



World Health
Organization

VACCINE SAFETY BASICS

learning manual

The content of this course has been compiled by leading international vaccine experts who are committed to the promotion of best practice in the implementation of immunization programmes across the world.

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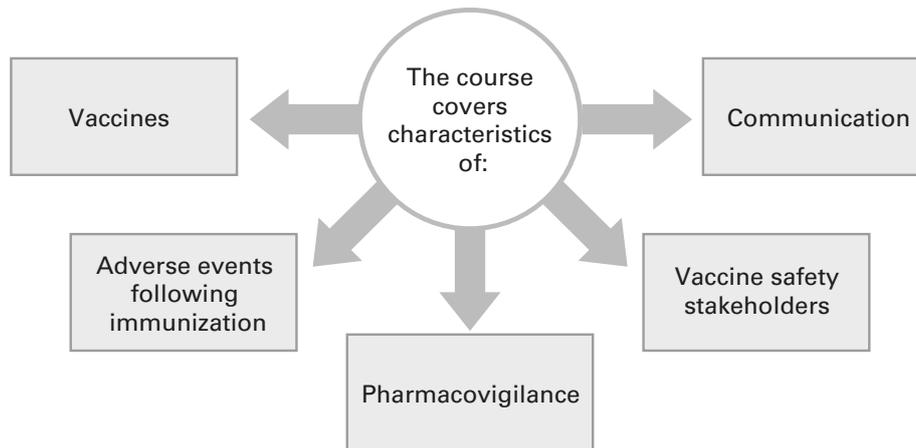
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INTRODUCTION

Goal

This course aims to establish a shared understanding among professionals whose work is linked to vaccine safety issues. This may include nurses/midwives/community health workers, as well as pharmacists medical doctors and programme or technical officers.



Rationale

Professionals involved in vaccine safety come from different backgrounds. As their jobs are all interrelated and co-dependent, they need a 'common language' in order to ensure smooth collaboration.

This Learning manual on Vaccine Safety Basics is based on the E-learning Course on Vaccine Safety Basics, which is available at www.vaccine-safety-training.org.

It has been designed to reach out to users that do not have internet access. In case you have internet access, we encourage the online use of the E-learning Course on Vaccine Safety Basics, which enables the learner to benefit from interactive case studies and online assessments.

The Learning manual on Vaccine Safety Basics meets different starting points, learning needs and country contexts. It offers the learner options to work at the speed and depth he prefers, recognizing his prior knowledge. Accommodating the different mechanisms between regions and nations is a challenge to any global course. For this reason we ask you from time to time to shift your focus to your own local context and look how vaccine safety is ensured in your country.

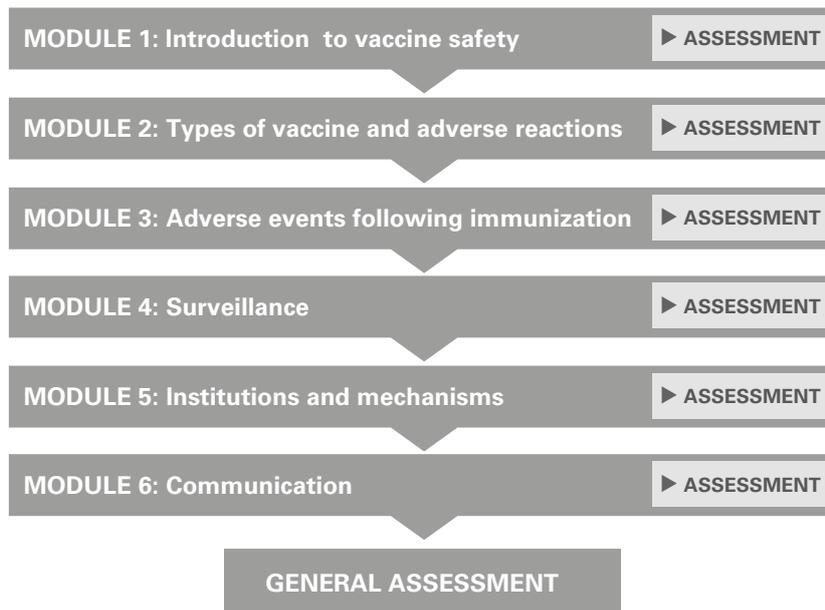
GETTING STARTING

Modules

The modules introduce you to vaccine safety issues and provide you with the technical information required to look at the case studies and take the assessments.

Each module will take you about 1½ hours to complete, but you may find that it takes you a little more or a little less time than this. You can study this course at your own pace, pausing your learning at any point.

You will optimally benefit from the course by following the training path illustrated below.



