers necessary for immunization safety surveillance should be supplied and maintained. All necessary data should be entered into the forms/records/registers.

Reporting of AEFI

The next higher administrative/operational level should be immediately informed of all serious events (including death) and/or unusual AEFI.

Other cases should be reported routinely, as instructed by the higher administrative/operational level.

Investigation of AEFI

If the capacity to carry out an investigation exists, the investigation may be done at this level. All investigations required for reported AEFI, as listed in the national guidelines, need to be done as early as possible. Investigations should be appropriately supported with laboratory-testing (See sections 6.6 and 6.7). Communication with the staff and the community is essential. The public should be kept informed of 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. The findings of the investigation should be shared with the service provider and should be submitted to the next higher administrative/operational authority.

Corrective action

Corrective action, particularly in relation to immunization error-related events, should be taken immediately on the basis of the findings of an investigation.

Analysis of AEFI data

It is recommended to keep line listing and detailed information separately. Depending on the capacity of staff available, analysis may be limited to the basic variables.

Public education/communication

Whenever an opportunity is available, the public should be informed of what is being done. People should be educated regarding AEFI.

4.5.2 Roles and responsibilities at the subnational level of immunization services

The use of the term "subnational level" in these guidelines will vary according to the administrative structure of a country's health-care service. The term may refer to one or more administrative levels in a country. Hence, "subnational level" represents all

intermediate levels between the national level and the lowest administrative level in a specific country.

(For instance, country A may have an administrative structure with four levels: national, provincial, district and divisional. The provincial and district levels constitute the intermediate levels in the country.)

Reporting of AEFI

The subnational level should inform the national level immediately of serious events (including deaths) and/or unusual AEFI. Other cases should be reported routinely, as stipulated by the national authority. All records on AEFI surveillance should be maintained.

Investigation of AEFI

All investigations required for reported AEFI, as listed in the national guidelines, need to be carried out as early as possible. In most settings, the capacity to conduct a comprehensive investigation is not available at the level of the immunization service provider; therefore, collection of preliminary information on detailed investigations is often the responsibility of the subnational (intermediate) level. It is therefore important that countries invest effort in building capacity for AEFI investigation at the subnational level. The findings of the investigation should be shared with the immunization service provider and submitted to the authorities at national level.

Causality assessment

In large countries, where experts, expertise and resources are available, preliminary causality assessment can be carried out at the subnational level and causality determined for serious AEFI. However, AEFI cases with pending conclusions may be referred to the national level for further evaluation and final classification.

Corrective and preventive actions

Both corrective and preventive actions should be taken as early as possible. However, such actions should be based on the findings of the investigation. In practice, the subnational level has the greatest responsibility for implementing corrective actions in terms of both logistics and administration. For example, if any immunization error-related reactions are observed, preventive actions such as strengthening supportive supervision, training and even logistic replacements should be implemented by authorities at this level.

Analysis of AEFI

Analysis of data relevant to this level is necessary. Reports need to be produced on the basis of the findings of data analyses and investigations.

Monitoring, supervision and training

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

Public education/communication

Whenever an opportunity arises, the public should be informed of what is being done and should be educated regarding AEFI.

4.5 3 Roles and responsibilities at the national level of immunization services

Investigation and causality assessment of AEFI

Investigations that require the services of national-level experts need to be prioritized (e.g. serious cases, deaths, AEFI with public concerns). Causality assessment by the national expert committee should be facilitated by all levels of the immunization programme, the NRA and the government. If necessary, further research should be conducted to test a hypothesis generated by the surveillance system/investigation.

Corrective and preventive actions

Both corrective and preventive actions should be taken as early as possible. However, such actions should be based on the findings of the investigation. Vaccines should be withdrawn or suspended only if available data are strongly supported by a causative link to the vaccines. Preventive actions can lead to policy or/and programme strategy changes.

Analysis and sharing of AEFI data

Reports should be produced on the findings of data analyses and investigations. AEFI data must be shared periodically among all stakeholders responsible for the country's immunization programme, including immunization programme managers, the NRA and NCL, academia and, when necessary, manufacturers and the public (Figure 1). Countries are encouraged to share data regionally and globally through the WHO Programme for International Drug Monitoring in order to generate additional and new information on vaccine safety.

Feedback

Feedback is one of the most important elements of any surveillance system. Feedback ensures and encourages reporting, which is the basis of AEFI surveillance, through the continued interest of the staff at the subnational and service-delivery levels. In addition, feedback is a learning process for the service-provider level and helps staff to improve the immunization services. Weekly, monthly, quarterly and annual reports with statistics, updates, new developments, findings of investigations and lessons learned are effective means of feedback in AEFI surveillance.

Public education/communication

Whenever there is a need, informing the public and media through special awareness programmes is necessary. Developing a communication plan is also essential.

Monitoring, supervision and training

Staff awareness on AEFI should be assessed when monitoring and supervising immunization services. Guidance and adequate training on AEFI surveillance and good quality immunization practices should be provided to the staff. Whenever necessary, the

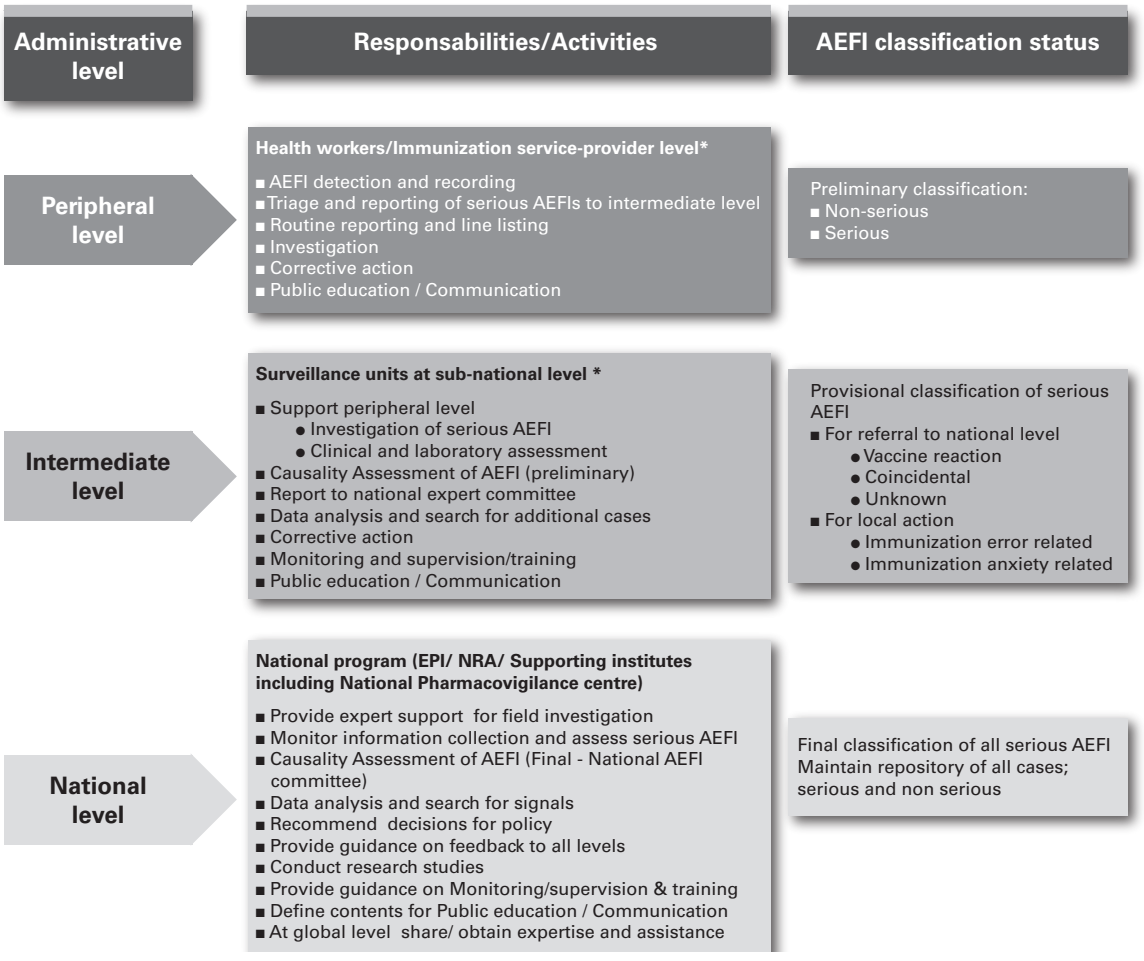
staff must be re-trained. Training materials should be developed, with WHO support if necessary.

Resource allocation

Sustainability depends on the availability of adequate resources at each level of the surveillance system. Therefore, it is important that the national level (and possibly subnational level) identify and allocate resources.

Note: National pharmacovigilance centres, which aim to ensure the safety of medicinal products, can play an active and important role in immunization safety in their country. Advantages of pharmacovigilance centres are their independence and the availability of experts, especially where national authorities need to strengthen collaboration in immunization safety activities.

Figure 1. Programme implementation level, responsibility and surveillance activities



4.5.4 Roles and responsibilities of immunization providers in the private sector

Case detection and reporting

The provision of health-care services in the private sector results in opportunities for AEFI case detection and reporting. Individuals receiving vaccines at public-sector immunization services could receive medical care for AEFI in the private sector. It is therefore necessary to develop a link to report AEFI cases from the private sector to the public health authorities. Several countries have integrated communicable disease

notification systems with reporting by both public and private sectors. It is proposed to adopt a similar system to ensure reporting of AEFI from the private sector. The use of a standard reporting form, incorporating a minimum set of co-variables recommended by WHO, is advised.

Investigation of AEFI

Investigation is required for all AEFI reported from the private sector, as outlined in the national guidelines. Public-private joint investigation is necessary when an AEFI is serious or there is increased public concern. Findings need to be communicated to both the immunization staff and the community.

Corrective action

In the private sector corrective action based on the findings of the investigation, particularly regarding immunization errors, should be taken immediately as in the public sector.

KEY POINTS

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.

- The AEFI surveillance system involves different stakeholders (the immunization programme, the NRA and the NCL) and functions at different levels from service delivery to national level.
- Feedback to all levels of the immunization and reporting system, and if necessary to the public, is essential for building trust in the immunization programme.

4.6 Terms of reference of the National Immunization Safety Expert Committee

The Immunization Safety Expert Committee plays a critical role in confirming the causality assessments of selected investigations and in determining causality when this has not been established with confidence by the investigator.

Maintaining an active expert committee is a challenge. It is advised that only the most critical cases – particularly those where causality needs to be assessed or those of public or national concern – should be referred to this committee.

The committee should include a wide range of specialists whose expertise is important in the reviewing of AEFI. Areas of expertise could include paediatrics, neurology, general medicine, forensic medicine, pathology, microbiology, immunology and epidemiology. Medical experts should be invited for the review of specific events. The committee needs to be independent and have support from, and work in close communication with, both the immunization programme and the NRA.

The following generic terms of reference may be adapted by the National Immunization Safety Expert Committee:

- assessing potential causal links between AEFI 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, making arrangements to investigate further to establish causality, and making the necessary recommendations to rectify problems (the expert committee may use the WHO Aide-mémoire on causality assessment as resource material[18] and is encouraged to use in its investigations the comprehensive case definitions developed by the Brighton Collaboration[19]);
- making final decisions on causality assessment following inconclusive investigations and ensuring quality control of the immunization surveillance system;
- communicating with other national and international experts, when required, to establish causality and to resolve vaccine quality issues;
- advising the national immunization programme (manager) and NRA on AEFI-related issues when requested by these institutions; and
- advising the Ministry of Health on vaccine and immunization safety-related matters when requested by the ministry.

Governance and function of the National Immunization Safety Expert Committee

Independence and transparency: Complete independence from government and all industry-associated experts may not always be possible to achieve since it would mean excluding much potential expertise. Therefore, the committee should discuss how conflicts of interest/competing interests should be declared and decide which conflicts may hinder an individual expert from taking part in the causality assessment of a specific event for a given vaccine and which conflicts will not.

Role of the immunization programme and the NRA: Staff of both the immunization programme and the NRA play a critical role. They should support the expert committee and serve as the secretariat to facilitate the committee's review (including preparing documents for review). However, it is essential that they are uninvolved in decisions on causality by the committee.

No industry participation: It is important to emphasize that employees of vaccine manufacturing companies cannot be members of the expert committee. This is because they will have conflicts of interest which could undermine the credibility and acceptance of the committee's conclusions. However, the committee may choose to question company representatives if the industry is potentially the best source for certain

[18] Aide-mémoire on causality assessment. Geneva: World Health Organization (http://www.who.int/vaccine_safety/publications/AEFI_aide_memoire.pdf, accessed 1 August 2014).

[19] Standardized case definitions for global use. Basel: Brighton Collaboration (https://brightoncollaboration.org/public/what-we-do/setting-standards/case-definitions.html, accessed 1 August 2014).

information. For example, the committee might invite the industry to describe a specific production process in one of their meetings.

4.7 Monitoring and evaluating the immunization safety surveillance system

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

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

Note: At present, the WHO working group is developing more specific indicators. Once the indicators are finalized, they will be incorporated into this manual.