Assessments

To ensure an interactive learning experience, you have the opportunity to take:

- Training questions within the module,
- Assessments testing your knowledge at the end of each module,
- A general assessment testing your understanding at the end of the whole course. This assessment is only accessible online. Please visit: www.vaccine-safety-training.org, click “Start course” and “General assessment” to register. Should you pass the general assessment, you will be provided with a downloadable document confirming your successful participation in the exam.

MODULE 1

Introduction to vaccine safety

Overview

Vaccination is one of the great public health achievements of human history. Vaccines used in national immunization programmes (NIPs) are considered safe and effective when used correctly. Vaccines are, however, not risk-free and adverse events will occasionally occur following vaccination. Public trust in vaccine safety is key to the success of vaccination programmes.

This module serves as an introduction to the whole course. You will learn about the importance of immunization programmes and how vaccines work. You will understand the relationship between vaccine coverage, adverse events and disease spread. You will also learn about the importance of vaccine regulations in ensuring the effectiveness of vaccine initiatives.

Module outcomes

By the end of this module you should be able to:

- 1 Explain the importance of Vaccination in the control of infectious diseases,
- 2 Describe the basic principles of vaccination,
- 3 Explain how the public are less tolerant of the risks associated with vaccines (although very low) than they are of those associated with drugs used to treat disease,
- 4 List the main types of vaccine and illustrate them with examples,
- 5 Describe the importance of post marketing vaccine safety surveillance,
- 6 Identify some vaccines that have been associated with adverse vaccine reactions.

Importance of immunization programmes

Each year, vaccines prevent more than 2.5 million child deaths globally. An additional 2 million child deaths could be prevented each year through immunization with currently available vaccines.²

Why are vaccines so special?

- **Vaccines promote health:** unlike many other health interventions, they help healthy people stay healthy, removing a major obstacle to human development.
- **Vaccines have an expansive reach:** they protect individuals, communities, and entire populations (the eradication of smallpox is a case in point).
- **Vaccines have rapid impact:** the impact of most vaccines on communities and populations is almost immediate. For example, between 2000 and 2008, vaccination reduced global deaths from measles by 78% (from 750,000 deaths to 164,000 deaths per year).³
- **Vaccines save lives and costs:** recently, a panel of distinguished economists put expanded immunization coverage for children in fourth place on a list of 30 cost-effective ways of advancing global welfare.⁴



This image shows a child with smallpox, a serious, contagious, and sometimes fatal infectious disease. The only prevention of smallpox is vaccination.



Key point

The impact of vaccination on the health of the world's peoples is hard to exaggerate. With the exception of safe water, nothing else, not even antibiotics, has had such a major effect on the reduction of mortality (deaths) and morbidity (illness and disability) and on population growth.⁶

History of vaccine development

Although inoculation against smallpox was practiced over 2000 years ago in China and India, a British physician, Edward Jenner, is generally credited with ushering in the modern concept of vaccination. In 1796 he used matter from cowpox pustules to inoculate patients successfully against smallpox, which is caused by a related virus.

By 1900, there were two human virus vaccines, against smallpox and rabies, and three bacterial vaccines against typhoid, cholera, and plague.

A worldwide case detection and vaccination programme against smallpox gathered pace and, in 1979, the World Health Assembly officially declared smallpox eradicated — a feat that remains one of history's greatest public health triumphs.

You can read more about the state of the world's vaccines and immunization in this Executive Summary from WHO:



vaccine-safety-training.org/tl_files/vs/pdf/who_ivb_09_10_eng.pdf



Question 1*

Smallpox has been declared eradicated in 1979. Can you tell the difference between eradication and elimination of a disease? Select the two correct definitions for eradication and elimination of a disease:

- A. **Eradication** refers to the complete and permanent worldwide reduction to zero new cases of the disease through deliberate efforts.
- B. **Eradication** refers to the reduction to zero (or a very low defined target rate) of new cases in a defined geographical area.
- C. **Elimination** refers to the complete and permanent worldwide reduction to zero new cases of the disease through deliberate efforts.
- D. **Elimination** refers to the reduction to zero (or a very low defined target rate) of new cases in a defined geographical area.

During the 20th century, other vaccines that protect against once commonly fatal infections such as pertussis, diphtheria, tetanus, polio, measles, rubella, and several other communicable diseases were developed. As these vaccines became available, high-income industrial nations began recommending routine vaccination of their children. There are now over 20 vaccine-preventable diseases.

Based on the emerging success of the smallpox programme, in 1974, the World Health Organization (WHO) launched the Expanded Programme on Immunization (EPI)⁸¹. The initial EPI goals were to ensure

* The answer to all questions can be found at the end of this manual (page 202).

that every child received protection against six childhood diseases (i.e. tuberculosis, polio, diphtheria, pertussis, tetanus and measles) by the time they were one year of age and to give tetanus toxoid vaccinations to women to protect them and their newborns against tetanus.