KEY NOTE

Annual data reports should include:

- The 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);
- the rate of each adverse event by vaccine nationally and by region;
- unusual or unusually severe events or large clusters; and
- summary findings of important investigations and lessons learned.

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

4.8 Differences between surveillance of AEFI and adverse events linked to other medical products

Vaccines are administered to healthy people for the prevention of disease while most medicines are used to treat or control disease in sick people. Thus, a much higher level of risk is acceptable for a medicine compared to a vaccine. An involuntary risk is perceived as greater than a risk taken voluntarily. This fact reduces tolerance of AEFI if there is an element of compulsion in the immunization programme. Further, vaccines are given mainly to infants, and the large number of doses given (particularly in immunization campaigns) lead to particular public concern or sensitivity about vaccines. Also, unlike medicines (except for public health programmes such as de-worming, malaria and vitamin supplementation), vaccines are administered not only for the benefit of the individual but also for the benefit of the community. Hence AEFI, unlike adverse drug reactions, may be perceived as being the responsibility of the community.

These differences do not preclude a monitoring system for adverse drug reactions being used to monitor AEFI. However, the system must be sensitive to the specificity of vaccines. Further, 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 surveillance for adverse drug reactions if the system's resources are to be shared.

The reporting pathways for the immunization programme may not be part of the usual reporting trails for medicines and the most efficient way to collect to the reporting of many coincidental events which are only temporally related to immunization, and which require specific domain knowledge for comprehensive investigation and correct interpretation. The priority for immunization safety surveillance is to identify and correct immunization error-related events (particularly in resource-poor countries) and to minimize other possible AEFI, including vaccine adverse reactions (Table 7).

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 medicine exclusively used for therapeutic purposes in a relatively smaller number of individuals. Hence, response and communication about AEFI are likely to be both more important to the health of the population, of greater interest, and more challenging.

Table 7. Checklist for the immunization safety surveillance system

CHECKLIST FOR THE IMMUNIZATION SAFETY SURVEILLANCE SYSTEM

1. Be prepared

- Clarify the respective roles of the NRA and the immunization programme, and agree on the overall goal and specific objectives of the system.
- Identify the resources available and needed, and establish political commitment to immunization safety surveillance.
- Appoint or designate regional/national assessors for immunization safety.
- Establish an 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 reporting and investigation forms.
- Designate and train staff (at all levels) to make reports, complete report forms and investigate AEFI.
- Inform all health workers/clinicians of the need to report immediately an AEFI, and indicate which ones should be reported.
- Consider the establishment of a compensation scheme for specified AEFI.

2. Receive a report (investigating authority)

- Decide if the report is a genuine AEFI according to the definition, and whether investigation and/or advice to the public/media are needed.
- Travel to the location of the AEFI, or delegate responsibility to another trained person or team.
- Decide if there is a need to communicate with the community and/or media to alleviate concerns.

3. Investigate and collect data

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

4. Analyse the data

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

5.Feedback

- Provide periodical (weekly/monthly/quarterly) feedback to operational levels of the health system and also to other stakeholders
- Feedback could be in the form of newsletters, bulletins or special notes. In special events, verbal feedback is encouraged.

6. Follow-up action

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

7. Evaluation

- Evaluating the immunization safety surveillance system is necessary to monitor its impact on vaccine safety and on the national immunization programme
- The country should develop evaluation indicators to monitor the surveillance system

Summary

- Immunization safety surveillance should be a collaborative venture between the immunization programme and, when it exists, the NRA, because both parties are responsible for the safety of vaccines. In countries where they are functioning, pharmacovigilance centres should also be part of the country's system of immunization safety surveillance.
- It is important to set clear objectives and follow each step to establish surveillance.
- Identifying clear roles and responsibilities of different stakeholders at different levels is necessary to achieve functioning immunization safety surveillance in a country.
- To ensure capacity among vaccination staff, immunization officers and the immunization safety expert committee, training should be undertaken at the country level, supported by international resources, such as the Global Vaccine Safety Initiative training materials.
- There are three criteria for evaluating the performance of the immunization safety surveillance programme: (i) AEFI reporting rates, (ii) quality of information and (iii) audit of response to AEFI.

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5 Reporting AEFI

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

Suspicion alone is sufficient for reporting, and the primary reporter is not expected to assess causality. Rapid detection and evaluation of a possible link to vaccines is essential to ensure the continued safety of vaccines. Thus, in case of a suspected AEFI, it is preferable to submit a report to a suitable technical authority on time rather than waiting for all aspects of an investigation to be completed. This is particularly true for serious reports. In many settings the primary reporter submits a report to the immediate reporting authority which is generally a local public health authority. The report is then transferred up through the intermediate level to the national level, and to the central immunization programme and/or NRA. The reporters at different levels may seek to clarify or request additional information before sending the report onward. This chain of movement varies according to the government structure.

To improve detection, the primary reporting level should have a good knowledge of AEFI types and the purpose of AEFI surveillance. Regular orientation, training and awareness programmes are necessary to update knowledge and maintain enthusiasm among primary reporters.

5.1 Which events should be reported?

Any AEFI that is of concern to parents or health-care workers should be reported. In particular, health workers must report:

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

Reporting all minor AEFI such as high fever and minor local reactions is optional. These are expected vaccine reactions and, if reported, the volume of reports would overwhelm the system with information of limited value. However, it is helpful to monitor and record crude numbers and compare them with background rates that could identify

product quality defects, immunization errors or even increased susceptibility of vaccine reactions among a particular population.

Table 8. List of examples of reportable AEFI

Reportable AEFI	Time onset following immunization*
▪ Acute flaccid paralysis for OPV recipient ▪ Acute flaccid paralysis for contact of OPV recipient	▪ 4-30 days following immunization ▪ 4-75 days following immunization
Anaphylaxis (after any vaccine)	Within 48 hours of immunization
Brachial neuritis (after tetanus-containing vaccine)	2-28 days following immunization
Disseminated BCG infection after BCG vaccine	Between 1 and 12 months
Encephalopathy ▪ after measles/MMR vaccine ▪ after DTP vaccine	 ▪ 6-12 days following immunization ▪ 0-2 days following immunization
Hypotonic hyporesponsive episode (HHE) after DTP/PVV vaccine	Median time is 3-4 hours after immunization, but ranges from immediate to 48 hours. However, it can occur even after 48 hours
Injection site abscess (bacterial/sterile) after any injectable vaccine	Not specific. However, commonly within first 14 days of immunization
Intussusception (after rotavirus vaccines)	Commonly within 21 days, risk increased after the first 7 days and usually first dose
▪ Lymphadenitis after BCG vaccine ▪ Osteitis/osteomyelitis after BCG vaccine	Between 1 and 12 months
Persistent (more than 3 hours) inconsolable screaming after DTP/PVV vaccine	Common immediately and up to 48 hours of immunization. However, it can occur even after 48 hours
Sepsis (after any injectable vaccine)	Within 7 days following immunization
Seizures, including febrile seizures after measles/MMR after DTP/PVV	 6-12 days following immunization 0-2 days following immunization
Severe local reaction (after any injectable vaccine)	Within 7 days following immunization
Thrombocytopaenia (after measles/MMR)	Median time is 12-25 days after immunization, but the range is 1-83 days
Toxic shock syndrome (TSS) (after any injectable vaccine)	Commonly within 72 hours following immunization
Death Hospitalization Disability Any other severe and unusual events that are attributed to immunization by health workers or the public	No time limit, but in general those within 30 days following any immunization

* The time interval to onset will depend on the antigen and the adverse reaction. For detailed information on antigen or adverse reaction-specific onset intervals, refer to the Brighton Collaboration case definitions (https://brightoncollaboration.org/public/what-we-do/setting-standards/case-definitions.html), WHO position papers and observed rates information sheets (http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/index.html, accessed 1 August 2014).

A list of suggested reportable events is presented in Table 8. Each country should decide which events are appropriate for inclusion in its reporting system. However, countries are encouraged to include a broad range of events in order to increase global harmonization of AEFI data.

It is important to note that the time interval between immunization and onset of the event may not always be precise or well established. Consequently, the inclusion of time interval in surveillance case definitions is reserved only for selected adverse reactions. It is recommended that surveillance case definitions should be simple. The case definitions developed by the Brighton Collaboration have different levels of diagnostic certainty and are used widely. However, if countries have difficulty in adapting them to their local situations, they can adopt their own valid surveillance case definitions for reporting purposes.

Local reactions occurring at increased frequency, even if not severe, should also be reported. These may be markers for immunization errors or for problems with specific vaccine lots.

5.2 When to report?

Immediately. A report must be made as quickly as possible so that an immediate decision can be made on the need for action and investigation. For incidents with many cases or a high level of community concern, an urgent telephone call/fax/email to the decision-making administrative/operational level is appropriate.

5.3 How to report?

Reports should be made on a standard AEFI reporting form.[20] Annex 2 provides an example of such a form. It is the responsibility of the immunization service provision unit to supply these forms. The report should be kept simple but should ensure that health workers can input essential information.

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

For optimal vaccine safety monitoring and meaningful analysis of AEFI data, systematic and standard collection of critical parameters is essential. A limited number of variables are required to manage AEFI information properly. These include a unique identifier for the report, the primary source of information, patient characteristics, details of the event(s), vaccine(s) of interest, and the possibility of collecting additional information if needed. Any additional information that is collected would be useful for investigation.

[20] Reporting form for adverse events following immunization (AEFI). Geneva: World Health Organization (http://www.who.int/vaccine_safety/REPORTING_FORM_FOR_ADVERSE_EVENTS_FOLLOWING_IMMUNIZATION.pdf, accessed 1 August 2014).

A WHO working group developed a core data set that includes 22 variables[21] (Table 9). This simple structure provides a harmonized template that simplifies AEFI reporting and allows for comparisons and pooling of essential information for action.

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

Category	Core variable
Identity	Date AEFI report first received at the national centre
	Country where this 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 and expiry date
	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
	Telephone number
Other	Comments (if any) by national officer before the report is uploaded to the Global Database

* Ten critical (mandatory) core variables.

If signals are detected, or in serious cases, additional data are essential to determine the association of the event with the vaccine. An additional 33 variables of interest have been developed for more detailed case review. It is proposed that reporting tools used by countries should include a dictionary to standardize the terminology used to record signs, symptoms or diagnosis, and a vaccine dictionary in order to identify suspected vaccine at national or global levels.

[21] AEFI core variables. Geneva: World Health Organization (http://www.who.int/vaccine_safety/AEFI_Core_Variables_2013.pdf, accessed 1 August 2014).

KEY POINTS

Any AEFI that is of concern to 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, it is recommended that countries incorporate a minimum set of 22 core variables in their reporting form, making the form useful both in the country itself and globally.

5.4 Reporting AEFI during immunization campaigns

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

During mass immunization or a special immunization programme, it is of utmost importance to ensure AEFI reporting for two reasons:

- Mass immunization and special immunization programmes cover a large number of individuals in a particular target group in a specified time period. Therefore, an excess number of adverse events may be reported within a short time period. The rate of events remains unchanged, but the increased number of events tends to be noticed by both staff and the public, particularly when injectable vaccines are used and at a time of high social mobilization. Unless an event is properly investigated or analysed, it can cause concern among the public and may also affect the immunization programme.
- During special immunization programmes, a new vaccine may be introduced with no prior experience of, or little information on, adverse reactions. There is a possibility of detection of signals through strengthening surveillance during special immunization programmes. For example, cases of intussusception were reported following the introduction of a new oral rotavirus vaccine (Rotashield) in the USA in 1998-1999.[22]

5.5 Barriers to reporting

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

- considering that the event did not occur after immunization (however, all events following immunization as per the definition should be reported);
- lack of knowledge about the reporting system and process;
- apathy, procrastination, lack of interest or time, inability to find the reporting form;
- fear that the report will lead to personal consequences;

[22] Murphy TV, Gargiullo PM, Massoudi MS et al. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med. 2001;344:564–572. doi:10.1056/NEJM200102223440804.

- guilt about having caused harm and being held responsible for the event; and
- diffidence about reporting an event when not confident about the diagnosis.

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

Positive feedback to health workers is essential. The feedback should include the outcome of investigations or causality assessment when these are carried out, and recommendations on the management of the vaccinee, particularly with regard to the need for future vaccination.

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

5.6 Private-sector reporting

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

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

To maintain uniformity of reporting data, AEFI reporting forms used in the AEFI surveillance system should be made available to the private sector as well.

5.7 Vaccine Adverse Events Information Management System (VAEIMS)

The VAEIMS is a software that has been developed by the International Vaccine Institute in collaboration with WHO. The purpose of the software is to transfer AEFI data using the core variables from the periphery of a health-care system, efficiently and effectively, into a central database for processing and conversion into information that can guide actions. The design of VAEIMS takes account of the diverse systems of data collection, collation, transmission, analysis and feedback in different countries. It is tailor-made to local conditions, and is able to provide quick and reliable information to decision-makers at different levels in a country, and to a global audience.