Since then, new vaccines have become available. Some of them, such as hepatitis B, rotavirus, *Haemophilus influenzae* type b (Hib) and pneumococcal vaccines, are recommended by the WHO for global use. Others, such as yellow fever vaccine, are recommended in countries where disease burden data indicate they should be used.

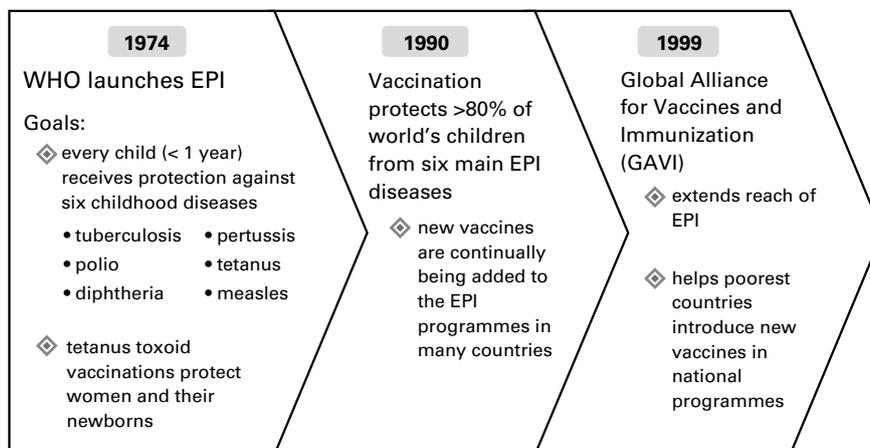
Regulatory and safety issues of vaccines before and after licenses are granted are discussed later in this module

		1955 Polio (IPV) 1962 Polio (OPV) 1963 Measles 1967 Mumps 1969 Meningitis A 1970 Rubella		
1798 Smallpox 1885 Cholera 1885 Rabies 1891 Anthrax 1896 Typhoid 1897 Plague	1923 Diphtheria 1923 Tuberculosis 1924 Tetanus 1926 Pertussis 1927 Tetanus 1935 Yellow fever 1943 Typhus	1972 <i>Haemophilus influenzae</i> 1976 Viral influenza 1976 Pneumococcal polysaccharide 1977 Meningitis C (polysaccharide)	1981 Hepatitis B 1986 Meningitis B 1989 Hepatitis A 1995 Varicella zoster 1998 Rotavirus 1999 Meningitis C (conjugate)	2000 Pneumococcal conjugate 2006 Human papilloma virus
1800–1899	1900–1949	1950–1979	1980–1999	2000

By 1990, vaccination was protecting over 80% of the world’s children from the six main EPI diseases, and other new vaccines are continually being added to the EPI programmes in many countries.

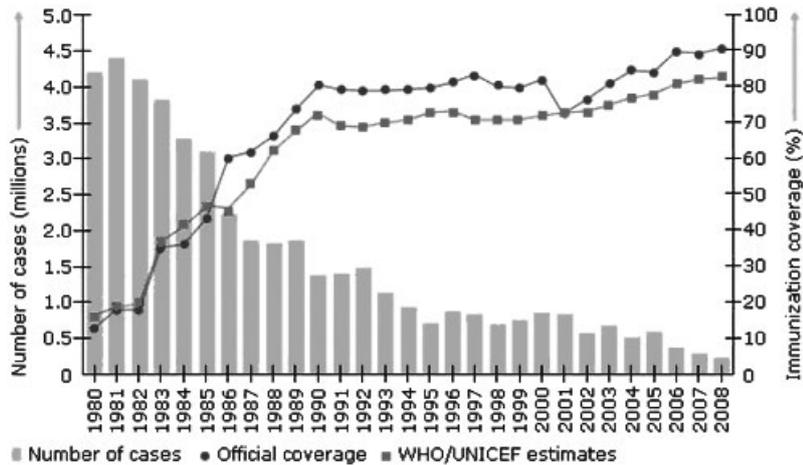
In 1999, the Global Alliance for Vaccines and Immunization (GAVI) was created to extend the reach of the EPI and to help the poorest countries introduce new and under-used life-saving vaccines into their national programmes.

Strengthening immunization: WHO’s Expanded Programme on Immunization

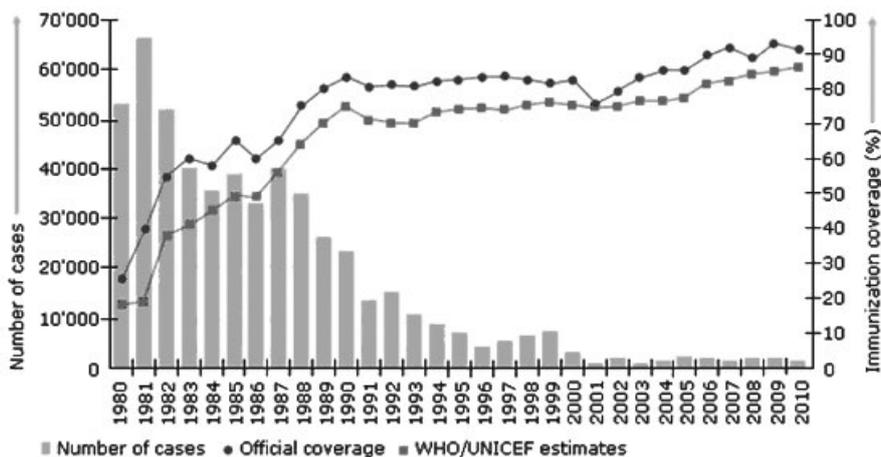


Although around 24 million infants are still not receiving the full complement of EPI vaccines in the first year of life, the success of the EPI can be judged by the reduction in worldwide cases of measles and poliomyelitis (see graphics). These two diseases are among several (including neonatal tetanus) targeted by the WHO for elimination through vaccination.

Global annual reported incidence of measles and immunization coverage between 1980–2008⁵



Global annual reported cases of Poliomyelitis and immunization coverage (3rd dose) between 1980–2010



Expectations towards safety of vaccines



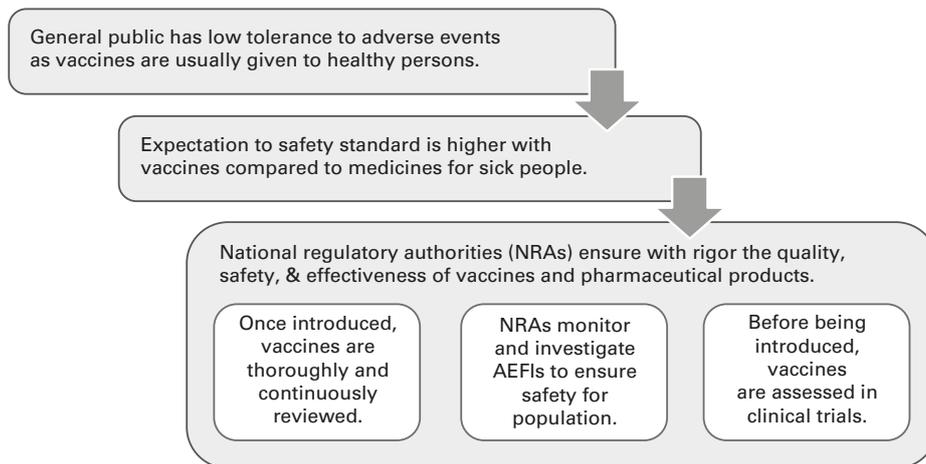
Key point

Although vaccines used in national immunization programmes (NIPs) are considered safe and effective, vaccines are not risk-free and adverse events will occasionally occur following vaccination. Public trust in vaccine safety is key to the success of vaccination programmes.

Vaccines used in NIPs are safe and effective. However, like other pharmaceutical products, vaccines are not completely risk-free and adverse events will occasionally result from vaccination. Although most adverse events are minor (e.g. redness at injection site, fever), more serious reactions (e.g. seizures, anaphylaxis) can occur albeit at a very low frequency.

The general public has low tolerance to any adverse events following vaccination, because vaccines are given to healthy persons to prevent disease. For this reason, a higher standard of safety is expected of immunizations compared with medications that are used to treat people who are sick (e.g. antibiotics, insulin). This lower tolerance for risks from vaccines translates into a greater need to detect and investigate any adverse event following immunization (AEFI) than is generally expected for other pharmaceutical products.

Low public tolerance requires safe vaccination



National regulatory authorities (NRAs) are responsible to ensure the quality, safety, and effectiveness of vaccines and other pharmaceutical products. Before their introduction into an immunization programme, vaccines undergo several steps of evaluation to assess their safety and efficacy in clinical trials. Once introduced, vaccines undergo very thorough and continuous reviews of their manufacturing process and NRAs continue to monitor and investigate adverse events following immunization to ensure that they are safe for the entire population.

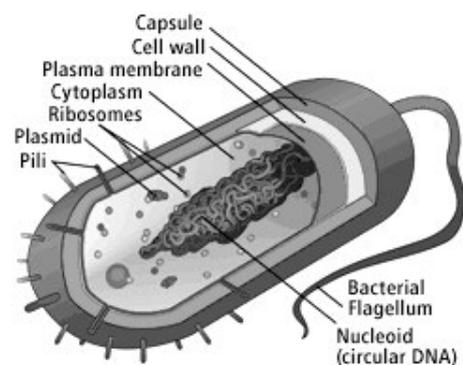
How the immune system works

To understand how and why vaccine reactions occur, it is first necessary to understand how the immune system helps to protect the body against infection. It is designed to identify and destroy harmful foreign organisms (pathogens) from the body, and neutralize the toxins (poisons) that some bacteria produce.