VAEIMS allows the transfer of data from the each national database to Vigibase (the global database) as it is E2B-compatible (ICH guideline on electronic reporting of adverse events) for global sharing of AEFI data. The web-based version or offline

version of VAEIMS is available to all countries free of charge. The features of the web-based VAEIMS include "live" data upload, data-sharing and analysis. At a later phase of development of VAEIMS, the reporting of AEFI from the periphery to the national level will be facilitated by making it possible to collect data using mobile telephones.

Summary

- A list of AEFI to be reported should be made available.
- Case definitions (e.g. by Brighton Collaboration) for each reportable event should be made available.
- AEFI reporting should be made on standardized reporting forms using a minimum set of core variables in order to make the global evaluation of signals possible and thus benefit countries in their evaluations of AEFI.
- Private-sector reporting is encouraged.
- Sharing reports regionally and globally (via the WHO Programme for International Drug Monitoring /UMC) is encouraged.
- Identifying barriers to reporting and taking appropriate action to address these barriers will improve reporting.

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- Pharmacovigillance and drug safety for the UK and Europe (blog) (http://www.pharmacovigilance.org.uk/tag/e2b/, accessed 23 August 2014).

6 Investigating AEFI

6.1 Why AEFI reports should be investigated

The ultimate goal of a case investigation is to find the cause of an AEFI and to implement follow-up actions. Investigation should identify any immunization error-related or vaccine product-related reactions because these are preventable. If coincidental events are recognized, proving them will be important to maintain public confidence in the immunization programme.

The purposes of investigating an AEFI case are the following:

- to identify the details of vaccine(s) administered and to determine the timing between administration of the vaccine and the onset of the event;
- to confirm the reported diagnosis or establish a diagnosis;
- to document the outcome of the reported adverse event;
- to identify the cause of the AEFI;
- to determine whether a reported event is a single incident or one of a cluster and, if it is part of a cluster, where the suspected immunizations were given and what vaccines were used;
- to examine the operational aspects of the programme (even if an event seems to be vaccine-induced or coincidental, immunization-related errors may have increased its severity) and to prevent immunization-related errors;
- to determine whether similar events are occurring in individuals who have not received the same vaccine.

The term "investigation" used here can be a simple assessment or a more rigorous scientific evaluation of the reported AEFI in order to recognize its possible cause(s). The extent of the investigation depends on the nature of the reported AEFI or/and the country's protocol to carry out the investigation. Accordingly, users of this manual need to adapt their investigation according to the country setting and requirements rather than strictly adhering to the manual, which describes how to carry out scientific investigations of more serious AEFI reported by the surveillance system.

6.2 Which AEFI reports should be investigated?

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

The reported AEFI must be investigated if it:

- appears to be a serious event (as defined by WHO) of known or unknown cause;
- belongs to a cluster of AEFI;
- is a previously unrecognized event associated with an old or newly introduced vaccine;
- involves an increased number or rates of known cause;
- is a suspected immunization error;
- appears on the list of events defined for AEFI surveillance; and
- causes significant parental or public concern.

Improved reporting can lead to more AEFI reports without a real increase in true adverse reaction rates or concerns about the vaccine product or its quality. The investigator should determine if there is a real increase in these reaction rates, as well as identifying the cause of the increase. For example, a change in vaccine manufacturer or in vaccine lot can lead to a change in the reaction rate.

Criteria should be established to define the type of AEFI that requires investigation. Protocols then need to be established at the intermediate-level and national units responsible for AEFI surveillance to ensure that all reports requiring investigation are adequately investigated.

6.3 Who should investigate AEFI?

The profile of investigators who carry out detailed AEFI field investigation will be determined by the operational structure and the expertise available to the surveillance system in the country. Many developed countries have national capacity and expertise to conduct investigation up to the lowest level of the health system but this may not be available to many low and middle income countries. Having a plan for responding to serious AEFI requires each country to have identified adequate expertise tailored to its particular cirumstances.

Sometimes the cause of the reported AEFI is very obvious, as in the case of immunization error-related events. A basic preliminary investigation by local programme managers may be sufficient to identify the cause.

6.4 When to investigate AEFI

The urgency of the investigation will depend on the situation. Not all AEFI require detailed field investigation, as described above. However, if it is determined on the basis of the preliminary information that a detailed field 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, a criterion for initiating investigation could be fixed as within two working days for serious events and five working days for non-

serious events. The criteria and timelines of an investigation (e.g. continuing problem, high community concern) should be specified in advance.

6.5 How to investigate AEFI

An AEFI investigation follows standard principles of epidemiologic investigation (Figure 2). It is important to investigate suspected adverse events promptly and completely. The investigator will primarily need to focus on the reported reaction as well as gather information from the patient/parent, health workers and supervisors, and community members. The information collected (and conclusions) should be recorded on an AEFI investigation form. (Annex 3).

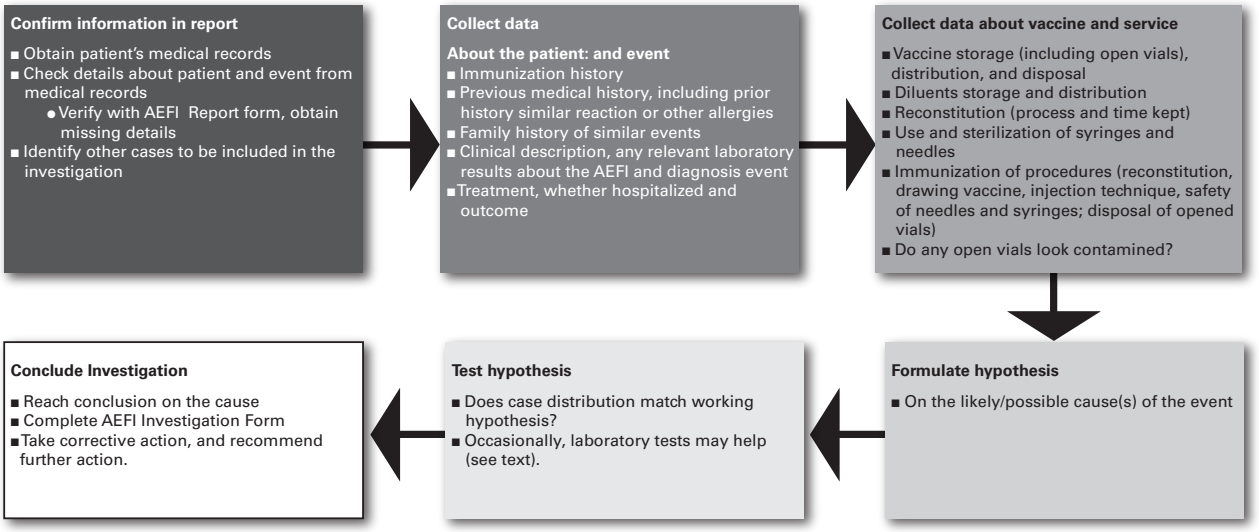
In low- and middle-income countries, immunization error-related events and coincidental events are the commonest AEFI. Therefore, the investigator should examine the diagnosis and background disease rates carefully and examine the evidence for any errors in the storage, handling or administration of vaccines in considering immunization error-related events. Attention can then focus on finding out more about the particular error and taking the necessary corrective action. The investigator should attempt to identify system problems rather than blaming individuals. For example, if an investigation reveals that most abscesses are reported from one immunization clinic due to the faulty immunization technique of a health-care worker, rather than blaming the worker, the investigators should endeavour to find reasons why that health-care worker uses the incorrect technique. The underlying cause could be due to a system failure such as lack of training or lack of supportive supervision and this should be addressed.

The core variables listed by WHO for reporting (Table 9) is insufficient for the purpose of comprehensive investigation. Countries are encouraged to use specially designed data collection forms for the investigation. The sample AEFI investigation form (Annex 3) may be adapted to country and situation requirements.

Investigator(s) may use WHO's Aide-mémoire on AEFI investigation as resource material.[23] This provides key definitions, guidance for preparing for an investigation, and a checklist of useful information for each step of an investigation.

[23] Aide-mémoire on AEFI investigation. Geneva : World Health Organization (http://www.who.int/vaccine_safety/publications/AEFI_Investigation_Aide_Memoire.pdf, accessed 1 August 2014).

Figure 2. Steps in an AEFI investigation



It is essential to have clear working case definitions, taken from the guidelines on reporting or defined during the investigation at the outset. Countries are encouraged to use the Brighton Collaboration case definitions and adapt them into their own surveillance systems. The use of common case definitions will lead to more meaningful use of data from different countries at regional and global levels (e.g. comparison of vaccine reaction rates). The investigation should 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 between those who received the vaccine and those who did not.

Proper investigation requires a working hypothesis, and this should be established as soon as there is sufficient information. The working hypothesis may be a simple statement linking the suspected cause with the reported AEFI. For instance, an abscess following immunization may initially be investigated with the following hypothesis: "An abscess following immunization due to incorrect technique". The working hypothesis may change during the course of the investigation. In this example, additional information may reveal that there are similar cases from more than one clinic and therefore the working hypothesis could be modified as "Abscess following immunization due to cold chain failure in vaccine storage". The focus of the investigation should be to seek to confirm the working hypothesis.

6.6 Laboratory testing: vaccine

Laboratory testing may sometimes confirm or exclude the suspected cause. However, testing should be requested on the basis of clear suspicion and not as a routine procedure, and never before the working hypothesis has been formulated. Laboratory testing is always costly. It is important to note that there is a need for a good laboratory network (including the manufacturers) to support immunization safety surveillance. Determination of which samples to test, if any, depends on the working hypothesis for the cause of the event (Table 10). WHO's guidelines on nonclinical evaluation of

vaccines can help.[24] 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. It is important to monitor the cold chain of vaccine vials under suspicion, irrespective of whether they need laboratory testing or not.

6.7 Laboratory testing: human specimens

For biochemical, histopathological and microbiological examination, specimens should be processed at the local hospital. In case facilities are unavailable locally, specimens should be forwarded to the most suitable laboratory in the country or even an accredited laboratory abroad if warranted.

Table 10. Laboratory testing to investigate AEFI by working hypothesis

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

The date and time of collection and the type of each sample collected should be recorded together with clinical investigations and medical records related to the incident. It is necessary to obtain a detailed history which includes past medical history, medicine history, immunization history, history of allergies and findings of medical records and so on. It is advised to consult the clinician(s) treating the patient to make a decision on the samples to be tested (see Table 11).

[24] WHO guidelines on nonclinical evaluation of vaccines. In: WHO Expert Committee on Biological Standardization: fifty-fourth report. Geneva: World Health Organization; 2005: Annex 1 (WHO Technical Report Series, No 927; http://www.who.int/biologicals/publications/nonclinical_evaluation_vaccines_nov_2003.pdf, accessed 1 August 2014).

The collection and storage of specimens following serious AEFI (e.g. deaths, anaphylaxis, toxic shock syndrome) is important. Therefore, as soon as information is received about a suspected AEFI, the hospital staff or health-care workers (in a community setting) are advised to collect all relevant samples such as blood, urine, cerebrospinal fluid (CSF), vomitus, faeces, sputum, swabs etc. If there is a delay in transport to the laboratory, samples should be stored in a refrigerator at the recommended temperature, depending the type of sample and the facilities available.

KEY POINTS

Laboratory testing is not a routine requirement but may be a part of an investigation.

- Laboratory testing is costly and is recommended only when it is necessary.
- However, securing samples (vaccine vials, syringes, blood etc.) is important because later investigation may require them.
- Therefore, proper storage and transport of suspected samples is recommended.

TABLE 11. **GUIDE TO HUMAN SPECIMEN SAMPLES COLLECTION FOLLOWING SELECTED AEFI**

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

6.8 Investigating AEFI clusters

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

Cluster investigation begins by establishing a case definition for the AEFI and related circumstances and by identifying all cases that meet the case definition. The investigation should promptly characterize all known cases and research similar ones (Figure 3).

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

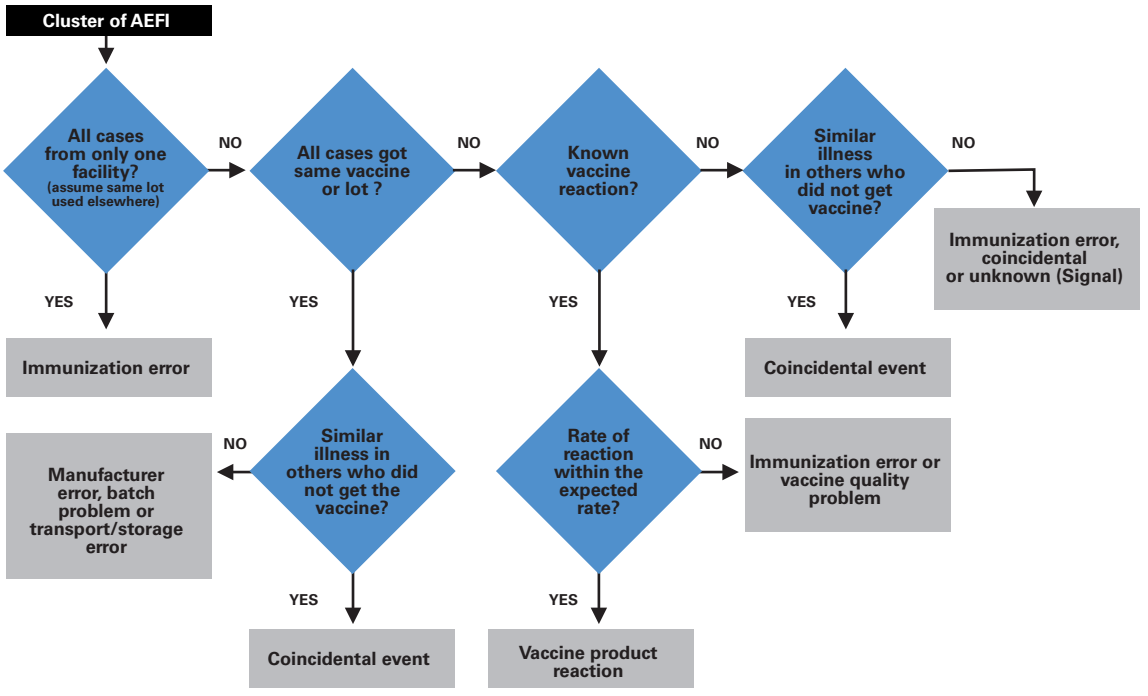
- detailed data on each patient;
- programme-related data (storage and handling, etc.); and
- immunization practices and the relevant health workers' practices.

Common exposures among the cases can be identified by reviewing:

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

When an AEFI cluster has been identified, the cause-specific definitions provide a framework for investigation and causality assessment. Usually, the key considerations will be to investigate the possibility of a vaccine quality defect or an immunization error-related AEFI. For relatively new vaccines or established vaccines used in new target populations, a cluster may represent a previously unrecognized vaccine product-related reaction (i.e. a signal). Awareness of vaccine reaction rates and background rates of reported events is essential for assessing a cluster in terms of the strength of the signal it may provide.

Figure 3. Identifying the causes of an AEFI cluster



If all cases received vaccines from the same health worker/facility and there are no other cases, an immunization error is likely. If all cases received the same vaccine or lot, and there are no similar cases in the community, a problem with the vaccine or the respective lot is likely. If the event is a known vaccine reaction but is found to occur at an increased rate, an immunization error or a vaccine problem are likely causes. Finally, if cases in the unvaccinated population are occurring at about the same rate/proportion as among the vaccinated from the same area in the same age group, the adverse event was probably coincidental (Table 12).

Table 12. Cause-specific cluster characteristics

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 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 as anxiety-related reactions during immunization programmes targeting adolescent girls

In a cluster analysis, if a previously unknown event is reported only among the vaccinated group, it can be a potential signal provided that both immunization error-related reactions and coincidental events are excluded. Such AEFI require comprehensive assessment and further studies to understand their true causality (Figure 3).

6.9 Investigation of deaths

A field investigation of a death following immunization has to be conducted without delay as the death can cause significant community concern (Table 13). All administrative levels, including the national immunization programme, should be notified of the death. It is recommended that death investigation should be carried out by a team comprising clinical, laboratory and forensic experts. The team should be supported by the programme managers. All relevant information on the event should be available to the investigation team.

An autopsy is preferred and is recommended following all deaths suspected to be caused by vaccine or immunization. However, the decision to conduct the autopsy should be taken within the context of religious, cultural and the legal framework of the country.

At the time of autopsy, the autopsy surgeon should be provided documents outlining detailed preclinical and clinical history, including laboratory and radiological findings. Where possible, a visit to the scene of the death to gather additional evidence; radiological examination; histopathological examination; and toxicological and microbiological examinations will be useful. Samples for microbiology, immunology, histopathology and virology should be collected according to the instructions given by the relevant laboratories. Adherence to a standard autopsy protocol which allows for a comprehensive causality assessment of a reported death following immunization is important and necessary.

If an autopsy is not possible, a verbal autopsy can be carried out in accordance with established guidelines and protocols. WHO protocols for verbal autopsy standards are a useful reference.

TABLE 13. **ACTIONS TO SAFEGUARD THE PUBLIC DURING AN INVESTIGATION**

Stage of investigation	Actions
Incident detected	■ Assess and investigate with an appropriate degree of urgency ■ Possibly quarantine suspect vaccines and take other immediate counter actions, as appropriate ■ Begin communication with all concerned parties
Investigation starts	■ Ensure that the investigator has adequate resources, and provide more if needed ■ Increase surveillance to identify similar cases in and out of area: sometime enhanced or active surveillance is required to gather more information/data Define any suspect vaccine ■ Maintain continued communication on progress of the investigation with all concerned parties: do not suggest any hypothesis
Investigator develops working hypothesis	■ Do not communicate the working hypothesis until confirmed (the working hypothesis is for the investigation team only and not for the public since, if the investigation reveals something different from the working hypothesis, this may affect public trust) ■ If programme-related errors are the working hypothesis, correct them ■ If a vaccine problem is suspected, quarantine suspect vaccines
Investigator confirms working hypothesis	■ Advise the community of the cause and the planned response ■ Communicate with all concerned parties on findings

Summary

- Investigation should be timely, comprehensive and methodical.
- Laboratory investigations are important but should not be routine. They should be conducted if only indicated and necessary.
- It is recommended to secure investigational items (vaccine, syringes, blood etc.) in proper condition in case if they may be needed later for laboratory investigations.
- Autopsy investigations are often essential to exclude any coincidental causes of an AEFI.

Bibliography:

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- Verbal autopsy standards: ascertaining and attributing cause of death. Geneva: World Health Organization; 2007 (http://www.who.int/healthinfo/statistics/verbalautopsystandards/en/index1.html, accessed 23 August 2014).

7 Analysis of AEFI data

Immunization and vaccine safety surveillance should incorporate inbuilt mechanisms for structured, systematic and continued data collection. Epidemiological analysis of data is required to measure the impact of vaccines used in the country immunization programme and to disseminate findings to advise programme managers, the 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 rates. In considering concerns with specific lots, it is important to have as accurate a denominator of vaccine use as possible. It is always the rate and not the number of reports that should be evaluated (in comparison with known vaccine product-related rates by lots, by different manufacturing products, and by historical rates). For more information, refer to the Guide to the WHO information sheets on observed rates of vaccine reactions.[25]

Analysis of data on AEFI should consider the following:

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

[25] Guide to the WHO information sheets on observed rates of vaccine reactions. Geneva: World Health Organization (http://www.who.int/entity/vaccine_safety/initiative/tools/Guide_Vaccine_rates_information_sheet_.pdf, accessed 1 August 2014).

7.1 Who should analyse the data?

Data analysis could be carried out at different levels of the immunization safety surveillance system: the programme implementation level, the subnational level and the national level. The extent and purposes of analysis will vary at each level. Analysis of data at the service provider level is very important for identifying immunization errors and ensuring that corrective action is carried out in a timely manner. Data analysis at higher levels with larger denominators is important to identify rare vaccine safety events and also detect signals. The details are described in Table 14.

Table 14. **Purpose of data 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	These are programme operation/surveillance performance indicators (timeliness, completeness).
	Reported AEFI by place (clinics, hospitals), persons and time	Identification of immunization error-related events will lead to corrective action.
	Reported AEFI by antigen	Will also identify vaccine reactions and coincidence.
Subnational level (regional/ provincial/ district/ town)	Number of reports by local levels	These are programme operation/surveillance performance indicators (timeliness, completeness) at local level.
	Reported AEFI by place (clinics, hospitals), persons and time	Identification of immunization error-related events will lead to corrective action.
	Cluster analysis	Cluster analysis leads to identification of immunization error related events, coincidence and vaccine reactions.
	Reported AEFI by antigen	Will identify vaccine reactions and coincidence.
National level	Number of reports by intermediate levels	These are programme operation/surveillance performance indicators (timeliness, completeness) at intermediate level.
	Reported AEFI by place (clinics, hospitals), persons and time	Cluster analysis leads to identification of immunization error related events, coincidence and vaccine reactions.
	Cluster analysis	Will identify vaccine reactions, including detection of signals.
	Reported AEFI by antigen	Leads to operational and policy decisions being taken in the country.

7.2 How should the data be analysed and interpreted?

Step 1: Following verification of cases, all reported AEFI data should be line-listed and/or entered into a database. Line-listing will help initial identification of clustering or any unusual or significant reporting events that need further analysis (Annex 4).

Step 2: AEFI data should be tabulated by place, person, time, antigens and type of event (e.g. 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, an increased number of abscesses by one immunization centre is more likely to be due to immunization-related error. However, further investigation is necessary to confirm causality.

Step 3: AEFI rates should be calculated. The number of doses administered for each antigen is the denominator for calculating reported AEFI rates for each antigen in a given time period (month, quarter-year or year). Analysis should be expanded to include AEFI rates by first, second or third dose if the antigen is administered more than once. For this, the number of doses administered of the given antigen – by first, second or third dose should be used as the denominator.

For instance, in a hypothetical country X, the registered child population under 1 year of age is 5000. The coverage of measles vaccine is 90%. During the year, 20 febrile seizures were reported following measles vaccination. The numerator for this vaccine reaction (febrile seizures) is 20.

Selecting a proper denominator can be challenging; some options that could be considered and their limitations are outlined in Table 15.

Table 15. 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 underestimate rate
Coverage x population	May be less accurate because of variability in coverage estimates
Target population	Proxy measure for vaccine population (may also underestimate)

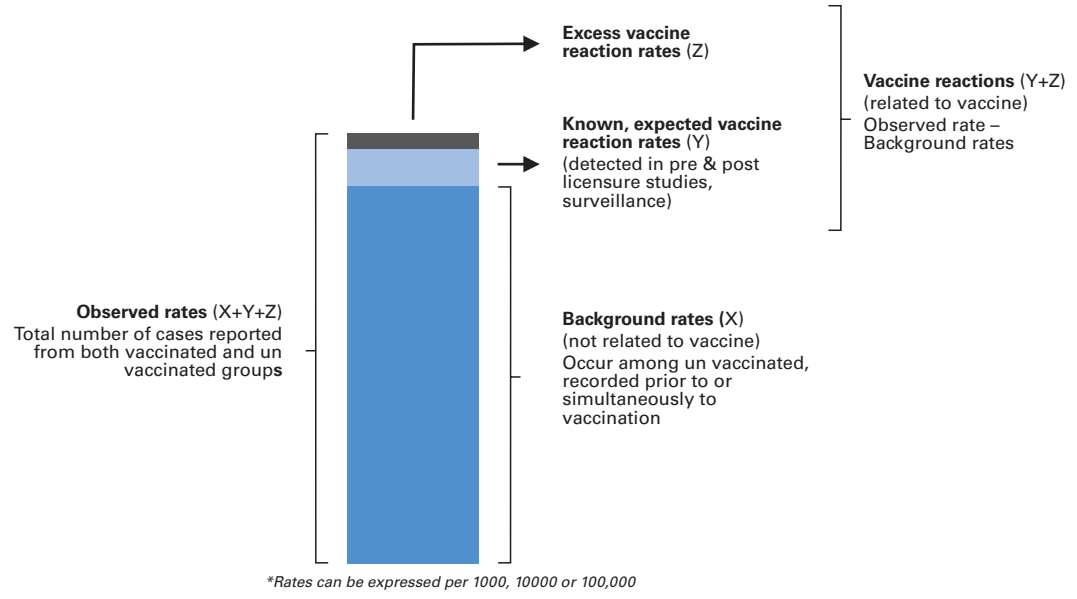
In the example of country X, since no other data are available, coverage can be used to obtain the denominator; therefore denominator = population x coverage = 5000 x 90% = 4500. Thus the reported rate of febrile seizures is 20 (numerator)/4500 (denominator) x 100 (multiplier) = 0.44%.

Use of a proper multiplier is important as it must vary by purpose and level of analysis. At local level, percentage (%) is the best choice, whereas subnational and national levels may use 1000, 100 000 or 1 million as the multiplier. For common, minor vaccine reactions, percentage is recommended, and for rare serious reactions, 10 000 (104), 100 000 (105) or 1 000 000 (106) can be used (Table 3).

Step 4: Rates should be compared and interpreted. Expected vaccine reaction rates that are available for each type of AEFI and antigen (see Annex 1 and WHO vaccine reaction information sheets) provide a guide to decision-making on corrective action for reported AEFI. It is also important to know the background rates of reported medical events in the country. Background rates are independent and are not related to the vaccine. Observed (reported) rates include both background rates and vaccine-related rates. Comparison of background rates with reported (observed) rates of AEFI will provide support for a conclusion on the causality of these events being due to a vaccine reaction (Table 16).

Figure 4 shows a comparison of the background rate with the observed rate of an event to determine the vaccine reaction rate (i.e. the rate of events that are actually caused by the vaccine).

Figure 4. Vaccine reaction rate, observed rate and background rate



Note: Vaccine reaction rate = observed (reported) rates – background rates (not related to vaccine).

Vaccine reaction rates are further divided into two subcategories: expected vaccine reaction rates and excess vaccine reaction rates. The WHO vaccine reaction information sheets[26] give the "expected" vaccine reaction rates (the "Y" component in Figure 4), which are based on pre-licensure and post-licensure data. These expected vaccine reaction rates are known rates due to the inherent properties of the vaccines and the response by recipients. If the value exceeds the "expected" vaccine reaction rates, one should consider whether this is a true increase in the vaccine reaction rate or if the values are due to other factors.