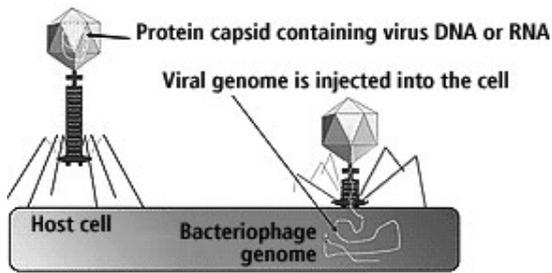
The pathogens causing the vaccine-preventable diseases described in this module are mainly microorganisms such as bacteria or viruses.

- **Bacteria** are single-celled life-forms that can reproduce quickly on their own.
- **Viruses**, on the other hand, cannot reproduce on their own. They are ultramicroscopic infectious agents that replicate themselves only within cells of living hosts.

Bacterium (example). Source: wikipedia.org



Virus infecting cell. Source: wikipedia.org

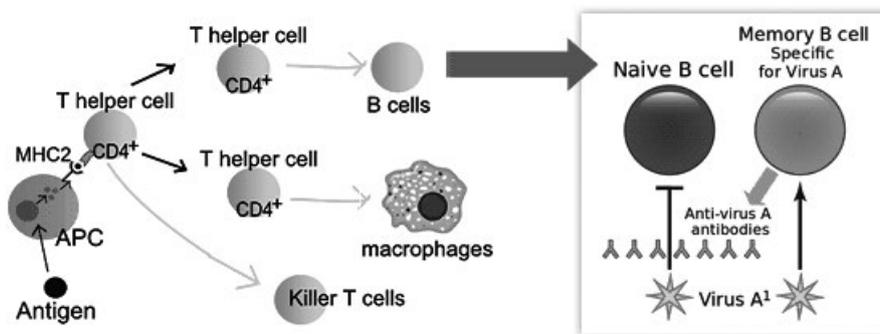


The immune system responds to bacteria and viruses in a very complex way: it recognizes unique molecules (antigens) from bacteria and viruses and produces antibodies (a type of protein) and special white blood cells called lymphocytes that mark the antigens for destruction.

During the primary immune response to the first encounter with a specific pathogen, some lymphocytes called memory cells develop with the ability to confer long-lasting immunity to that pathogen,

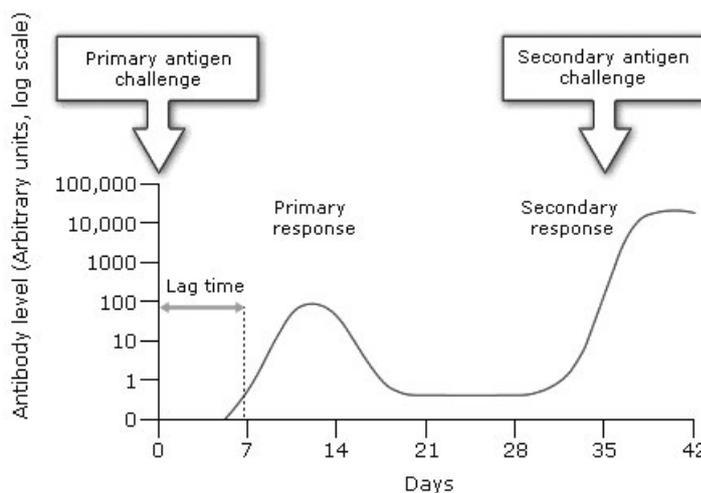
often for life. These memory cells recognize antigens on the pathogens they have encountered before, triggering the immune system to respond faster and more effectively than on the first exposure.

Primary and secondary immune response. Source: wikipedia.org



The graph below compares the primary and secondary immune responses to the same pathogen. The secondary response may eliminate the pathogens before any damage occurs.⁵⁹

Primary and secondary immune responses to the same pathogen



Key point

- Immunization triggers an immune system response by which the vaccinee develops long-term protection (immunity) that would normally follow recovery from many naturally occurring infections.