In addition, these reported vaccine reaction rates depend on the reporting source – such as type of surveillance (active, passive, enhanced passive), special studies etc. Further, these reports may also differ, as outlined in the manufacturer's package information, and therefore the rates should be interpreted with caution.

Table 16. Factors to consider when comparing rates of AEFI

Vaccines Although a vaccine may have the same antigens as another, different manufacturers may produce vaccines (or lots of the same vaccine) that differ substantially in their composition, including the presence (or not) 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 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 events may be defined differently in surveillance/research studies that do not use the same case definition. Not using standardized case definitions may consequently affect the estimation of the AEFI rate. The Brighton Collaboration has developed case definitions for many vaccine reactions (www.brightoncollaboration.org).
Time period It is important that estimates of AEFI rates are limited to a given time period (e.g. quarterly, annually) to enable a valid comparison to be made. This is helpful when interpreting AEFI rates due to possible vaccine reactions or coincidental events. It also adds to the validity of the rates as the denominator (vaccine doses administered in a given time period) contributes to more accurate estimates.
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-licensure 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 instance, reports of death post-vaccination may be higher in a country that has a higher background rate of deaths due to coincidental infections.

[26] WHO vaccine reaction rates information sheets. Geneva: World Health Organization (www.who.int/vaccine_safety/initiative/tools/vaccinfosheets, accessed 1 August 2014).

In the scenario presented here, we can compare the observed rate of 0.44% febrile seizures reported in country A with the expected rate of febrile seizures following measles-containing vaccines, which is 0.03%. Thus the observed (reported) rate of 0.44% is greater than the expected vaccine reaction rate of 0.03% and therefore warrants investigation. We ask ourselves whether the case definition is correct, whether the onset interval concurs with the interval of the reported febrile seizures cases after vaccination or if something is wrong with the vaccine product. In any analysis of vaccine adverse events, confounders or sources of bias that should be considered include (but are not limited to) age, gender, race/ethnicity, season (e.g. for influenza vaccines) and country/region.

At the international level, data analysis aims mainly to identify the signals and compare pre-licensure and post-licensure safety data, and to share the findings with countries to support the decision-making. The data analysis also helps manufacturers to ensure vaccine safety during production of vaccines.

7.3 How should a cause be determined?

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

Comparing background data with reported (observed) data does not conclude the search for 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 non-vaccinated persons, provided that the effects of confounders and bias are ruled out. Estimating relative risk and attributable risk is necessary, and retrospective or prospective analysis of available data or the design of epidemiological studies (case series, case-control cohort studies) will strengthen the conclusion of causality.

Summary

Data analysis is important for identifying problems, generating a hypothesis and then testing the hypothesis.

- Data need to be cautiously interpreted: compare rates but not absolute numbers, give attention to case definitions and use accurate denominator data, if available. WHO information sheets on vaccine reaction rates provide rates of reactions to specific vaccines that can be helpful when comparing rates. Reported vaccine reaction rates depend on the reporting source such as type of surveillance and special studies, and therefore these rates must be interpreted with caution.
- Comparing background data with observed data does not prove 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 non-vaccinated persons.
- Analysis and interpretation of reporting rates will begin to identify vaccine and vaccination problems. Therefore it is important to have a comprehensive reporting system with a high reporting coverage. For this purpose, a search for additional cases, particularly during investigations, is necessary since underreporting is common in passive/spontaneous surveillance systems.

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- WHO vaccine reaction rates information sheets. Geneva: World Health Organization; 2012
  - List of information sheets with links: www.who.int/vaccine_safety/initiative/tools/vaccinfosheets, accessed 1 August 2014.
  - Guide to the WHO information sheets on observed rates of vaccine reactions: http://www.who.int/entity/vaccine_safety/initiative/tools/Guide_Vaccine_rates_information_sheet_.pdf, accessed 1 August 2014.

8 Causality assessment of an AEFI

Causality assessment is the systematic evaluation of the information obtained about an AEFI to determine the likelihood that the event might have been caused by the vaccine/s received. Causality assessment does not necessarily establish whether or not a definite relationship exists, but generally ascertains a degree of association between the reported adverse events and the vaccine/vaccination (Table 17). Nevertheless, causality assessment is a critical part of AEFI monitoring and enhances confidence in the national immunization programme. Vaccine recipients want to know whether they experienced the event due to the vaccine. They may believe that because one event followed another, it was causal. It may be difficult to explain that that this might not have been the case. Causality assessment may provide a more descriptive explanation that may reassure the vaccinee and lead to better management of the event that ultimately helps the vaccinee. In essence, determining whether or not an AEFI is attributed to the vaccine or vaccination decides the steps needed to be taken to address the event.

A companion document to accompany this chapter is the WHO publication Causality assessment of an adverse event following immunization (AEFI) – User manual for the revised WHO classification (see Bibliography). It should be acquired to complement this material.

Table 17. Usefulness and limitations of standardized case causality assessment

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

Causality assessment is important for:

- identification of vaccine-related problems;
- identification of immunization error-related problems;
- excluding coincidental events;
- detection of signals for potential follow-up, testing of hypothesis and research; and
- validation of pre-licensure safety data with comparison of post-marketing surveillance safety data.

The quality of the causality assessment depends on three factors:

1. the performance of the AEFI reporting system in terms of responsiveness and effectiveness (the quality of case reporting and follow-up investigation);
2. availability of adequate medical and laboratory services for the investigation and follow-up of cases, and access to background information on population disease/illness rates in the absence of vaccination; and
3. the quality of the causality review process, including access to appropriate expertise.

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

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

8.1 Levels of AEFI causality assessment

Causality assessment of AEFI applies to investigating relationships between a vaccine and an adverse event at three levels - the population level, the level of the individual AEFI case report, and in the context of the investigation of signals – all of which depend on an assessment of causality for individual cases. The details are outlined in the Table 18.

TABLE 18. **ASSESSING CAUSALITY AT DIFFERENT LEVELS**

Population level: Surveillance data and an appropriate statistical methodology are used to test the hypothesis that there is a causal association between the use of a vaccine and a particular AEFI. At the population level the aim is to answer the question "Can the given vaccine cause a particular adverse event?" This may sometimes be combined with causality assessment at the individual level (of AEFI 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.
Individual AEFI case report: The aim is to estimate the probability that the occurrence of a reported AEFI in a specific individual is causally related to use of the vaccine. The aim of causality assessment at the individual level is to address the question "Did the vaccine given to a particular individual cause the particular event reported?" 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.
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.

8.2 SCIENTIFIC BASIS : CRITERIA FOR CAUSALITY IN THE CAUSALITY ASSESSMENT PROCESS

Criteria for causality are generally considered to have been derived from work by Bradford Hill in 1965 as the minimum conditions necessary to provide adequate evidence in support of a causal relationship. While Hill indicated nine criteria, the following seven are most relevant to the question "Can the given vaccine cause a particular event?" The first criterion is essential.

Temporal relationship: Exposure to the vaccine must precede the occurrence of the event. 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 of causality.

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: The stronger the (statistical) association, the more likely that the relation is causally associated.

Consistency of the association: The association is consistent when results are replicated in studies in different settings, among different populations and using different methods.

Specificity: The vaccine is the only cause of the event that can be shown.

Definitive proof that the vaccine caused the event: There is clinical or laboratory proof that the vaccine caused the event.

Consideration of alternative explanations: In doing causality assessment, all reasonable alternative etiological explanations need to be considered.

Prior evidence that the vaccine in question could cause a similar event: The concept of "re-challenge" is more commonly used in medicine causality, but it has also been helpful for certain vaccine-event considerations (e.g. Guillain-Barré syndrome or GBS occurring on three separate occasions in the same individual within weeks of administration of tetanus vaccine).

8.3 Case selection for AEFI causality assessment

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

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

Other AEFI may also be subject to a causality assessment if there is a need to assess them in more detail given their potential need for a detailed investigation or follow-up, as outlined below:

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

8.4 Steps to be taken before starting a causality assessment

There are three prerequisites before a causality assessment is conducted, namely:

1. The AEFI case investigation should have been completed. Premature assessments with incomplete investigation could mislead the classification of the event. When an investigation is incomplete, follow-up efforts to obtain additional information and documents should be made.

2. There must be a "diagnosis" (see below) using standard or widely accepted criteria for the adverse event, clinical sign, abnormal laboratory finding, symptom and/or disease in question. In other words, it should be clearly understood which vaccine is being associated with what specific event that was reported.

8.5 Causality assessment method

The WHO publication Causality assessment of an adverse event following immunization (AEFI) – User manual for the revised WHO classification was developed by WHO as a method for assisting national committees for AEFI case review and causality assessment. It was patterned on an algorithm developed in the USA by the Clinical Immunization Safety Assessment network and with new AEFI definitions proposed by the Council for International Organizations of Medical Sciences (CIOMS).

The revised WHO causality algorithm focuses on two critical questions: "Is there evidence in literature that this vaccine(s) may cause the reported event even if administered correctly?" and "Did the event occur within an appropriate time window after vaccine administration?" WHO's Aide-mémoire on causality assessment outlines the algorithm and summarizes the process and should be kept handy.[27]

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 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 on the basis of the direction determined in the algorithm.

Step 1: Eligibility

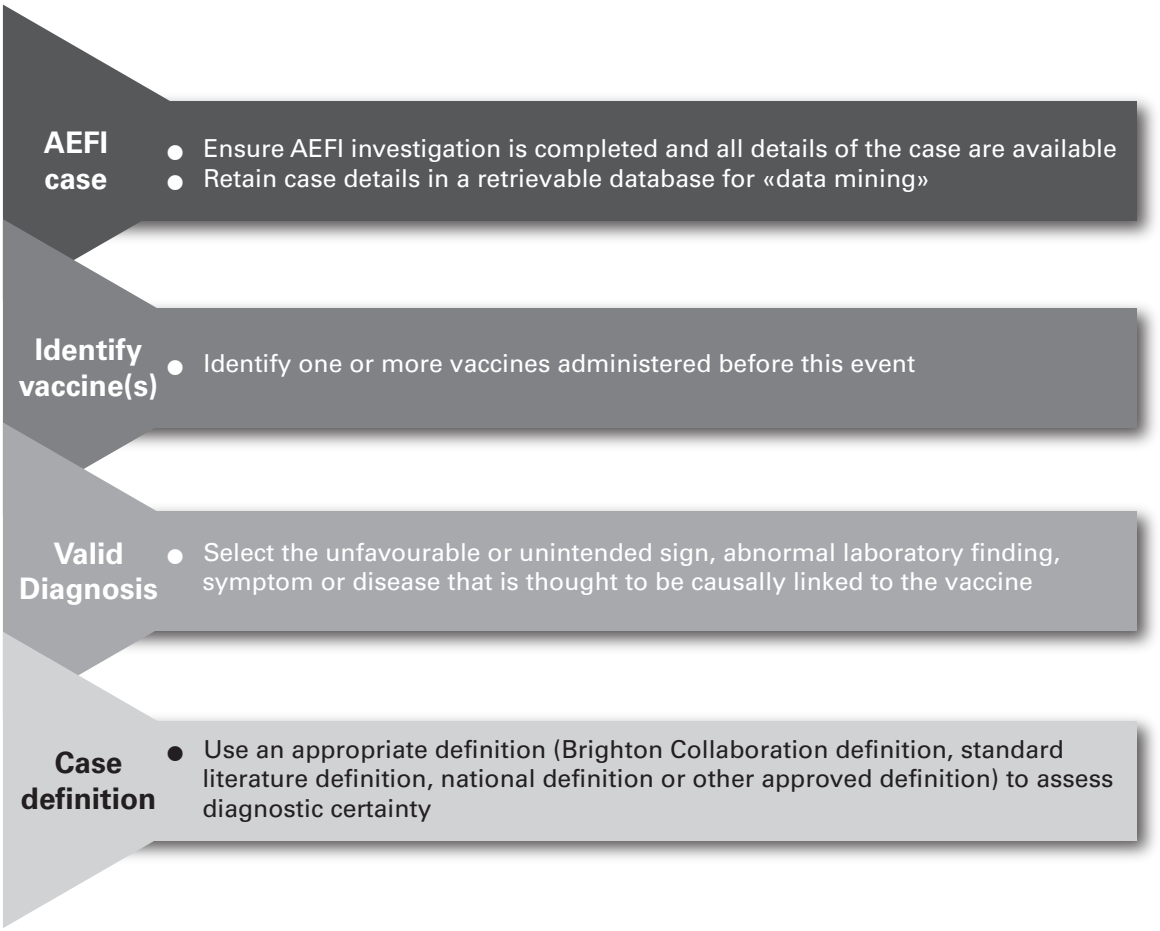
It may be self-evident, but to proceed with causality assessment it is necessary first to confirm that the vaccine was administered before the event occurred (Figure 5). This can be ascertained by eliciting a careful history from the relevant stakeholders to ascertain the timing of vaccination and of the onset of any signs and/or symptoms related to the event being assessed. It is also essential to be clear on the "diagnosis" of the reported AEFI. The valid diagnosis could be a clinical sign, symptom, abnormal laboratory finding or disease with clear details regarding onset. The diagnosis should also meet a standard case definition for the disease process that is being assessed. If available, it is best to

[27] WHO Aide-mémoire on causality assessment. Geneva, World Health Organization (http://www.who.int/vaccine_safety/publications/AEFI_aide_memoire.pdf, accessed 1 August 2014).

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

Another important point is that, while the revised process envisages the causality assessment of an individual AEFI case with a particular vaccine, in the event of multiple vaccines being given simultaneously a causality assessment may have to be conducted that takes each vaccine into account separately.

Figure 5. Causality assessment: eligibility



Source: Causality assessment of adverse event following immunization (AEFI): user manual for the revised WHO classification. Geneva: World Health Organization; 2013.

If an AEFI is reported and appears to not meet the eligibility criteria because of suspected inadequate information, it is important to make attempts to collect the additional information required in order to ensure that the case can be properly assessed for eligibility. Additionally, all cases reported (including those deemed, or eventually deemed, ineligible) should be stored in a repository (preferably electronic) so that they can be accessed should additional information become available through reports of similar cases, new evidence in the literature, or through periodic database analysis.

At the successful completion of this stage, the reviewers should define the "causality question" (Figure 6).

Figure 6. Causality question

Create your question on causality here:

Has the _____ vaccine/vaccination caused _____ ?

(The event for review in step 2)

Source: Causality assessment of adverse event following immunization (AEFI): user manual for the revised WHO classification. Geneva: World Health Organization; 2013.

Step 2: Checklist

The checklist contains elements to guide the assessor or committee of reviewers to collate the evidence for case review (Table 19). It is designed to assemble information on patient-immunization-AEFI relationships in the following key areas:

1. Is there evidence for other causes?
2. Is there a known association with the vaccine/vaccination in the medical literature? If so, did the event under assessment occur within an appropriate time window and, if so, was it associated with the vaccine product, an immunization error or immunization-related anxiety
3. Is there any strong evidence against a causal association?
4. Other qualifying factors for classification (e.g. background rate of the event, present and past health condition, potential risk factors, medication, biological plausibility, etc).

Table 19. The causality assessment checklist

I. Is there strong evidence for other cause?

- Does a clinical examination, or laboratory tests on the patient, confirm another cause?

II. Is there a known causal association with the vaccine or vaccination?

Vaccine product(s)

- Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?
- Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?

Immunization error

- Was there an error prescribing or non-adherence to recommendations for use of the vaccine?
- Was the vaccine (or any of its ingredients) administered unsterile?
- Was the vaccine's physical condition abnormal at the time of administration?
- Was there an error in vaccine constitution/preparation by the vaccinator?
- Was there an error in vaccine handling?
- Was the vaccine administered incorrectly?

Immunization anxiety

- Could the event have been caused by anxiety about the immunization?

II. **(time)**. If "yes" to any question in II:

- Was the event within the time window of increased risk, after vaccine administration?

III. Is there strong evidence against a causal association?

- Is there strong evidence against a causal association?

IV. Other qualifying factors for classification

- Could the event occur independently of vaccination (background rate)?
- Could the event be a manifestation of another health condition?
- Did a comparable event occur after a previous dosc of a similar vaccine?
- Was the exposure to a potential risk factor or toxin prior to the event?
- Was there the acute illness prior to the event?
- Did the event occur in the past independently of vaccination?
- Was the patient taking any medication prior to vaccination?

Source: Causality assessment of adverse event following immunization (AEFI): user manual for the revised WHO classification. Geneva: World Health Organization; 2013.

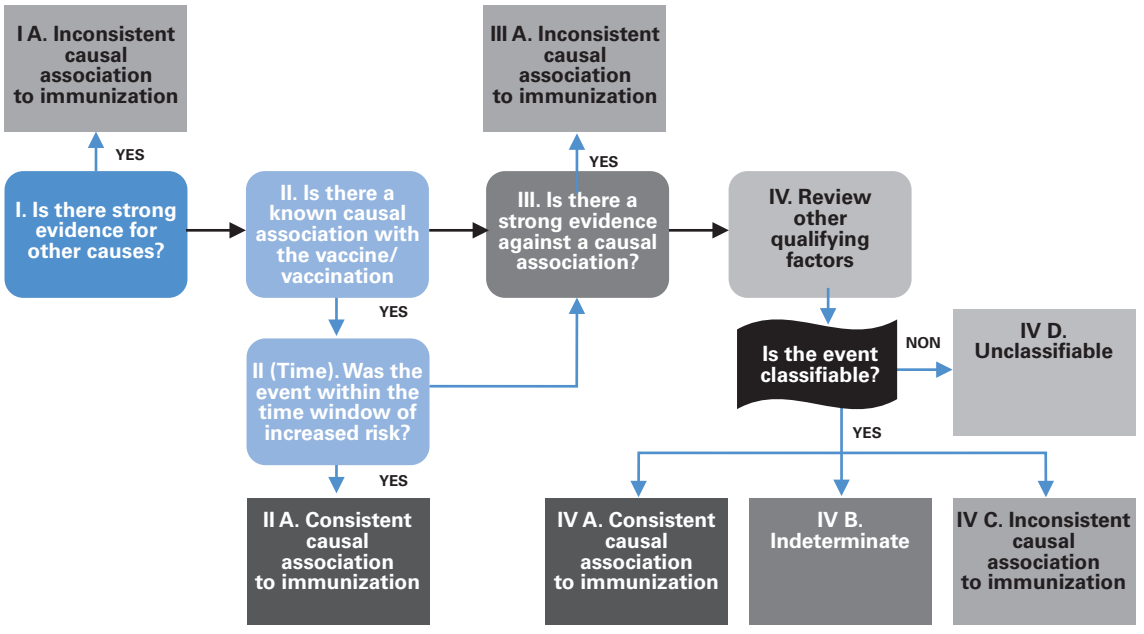
(See Annex 5 for the standard template of the checklist.)

Step 3: Algorithm

The algorithm (Figure 7) follows the key questions and related answers on the checklist. A stepwise approach using the algorithm helps determine if the AEFI could be consistent, or inconsistent, with an association to immunization, or is indeterminate or unclassifiable.

A detailed description of the algorithm and how to make use of it is in the user manual from which it is taken. In particular, some of the responses – such as those to IA, IIA and IIIA – have greater strength and these conclusions have greater weight. When the conclusion is "unclassifiable", the reviewers should determine the reasons why classification was not possible and all attempts should be made to obtain the necessary missing information or evidence to allow for a classification.

Figure 7. Causality assessment: algorithm



Source: Causality assessment of adverse event following immunization (AEFI): user manual for the revised WHO classification. Geneva: World Health Organization; 2013.

Step 4: Classification

The final classification is based on there being available adequate information for the case, as mentioned above. After working through the algorithm, a case can be classified as follows (Figure 8):

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.

Indeterminate

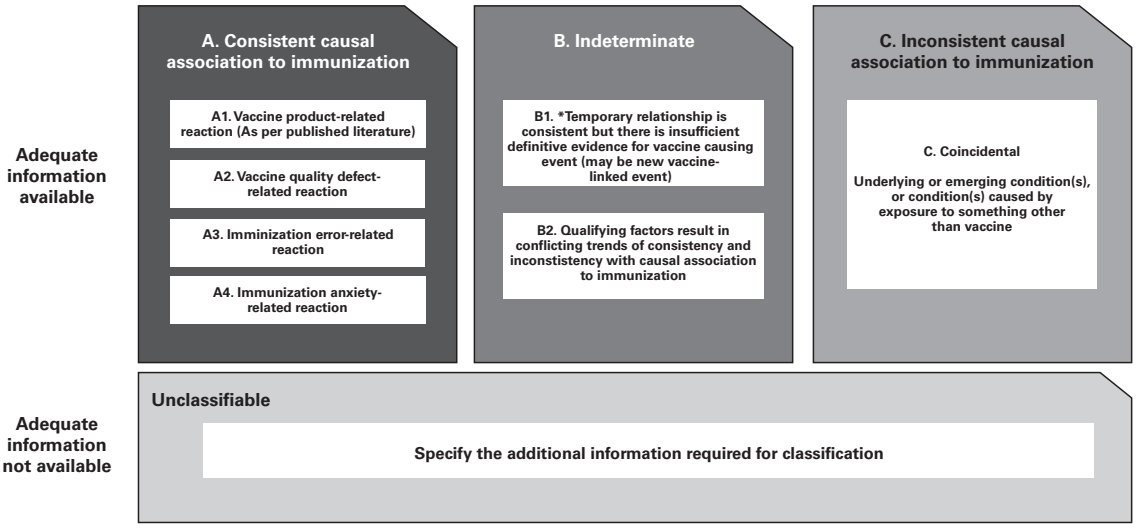
B1. The temporal relationship is consistent but there is insufficient definitive evidence for the vaccine causing the event. It may be a new vaccine-linked event. This is a potential signal and needs to be considered for further investigation.

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

Inconsistent causal association to immunization (coincidental)

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

Figure 8. Causality assessment: classification



*B1: Potential signal and maybe considered for investigation

Source: Causality assessment of adverse event following immunization (AEFI): user manual for the revised WHO classification. Geneva: World Health Organization; 2013.

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

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

8.6 Action to be taken after causality assessment

Regardless of the outcome of causality assessment, the lessons learned should provide insights on the immunization programme for the technical, immunization programme and administrative managers. Findings should be promptly and clearly communicated and the messages on any next steps to be taken should also be clear. These should include communicating reassurance or the need to take specific actions in the programme – including training, research, modifying systems, refining tools and so on – to avoid and/or minimize recurrences.

National immunization programmes need to establish standard protocols for responding to AEFI. These have to be decided by a national committee and approved by the existing decision-making system in the country. The following section provides some examples of the types of responses that can be taken to the different causality conclusions resulting from the assessment.

A. Consistent causal association to immunization

A1. Vaccine product-related reaction

It will be necessary to follow protocols adopted by each country when such cases are confirmed.

A2. Vaccine quality defect-related reaction

If this reaction is related to a particular lot or batch, the distribution of the lot or batch has to be ascertained and specific instructions must be provided on the utilization or non-utilization of the lot or batch. It is important to inform the NRA and the marketing authorization holder about the AEFI. The event should be communicated to the manufacturer through these bodies.

WHO should be contacted through the Organization's local country office or the WHO Uppsala Monitoring Centre (http://www.who-umc.org/) and the information communicated to ensure that other countries using the vaccine are alerted.

A3. Immunization error-related reaction

Training and capacity-building are critical to avoid recurrences of such reactions.

A4. Immunization anxiety-related reaction

Vaccination should take place in an ambient and safe environment.

B. Indeterminate

B1. Consistent temporal relationship but insufficient evidence for causality

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

B2. Conflicting trends of consistency and inconsistency with causality

These cases are classified on the basis of available evidence. If additional information becomes available, the case can be reclassified to a more definitive category. During the assessment, the reviewers should clarify what additional information would be helpful to finalize the causality assessment and should seek information and expertise from national or international resources. The Global Advisory Committee on Vaccine Safety (GACVS)[28] can be approached for guidance through WHO, particularly when an event is likely to affect the immunization programme significantly.

C. Inconsistent causal association to immunization (coincidental)

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

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.
- Regardless of whether an AEFI is attributable to the vaccine or the vaccination programme, causality assessment determines what steps need to be taken to address the event.

[28] For the Global Advisory Committee on Vaccine Safety (GACVS), see: http://www.who.int/vaccine_safety/committee/en/.

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9 Actions and follow-up to AEFI

Responding to AEFI may involve immediate short-term activities or/and long-term follow-up activities. Follow-up activities should be based on findings of investigations, causality assessments and recommendations by the investigation/expert committees.

Major follow-up actions may have an impact on the national immunization programme, as well as on regional and global programmes and planning.

9.1 Patient care

It is of utmost importance to ensure that proper and early treatment is received by affected vaccinees (patients), regardless of the diagnosis. 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 AEFI, how to treat them or refer them to a clinician/hospital, and must report AEFI as soon as possible (as recommended in the country guidelines).

9.1.1 Management of suspected anaphylaxis or collapse after vaccination

Sudden and severe events occurring post-vaccination, especially syncope, are frequently reported as anaphylaxis. However, anaphylaxis following vaccination is considered to be very rare and the risk (in general) is 1-2 cases per million vaccine doses.

The onset of anaphylaxis can occur after several minutes (> 5 minutes) but rarely up to two hours following vaccination. The progression of symptoms is rapid and usually involves multiple body systems, almost always with skin involvement (generalized erythema and/or urticaria), as well as signs of upper and/or lower respiratory tract obstruction and/or circulatory collapse. In young children (though anaphylaxis occurs at any age) limpness, pallor or loss of consciousness may reflect hypotension. In general, the more rapid the onset, the more severe is the reaction. Symptoms limited to only one system can occur, leading to delay in diagnosis. Biphasic reactions where symptoms recur 8-12 hours after onset of the original attack, and prolonged attacks lasting up to 48 hours, have been described.