How vaccines work



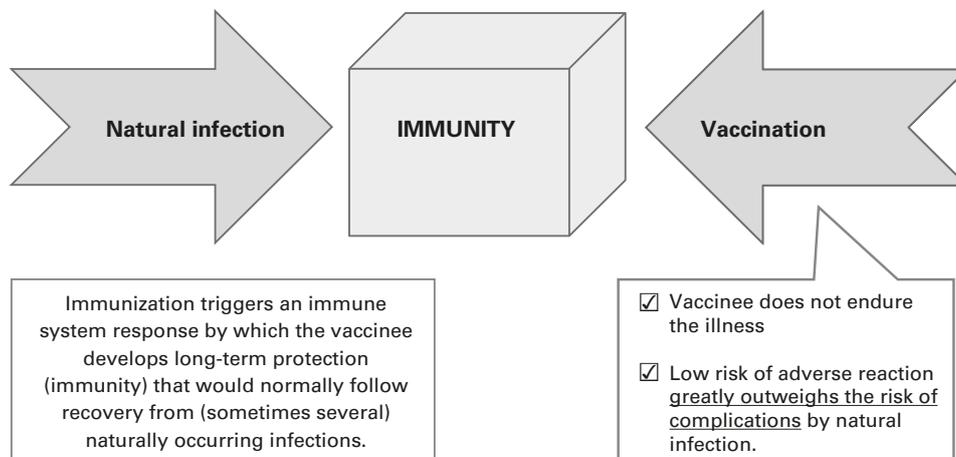
Key point

Vaccines stimulate the immune system to develop long-lasting immunity against antigens from specific pathogens.

The goal of all vaccines is to elicit an immune response against an antigen so that when the individual is again exposed to the antigen, a much stronger secondary immune response will result. Vaccines contain the same antigens that are found on pathogens that cause the associated disease, but exposure to the antigens in vaccines is controlled. By priming the immune system through vaccination, when the vaccinated individual is later exposed to the live pathogens in the environment, the immune system can destroy them before they can cause disease.

Thus, there are two ways of acquiring immunity to a pathogen – by natural infection and by vaccination. Natural infections and vaccines produce a very similar end result – immunity – but the person who receives a vaccine does not endure the illness and its potential life-threatening complications. The very low risk of an adverse event caused by a vaccine greatly outweighs the risk of illness and complications caused by natural infection. The following pages will discuss in further detail the attributes of vaccines and the characteristic causes for adverse events.

Vaccines reproduce a natural infection with less complications



Vaccine-preventable diseases



Question 2*

Can you recall the main vaccine-preventable diseases originally targeted by the EPI (Expanded Programme on Immunization)? Select them from the following boxes:

The initial EPI goals were to vaccinate every child – by the time they were one year of age – against:

- | | | |
|---------------------------------------|-------------------------------------|----------------------------------|
| <input type="checkbox"/> tuberculosis | <input type="checkbox"/> pertussis | <input type="checkbox"/> polio |
| <input type="checkbox"/> tetanus | <input type="checkbox"/> diphtheria | <input type="checkbox"/> measles |

Vaccines to prevent other diseases have become available since the introduction of EPI and are recommended by the WHO for global use. They cover diseases such as hepatitis B disease, diarrhoeal disease caused by rotaviruses, and pneumonia and other respiratory tract infections caused by *Haemophilus influenzae* type B and pneumococcal bacteria. Others, such as the vaccine against yellow fever, are recommended in countries where the disease burden is significant.

The main vaccine-preventable diseases targeted by the EPI and the associated vaccines

Tubercle bacillus	Bacillus Calmette-Guérin (BCG) vaccine
Poliovirus	Oral polio vaccine (OPV) vaccine, Inactivated polio vaccine (IPV) vaccine
<i>Corynebacterium diphtheriae</i> (Diphtheria)**	Diphtheria toxoid*** vaccine
<i>Clostridium tetani</i> (Tetanus)**	Tetanus toxoid (TT) vaccine
Pertussis**	Whole-cell pertussis (wP) vaccine, Acellular (cell-free) pertussis (aP) vaccine
Measles virus	Measles vaccine
Hepatitis B virus	Hepatitis B vaccine
Rotavirus	Rotavirus vaccine
<i>Haemophilus influenzae</i> type B (Hib)	Hib conjugate vaccine
<i>Streptococcus Pneumoniae</i> (Pneumococcal infection)	Pneumococcal vaccines
Yellow fever virus	Yellow fever vaccine

* The answer to all questions can be found at the end of this manual (page 202).