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.[29] Each vaccinating centre must have an emergency kit with adrenaline. The expiry date of the adrenaline should be written on the outside of the emergency kit and the whole kit should be checked three or four times a year. It is important to note that health-care workers may misdiagnose syncope attack as anaphylaxis and administer adrenaline as a part of the emergency care. If the correct dose of adrenaline according to age and weight is administered via the intramuscular route, no harm is likely to occur. However, an overdose, by administering intravenous or intra-cardiac adrenaline or by repeated administration, may cause harm.

Table 20. Conditions that may be mistaken for anaphylaxis post-immunization

Diagnosis	Onset: symptoms and signs
Vasovagal event	Symptoms are usually immediate (< 5minutes) and commence during the injection process. No skin rash, bradycardia not tachycardia, no respiratory involvement, spontaneous resolution when prone.
Hypotonic hyporesponsive episode	Onset 2-6 hours post-immunization, sudden pallor, hypotonia and unresponsiveness, usually in an infant. No skin rash, respiratory or cardiovascular compromise.
Seizure	Onset usually at least 6-8 hours post-vaccination with a killed vaccine. Sudden unresponsiveness usually with tonic-clonic movement, usually febrile, no cardiovascular compromise, no respiratory compromise unless apnea or aspiration.
Aspiration of oral vaccine (e.g. OPV or rotaviral vaccine)	Immediate respiratory symptoms (cough, gagging, stridor or wheeze) during administration, usually in infant. No skin rash or cardiovascular compromise.
Somatic conversion symptoms	Immediate or delayed respiratory symptoms, syncope, neurological symptoms without objective respiratory or neurological signs.
Severe coincidental diseases	Usually due to coincidental – unrecognized congenital heart disease or occult infections. May have respiratory or cardiovascular compromise but there are usually symptoms, signs or investigations to indicate alternate cause.
Immunization-error related	Immediate toxic drug reaction with symptoms and signs due to drug toxicity. Reported with immunization-error related which have resulted from inadvertent administration of a muscle relaxant or insulin.

29. Protocol for management of suspected anaphylactic shock. Winnipeg, Government of Manitoba; 2007 (http://www.gov.mb.ca/health/publichealth/cdc/protocol/anaphylactic.pdf, accessed 1 August 2014).

For all cases of suspected anaphylaxis it is important all symptoms and signs are well documented by health-care providers (e.g. immunization providers, ambulance records, Emergency Department clinical notes). The Brighton Collaboration case definition for anaphylaxis should be consulted for a list of possible symptoms and signs of the condition, and subsequent review can ascertain if the case definition of anaphylaxis is met. Elevated mast cell tryptase is included in the case definition and potentially this could be helpful, but it is rarely considered in a primary care or emergency department setting where children are likely to present post-immunization.

Because anaphylaxis is very rare, other causes of sudden and severe symptoms post-immunization that occur more commonly than anaphylaxis need to be considered. Table 20 lists those conditions which may be mistaken for anaphylaxis.

9.2 Follow-up actions

Depending on the nature of the event(s), the number of people affected, and community perceptions, an investigation may be conducted. In general, it is not advisable to discontinue the immunization programme while awaiting the completion of the investigation. If AEFI causality is not established – depending on the nature of the event, its extent and whether it is ongoing – a further investigation or epidemiological study may be warranted (Table 21). However, it must be accepted that in some cases the relationship to vaccine will never be clear.

Table 21. **Actions to be taken upon completion of the investigation/causality assessment**

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

Communication and training are two important follow-up actions that have long-term implications. They should not necessarily be focused on an individual event, but they should emphasize the need for programme managers and others involved in immunization to pay attention. Communication is dealt with in Chapter 10.

9.2.1 Logistics

The immunization supply chain, injection safety and waste management are all part of immunization safety surveillance. Countries are encouraged to improve their supply chain system and ensure safe injection practices.

With regard to vaccine-related reactions, decisions should be carefully thought out. The reliability of the evidence on which the decision is based, the impact on the immunization programme and availability of alternate sources of vaccine all need careful scrutiny. Communication with the vaccine manufacturer and WHO is advisable before any hasty decision is made.

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

knowledge and develop skills and confidence among the staff. Further, awareness can expand to involving all stakeholders linked to the immunization programme – including academia, teachers, volunteers, NGOs, policy-makers, politicians and the media.

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

9.3 Training and training opportunities for vaccine safety

WHO has developed a training programme targeting immunization service providers at different levels. The training modules are routinely updated and guidelines for both facilitators and trainees are available in printed and electronic forms. WHO is supporting countries to conduct both basic training and advanced causality assessment training programmes.

To strengthen vaccine safety capacity among staff in countries, WHO has developed an online platform that offers training to national public health officials, immunization programme managers, vaccination staff and members of AEFI review committees.[30] In 2012 an e-learning course was developed by WHO for those engaged in immunization safety surveillance activities.[31]

9.3.1 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 among all staff and officials working on vaccine safety-related issues.

Programme managers and all who are actively involved in and responsible for immunization services are encouraged to use the free online course. As the training course is self-guided and user-friendly, it can be taken in any setting and over any period of time. The e-learning course material is available at the link indicated. The course comprises six modules, through which the learner can acquire detailed information on immunological aspects of vaccine safety, characteristics of AEFI, vaccine pharmacovigilance components, surveillance systems, national and international vaccine safety institutions and their services. The course also includes a module on communication, including risk communication to vaccinees, their parents and communities, as well as advice on how to communicate effectively with the media. Modules include case studies, summaries and assessments.

[30] Technical support and trainings. WHO Global Vaccine Safety Resource Centre. Geneva: World Health Organization (http://www.who.int/entity/vaccine_safety/initiative/tech_support/en/index.html, accessed 1 August 2014).

[31] The WHO e-learning course on vaccine safety basics. Geneva: World Health Organization (http://www.vaccine-safety-training.org, accessed 1 August 2014).

9.3.2 Vaccine safety basic training

This basic course is designed for three days training. It consist of six modules covering the following areas: introduction to vaccine safety, types of vaccines and other components, AEFI and data analysis, AEFI surveillance (reporting, investigation and causality assessment), vaccine safety institutions and mechanisms, and communication. In addition, the course includes group work and evaluations of each module and of the overall course. The manual for facilitators and the workbook for participants are available.

The following are likely to benefit from this training:

- persons in the NRA dealing with clinical evaluation of biological products and vaccines;
- persons in the NRA responsible for pharmacovigilance (preferably those specifically involved in vaccine safety);
- the national immunization programme manager and Ministry of Health staff responsible for post-marketing surveillance of vaccines, particularly relating to AEFI;
- persons in the national immunization programme responsible for the management of disease surveillance;
- physicians with experience in the field of pharmacovigilance and/or immunization and who are concerned with vaccine and medicines policy;
- persons in the Ministry of Health responsible for press releases/media reports or reactions to reports in the media;
- persons in the Ministry of Health responsible for public education, social mobilization and support for vaccination, especially with respect to the national immunization programme;
- representatives of agencies who will support regional and national activities in vaccine safety.

9.3.3 Vaccine safety advance training

This advanced course is designed for five days training. It consists of 10 modules covering the following areas: course introduction, AEFI basic concepts, methods for monitoring and conducting surveillance of AEFI, investigation of AEFI, analysis of vaccine safety data, AEFI causality assessment with case definitions and case studies, global initiatives to support monitoring and causality assessment, causality assessment follow-up, and vaccine risk communication. In addition, the course includes group work and evaluations of each module and the overall course. The manual for facilitators and workbook for participants are available.

Summary

- Treating the patient is the first priority following an AEFI. Preparedness for managing serious adverse events is important and necessary. Each vaccination centre should have minimum facilities (emergency tray and trained personal) for managing anaphylaxis.
- Anaphylaxis is extremely rare. Syncope attacks are common and are often misdiagnosed as anaphylaxis. Administering a single and correct dose of adrenaline by the intramuscular route, even to a patient with syncope but misdiagnosed as anaphylaxis, does not cause harm.
- The response and follow-up to 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 serve as 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 reappear.
- For coincidental events, the main task is communication to maintain confidence in the immunization programme.
- Training is an important component of the vaccine safety surveillance system and its follow-up activity. Programme managers should use training as an opportunity to strengthen immunization programme in the country.

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10 Communication

Although managing a country's immunization programme requires in-depth knowledge of the technical aspects of vaccination, programme managers are also increasingly being asked to respond to communications issues caused by real or perceived AEFI. Communication with parents, the community, health staff and the media need to be carried out under many circumstances, from launching new vaccines and putting in place mass immunization campaigns to issuing reminders to maintain vaccinations up to date. When a vaccine safety investigation is under way as a result of a report of an AEFI, communications involve keeping the public informed about the investigation, the results, and actions already taken or to be taken regarding the AEFI. At the same time it is crucial to highlight the benefits of immunization even while communicating about an investigation.

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 the people involved. Uncertainty about AEFI should be acknowledged, there should be a full investigation, and the community should be kept informed. Premature statements about the cause of the event before the investigation is complete should be avoided. If the cause is identified as immunization-related error, it is vital not to lay personal blame on anyone, but to focus on system-related problems that resulted in the error(s) and the steps being taken to correct them.

In communicating with the community, it is useful to develop links with community leaders and local 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) must 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.

None of the advice or steps contained in this manual should be construed as suggesting that communicating vaccine safety is easy. In this age of instant communication, as outlined in a manual of WHO's Regional Office for Europe, "the ease with which information can be disseminated now means that negative comments about vaccines can go 'viral' on the Internet without balanced professional input. As a result, the media

have found rich pickings in vaccine safety issues".[32] Employing strong communication principles and strategies is not a substitute for evidence-based risk analysis, but having a communications plan for rapid implementation may prevent vaccine safety scares from become crises.

10.1 Communication with stakeholders

There are many parties to whom communications should be tailored in order to meet their particular needs. These include:

- parents and the community;
- health staff;
- particular stakeholders such as the Ministry of Health, NRA, NCL, politicians, professionals, academia, international agencies, WHO, UNICEF, and manufacturers;
- the media.

In addition, there are principles of communication that apply to most if not all audiences. These include the need to:

- listen empathetically to concerns;
- reassure and support but do not make false promises;
- communicate frequently;
- build up and maintain relationship among the stakeholders;
- inform audiences about possible common adverse events and how to handle them;
- prepare fact sheets on adverse events and other key information for all audiences;
- continuously communicate during the investigation period in order to ensure understanding both of the situation and of the balance of risk and benefit of vaccination. Do not apportion blame, especially not on the health worker(s), but focus on the correction and quality of the national immunization system.

While health staff, because of the nature of their work, should have some training, or at least experience in communication skills, communication with staff by public health authorities and investigators should be sensitive to their needs. Therefore:

- Communication should include all levels of health authorities involved.
- Reassure the staff of their knowledge, ability, skills and performance.
- Do not blame health worker(s) but focus on the correction and quality of the national immunization programmme.
- Keep health workers updated on the investigation process, progress, and findings.

[32] Vaccine safety events: managing the communications response. A guide for Ministry of Health EPI managers and health promotion units. Copenhagen: World Health Organization Regional Office for Europe; 2013 (http://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications/2013/vaccine-safety-events-managing-the-communications-response).

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

10.2 Communicating with the media

The media (newspapers, 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 health-care workers before responding to or addressing the media. The coordination should include preparation on dealing with public concern about this issue in order to minimize any potential harm to the immunization programme. It is also useful to have other groups and individuals that merit public respect and authority to publicly endorse and strengthen key immunization messages.

Communicating with the media requires particular skills that call for training. Reporters are highly trained professionals and are and their perspective must be properly understood. The media are interested in stories that will attract attention. While the success of a vaccination programme can attract attention, so can a programme that has not gone as planned. Dramatizing and personalizing events can both highlight success as well as create a sense of panic about an AEFI with a particular vaccine product – regardless of whether the AEFI is unrelated to immunization (coincidental) or is a localized immunization error. One other important fact is the media want early responses to their questions: therefore waiting for the conclusion of an investigation is rarely possible. Information may need to be disseminated early and often, and it is vital to be honest about what is known and what is not known, and to avoid being evasive and unresponsive.

At the same time, 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 risks and benefits of immunization. Building a personal relationship with key health reporters will help them to understand the public health perspective.

Effective communication with the media includes advance preparation. This is part of a communication plan and is particularly important before a new vaccine is introduced or before and during an immunization campaign. A communication plan can also provide ongoing communication support to routine immunization programmes. Table 22 lists the elements of a good media plan for communication.

TABLE 22. **MEDIA PLAN FOR COMMUNICATION**

Database of journalists	▪ Maintain a list of print and electronic media journalists covering health (local, national, international) with contact information. ▪ Always use a database where updating can be done immediately. ▪ Update regularly any changes in the media list.
Information packages	An information package may contain the following documents in both hard copy and e-copies: ▪ Frequently asked questions (FAQs) on immunization in general, for specific diseases, and for AEFI ▪ Fact sheet or a technical brief on a specific VPD, including the burden of the disease, background rates of AEFI and expected AEFI rates ▪ Recent updates such as statistics, progress made in the country, globally ▪ Contact addresses of spokespersons (experts) in the ministry. The information package needs to be updated regularly.
Media releases	Must specifically answer the 6 Ws for journalists: ▪ Who is affected/is responsible? ▪ What has happened? What is being done? ▪ Where has it happened? ▪ When did it happen? ▪ Why did it happen? ▪ Will it happen again?
Information specific to media characteristics	▪ Local media are read and believed by more people in the community than national media. ▪ National media have a wide reach and influence national agendas. ▪ International media can influence national agendas.
Spokesperson system:	▪ Identify in advance an appropriate spokesperson (or several spokespersons in the different agencies). ▪ Share contact details of spokesperson(s) with all relevant focal points at different levels of programme implementation. ▪ Ensure the spokesperson(s) has experience or some training in dealing with the media.

Other tips to keep in mind

Media interest is usually greatest initially when relatively little is known. In this environment, rumours can flourish and the potential for harm is huge. A media conference, convened early even if there is only very limited information to give, can provide a uniform message to all at the same time, thus avoiding conflicting messages. This will also prevent the circulation of rumours and build a relationship with 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. A media or press conference requires expert planning and expert communications input to ensure that messages are clear and unambiguous and that all expert spokespersons are well prepared.

Professional organizations and other stakeholders may have greater credibility than the government, particularly in a crisis situation. Providing them an opportunity for their unified support for immunization and the approach being taken to handle/investigate the problem can help considerably.

10.3 Preparing key messages

Messages should be as simple as possible. Use simple words and short sentences. It is helpful to tell a story, if possible. Create a "word picture" (a graphic or vivid verbal description) 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. VPDs caused millions of deaths and a huge amount of disability before the introduction of vaccines, and that situation would return without continued use of vaccines.
- It is risky not to immunize (risk of disease and complications).
- Vaccines may/do cause reactions, but these are rarely serious.
- Immunization safety is of paramount importance and maintaining confidence in immunization programmes depends on it.
- Any suspicion of a problem is investigated (an advantage of well established immunization safety surveillance). This investigation is an example of such an action being taken.

There are many sources of key messages such as these. They should be consulted and tailored to the local culture and understanding

It is rarely necessary to suspend an immunization programme during an investigation unless it is obvious that there is a problem with the vaccine that warrants such drastic steps. The vast majority of situations prove to be coincidental or due to a very localized problem (depending on the 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/press release. An effective press statement/ press release must specifically answer the six Ws and should include a one-page (400-500 words maximum) account written in short sentences outlining:

- a complete account of the event, framed in its context (e.g. an isolated event or a cluster of AEFI, or a coincidental event);
- 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 will be taken, and what steps have already been taken;

- reference to any relevant publication or website for further information;
- the sender's name and spokesperson's details;
- quotes from key officials, after seeking their permission (the quotes must be positive and carry the key messages);
- repetition of the key message.

Follow-up actions with communications

Keeping promises: If it has been promised that updates about the investigation will be disseminated, make sure that this is done by the promised date. If the findings have been delayed, ensure that the delay is communicated.

Providing answers to unanswered questions: If a question cannot be answered for any reason, get back to the requestors with the answers as soon as possible.

Keeping the public informed about subsequent developments: If any decision or action is taken at the highest levels following the AEFI investigations, or during the investigations, and the public must know about it, keep them informed though a press release to the media or other locally appropriate means.

10.4 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. Crises can often be avoided through foresight, care and training. If managed properly, the investigation and management of a vaccine safety situation will boost public confidence and acceptance and ultimately strengthen the immunization programme.

How does one 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 and understanding of the immunization programme is necessary.
- Train staff at all levels to respond adequately. Develop confidence in responding to the public and the media (particularly the local media) properly and correctly.
- Confirm all facts and prepare (see steps for a press conference or press release) 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 in the immunization programme. Be aware of the risks and benefits of immunization and the progress and findings of the investigation.
- Communication needs assurance from someone in authority with knowledge and expertise in the subject.
- It is recommended to prepare a communication plan in advance, as this will minimize the negative impact of AEFI-related matters.

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Annexes

Annex 1. Frequency of Vaccine Adverse Reactions of commonly used vaccines

BCG Vaccine Summary

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

DTP Vaccines Summary

Vaccine Adverse Reactions	Frequency category
Whole cell Pertussis vaccines	
Fever 100.1°F - 102°F	Very common
Injection site Redness	Very common
Swelling	Very common
Pain (Severe-Moderate)	Very common
Fussiness (Severe-Moderate)	Very common
Drowsiness	Very common
Anorexia	Very common
Vomiting	Common
Persistent screaming	Uncommon to Rare
HHE	Very rare
Seizures	Very rare
Encephalopathy	Very rare
Anaphylaxis	
A cellullar Pertussis vaccines	
Fever 100.1°F - 101°F	Very common
Fever 100.1°F - 102°F	Common
Injection site Redness	Common to Very common
Injectionsite swelling	Common to Very common
Pain (Severe-Moderate)	Uncommon to Common
Fussiness (Severe-Moderate)	Common to Very common
Drowsiness	Very Common
Anorexia	Very Common
Vomiting	Very Common
Persistent screaming	Uncommon
HHE	Rare
Seizures	Very rare

Tetanus vaccines Summary

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

Hepatitis B Vaccines Summary

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

Human Papiloma Vaccines (HPV) Summary

Vaccine Adverse Reactions	Frequency category
Bivalent HPV Vaccine	
Fever	Common
Headache	Very common
Injection site pain	Very common
Redness	Very common
Swelling	Very common
Rash	Uncommon
Arthralgia	Very common
Myalgia	Very common
Fatigue	Very common
Gastrointestinal disorders	Very common
Quadrivalent HPV Vaccine	
Fever 100.1°F - 101°F	Very common
Fever 100.1°F - 102°F	Very Common
Injection site Redness	Common
Injectionsite swelling	Common
Pain (Severe-Moderate)	Common
Fussiness (Severe-Moderate)	Common
Drowsiness	Common
Anorexia	Common
Vomiting	Common
Persistent screaming	Common
HHE	Very common
Seizures	Very rare

Hib Vaccines Summary

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

Polio Vaccines Summary

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

Measles Vaccines Summary

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

Pneumococcal vaccines Summary

Vaccine Adverse Reactions	Frequency category
Unconjugated vaccine (PPSV)	
■ Fever > 39°C	Uncommon
■ Injection site reaction	Very common
Conjugated vaccine (PCV)	
■ Fever > 39°C	Uncommon
■ Injection site reaction	Very common

Rubella Vaccines Summary

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

Varicella Vaccines Summary

Vaccine Adverse Reactions	Frequency category
■ Febrile seizures	Rare
■ Fever > 39°C	Very Common
■ Injection site reaction	Common to Very Common
■ Site rash (local/generalized)	Common

Mumps Vaccines Summary

Vaccine Adverse Reactions	Frequency category
■ Injection site reaction	Very common
■ Parotid swelling	Common
■ Aseptic meningitis	Very common

Rotavirus Vaccines Summary

Vaccine Adverse Reactions	Frequency category
■ Intussusception	Very rare

Yellow Fever vaccines Summary

Vaccine Adverse Reactions	Frequency category
■ Vaccine-associated viscerotropic disease	Very rare

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

Key

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

ANNEX 2. AEFI REPORTING FORM

REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

***Patient name*:** ***Patient's full Address*:** Telephone: Sex: ☐M ☐ F ***Date of birth (DD/MM/YYYY)*:** __ __ / __ __ / __ __ __ __ *OR Age at onset :* ☐☐*Years* ☐☐ *Months* ☐☐☐ *Days* *OR Age Group:* ☐< *1 Year* ☐ *1 to 5 Years* ☐ *> 5 Years*	***Reporter's Name*:** Institution / Designation, Department & address: Telephone & e-mail:

Health facility (or vaccination centre) name:

***Name of Vaccines Received**	***Date of vaccination**	***Time of vaccination**	Dose (e. g. 1st, 2nd, etc.)	***Batch/ Lot number**	Expiry date

Adverse event (s): ☐ Severe local reaction ☐ *>3 days* ☐ *beyond nearest joint* ☐ Seizures ☐ *febrile* ☐ *afebrile* ☐ Abscess ☐ Sepsis ☐ Encephalopathy ☐ Toxic shock syndrome ☐ Thrombocytopenia ☐ Anaphylaxis ☐ Fever≥38°C ☐ Other (specify)..... Date & Time AEFI started (DD/MM/YYYY): __ __ / __ __ / __ __ __ __ ☐☐ Hr ☐☐Min Was the patient hospitalized? ☐Yes ☐No Date patient notified event to health system (DD/MM/YYYY): __ __ / __ __ / __ __ __ __	Describe AEFI (Signs and symptoms):
Outcome: ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown ☐ Died If died, date of death (DD/MM/YYYY): __ __ / __ __ / __ __ __ __ Autopsy done: ☐Yes ☐No ☐Unknown	
Past medical history (including history of similar reaction or other allergies), concomitant medication and other relevant information (e.g. other cases). *Use additional sheet if needed :*	

First Decision making level to complete:

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

National level to complete:

Date report received at national level (DD/MM/YYYY): __ __ / __ __ / __ __ __ __	AEFI worldwide unique ID **:**
Comments:	

**Compulsory field*

ANNEX 3. AEFI INVESTIGATION FORM

AEFI INVESTIGATION FORM

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

Section A Basic details

Province/State **District** **Case ID**

Place of vaccination (✓): ☐ Govt. health facility ☐ Private health facility ☐Other (specify) _____
Vaccination in (✓): ☐ Campaign ☐ Routine ☐ Other (specify) _____

Address of vaccination site:

Name of Reporting Officer:

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

Designation / Position:

This report is: ☐ *First* ☐ *Interim* ☐ *Final*

Telephone # landline (with code): Mobile: e-mail:

Patient Name Sex: ☐M ☐ F

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

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

OR *Age at onset:* __ __ *years* __ __ *months* __ __ __ *days* ***OR*** *Age group:* ☐ *< 1 year* ☐ *1–5 years* ☐ *> 5 years*

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

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

Type of site (✓) ☐ Fixed ☐ Mobile ☐ Outreach ☐ Other _____

Date of first/key symptom *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ Time of first symptom *(hh/mm)*: __ __ / __ __
Date of hospitalization *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __
Date first reported to the health authority *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __

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

If died, date and time of death *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ *(hh/mm)*: __ __ / __ __
Autopsy done? (✓) ☐ Yes (date)_____ ☐ No ☐ Planned on (date)_____ Time_____
Attach report (if available)

Section B Relevant patient information prior to immunization

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

For adult women

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

For infants

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

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

Name **Case ID Number** AEFI Investigation Page 2/4

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

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

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

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

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

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

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

Provisional / Final diagnosis:

Name **Case ID Number** AEFI Investigation Page 3/4

Section D	**Details of vaccines provided at the site linked to AEFI on the corresponding day**									
Number immunized for each antigen at session site. Attach record if available.	Vaccine name									
	Number of doses									

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

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

Section E Immunization practices <u>at the place(s) where concerned vaccine was used</u>

(Complete this section by asking and/or observing practice)

Syringes and needles used:

• Are AD syringes used for immunization?	Yes / No / Unkn

If no, specify the type of syringes used: ☐ Glass ☐ Disposable ☐ Recycled disposable ☐ Other _____

Specific key findings/additional observations and comments:

Reconstitution: (complete only if applicable, ✓ NA if not applicable)

	Status		
• Reconstitution procedure (✓)			
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA
Same reconstitution syringe used for reconstituting different vaccines?	Yes	No	NA
Separate reconstitution syringe for each vaccine vial?	Yes	No	NA
Separate reconstitution syringe for each vaccination?	Yes	No	NA
• Are the vaccines and diluents used the same as those recommended by the manufacturer?	Yes	No	NA

Specific key findings/additional observations and comments:

Name **Case ID Number** AEFI Investigation Page 4/4

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

Section G Community investigation (Please visit locality and interview parents/others)

Were any similar events reported within a time period similar to when the adverse event occurred and in the same locality? Yes / No / Unknown If yes, describe:

If yes, how many events/episodes?

Of those effected, how many are
- Vaccinated:_____
- Not vaccinated:_____
- Unknown:_____

Other comments:

Section H Other findings/observations/comments

Annex 4. AEFI Line listing

	Name/ID
	Village/Town/District
	Date of birth (dd/mm/yyyy) and age
	Date of immunization(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]	[A2]	[A3]	[B]	[C]	[D]
Vaccine-related	Immunization error-related	Immunization anxiety-related	Indeterminate	Coincidental	Inadequate information to classify

Annex 5. Causality Assessment: Step 2 (Event Checklist)

[✔ (check) all boxes that apply]

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

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

World Health Organization

The global manual on surveillance of adverse events following immunization (AEFI) has been developed by a team of global experts. The document provides guidance on improving the quality and efficiency of AEFI surveillance activities for managers of immunization programmes, staff of national regulatory authority (NRA) at national and subnational levels, immunization service providers, staff of pharmacovigilance centres and other stakeholders in immunization services.

The manual provides information on the basic principles of immunization and vaccines and provides a clear understanding on the newer concepts of AEFI, establishing AEFI surveillance systems including the methodologies and tools of reporting, investigating and performing causality assessment using the revised classification of cause-specific AEFI. For informed decision making, the manual outlines the process of making the best use of surveillance data and responding to crisis, including a communication strategy on immunization safety for the public and the media.

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