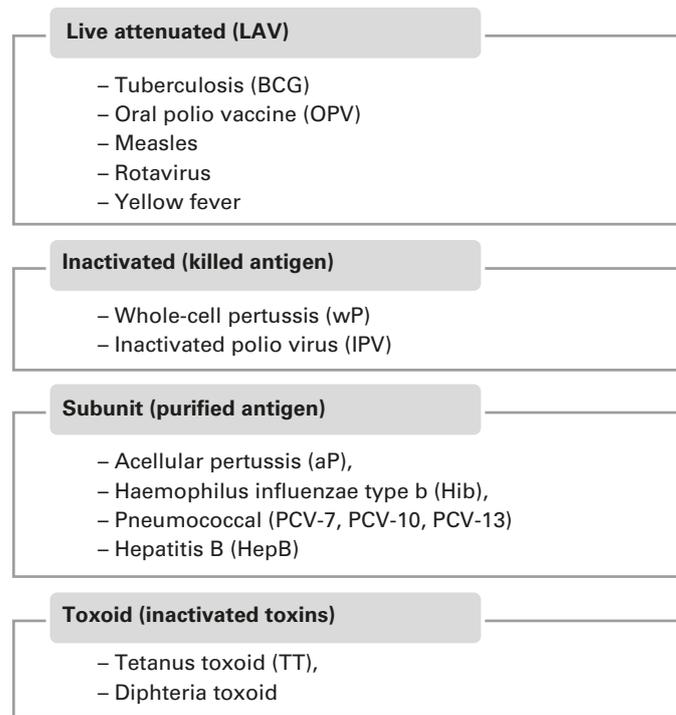
** Diphtheria, tetanus and pertussis vaccines are usually administered in combination vaccines (e.g. DTwP, DTaP) when given to infants and young children. These vaccines are also available in combinations with hepatitis B (e.g. DTwP-HepB, DTaP-HepB) and/or Hib vaccines (e.g. DTPwP-HepB+Hib, DTPaP-HepB+Hib).

*** Diphtheria toxoid is only available as a combined vaccine with tetanus toxoid and other childhood vaccines such as pertussis, hepatitis B, Hib, and IPV.

Types of vaccine

There are many types of vaccines, categorized by the antigen used in their preparation. Their formulations affect how they are used, how they are stored, and how they are administered. The globally recommended vaccines discussed in this module fall into the four main antigen types shown in the diagram.

Types of Vaccine



Vaccine manufacturers strive to develop vaccines that:

- Are effective in preventing or reducing severity of infectious disease,
- Provide durable, long-term protection against the disease,
- Achieve immunity with a minimal number of doses,
- Provide the maximum number of antigens that confer the broadest protection against infection,
- Cause no or mild adverse events,
- Are stable at extremes of storage conditions over a prolonged period of time,
- Are available for general use through mass production,
- Are affordable to populations at risk for infectious disease.

Adverse events

Classification

An adverse event following immunization (AEFI) is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. AEFIs are divided in 5 categories.

– 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.

Example: Extensive limb swelling following DTP vaccination.

– 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.

Example: Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio.

– Immunization error-related reaction –

An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.

Example: Transmission of infection by contaminated multidose vial.

– Immunization anxiety-related reaction –

An AEFI arising from anxiety about the immunization.

Example: Vasovagal syncope in an adolescent during/following vaccination.

– Coincidental event –

An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.

Example: A fever occurs at the time of the vaccination (temporal association) but is in fact caused by malaria.

Coincidental events reflect the natural occurrence of health problems in the community with common problems being frequently reported.

! Key point

- The difference between a reaction related to the vaccine and an adverse event which can have other causes should be explained to patients and parents. This ensures that they have all information they need to make an informed decision about receiving an immunization for themselves or their children.

Trusted and well-informed health care providers are best suited to provide such information. Information about the immunization(s) should be provided well ahead of the immunization visit. This gives parents the time to understand the information well and ask questions that will increase their trust.

Question 3*

It is important to understand the different meanings of an **adverse event following immunization** (or AEFI) and an **adverse vaccine reaction**. Can you tell the difference? Select the right answers:

- A. An **adverse vaccine reaction** is a vaccine-related event caused or precipitated by a vaccine when given correctly.
- B. An **adverse vaccine reaction** can be caused by errors in the administration of the vaccine.
- C. An **adverse vaccine reaction** can be the result of unrelated coincidence.
- D. An **adverse event following immunization** can be due to all of the causes stated in A, B, and C.

Causes

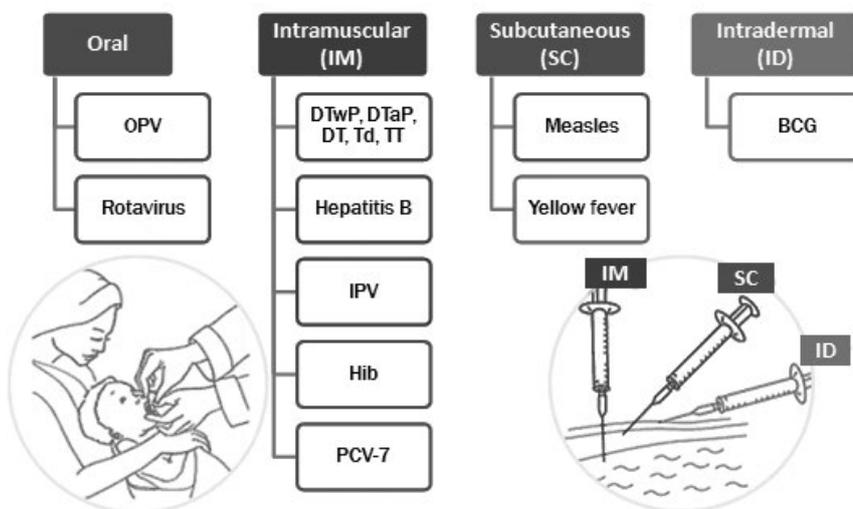
Vaccines contain different components to make them effective. However, each component in a vaccine adds a potential risk of an adverse reaction. Regulatory authorities must ensure that all vaccine components, singly and in combination, do not compromise vaccine safety.

Vaccines are prepared with different types of antigens, using different scientific methods such as attenuation, inactivation, and recombination DNA technology.

Some vaccines include components to enhance immune response, such as adjuvants and conjugated proteins.

Vaccines can also include antibiotics, stabilizers, and preservatives to reduce contamination during the manufacturing process and to maintain their effectiveness during transport and storage.

Routes of administration of several vaccines



Manufacturers usually recommend the route of administration that limits best adverse reactions of the respective vaccine.

* The answer to all questions can be found at the end of this manual (page 202).

**Question 4***

Select among the following the components that contribute to the risk of an adverse reaction (selection of several items is possible).

- Antigens Antibiotics Preservatives
 Adjuvants Stabilizers

Please note that Routes of administration (intradermal, subcutaneous or intramuscular injection, drops given orally, or intranasal administration) also contribute to the risk of an adverse reaction: They are recommended by the manufacturer for each vaccine and are determined to maximize vaccine effectiveness and limit adverse reactions.*

Frequency and severity

Under recommended conditions, vaccines should cause no adverse events and completely prevent the infection that they target. Unfortunately, current technology does not allow for such perfection. The key therefore is to minimize as much as possible adverse events and ensure a safe use of vaccines.

Adverse events following immunization (AEFIs) are classified by the cause of the event. As you have learned previously, when an AEFI is caused by the properties of the vaccine, it is classified as a vaccine (product or quality related) reaction. Other categories include immunization error-related, and immunization anxiety-related reactions and coincidental events.

**Key point**

- Vaccine adverse events are expected to occur with a certain frequency.
- AEFI surveillance monitors adverse events and follows up severe events that may have been due to the vaccine.

**Question 5***

Which of the following statements is **wrong**:

- A. An event that occurs in 12 out of a hundred persons is regarded as very common.
 B. An event that occurs in 2 out of a hundred persons is regarded as common.
 C. An event that occurs in 1 out of 20,000 is regarded as very rare.
 D. An event that occurs in 2 out of a thousand persons is regarded as common.
 E. An event that occurs in 1 out of 9,000 is regarded as rare.

* The answer to all questions can be found at the end of this manual (page 202).

Frequency and severity of adverse vaccine reactions

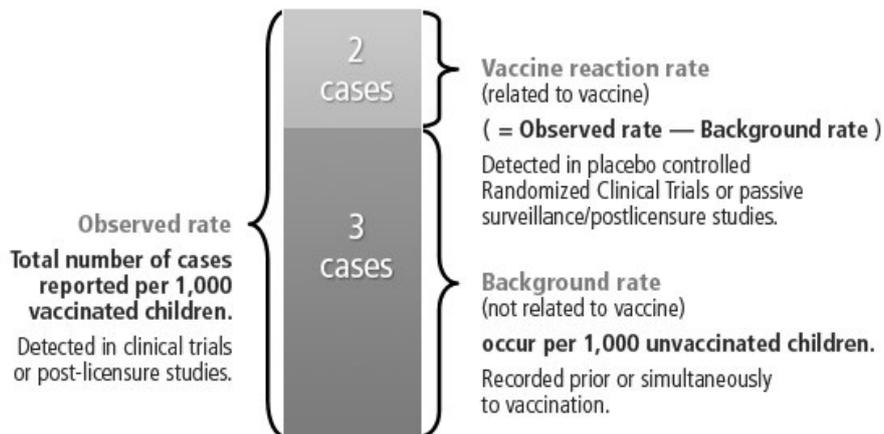
Frequency	Occurrence among persons vaccinated in percent	Severity of reactions
Very common	≥ 10%	Common and usually minor reactions: <ul style="list-style-type: none"> • Are part of the immune response to vaccine, • Reactions settle on their own, • Examples include: <ul style="list-style-type: none"> – Fever, – Malaise.
Common (frequent)	≥ 1% and < 10%	
Uncommon (infrequent)	≥ 0.1% and < 1%	Rare, usually more severe reactions: <ol style="list-style-type: none"> 1. Usually require clinical management, 2. Examples include: <ul style="list-style-type: none"> – Severe allergic reaction (e.g., anaphylaxis) including an exaggerated response to the vaccine antigen or component, – Vaccine specific reactions, such as BCG osteitis.
Rare	≥ 0.01% and < 0.1%	
Very rare	< 0.01%	

Background rates

Background rates of vaccine adverse reactions worldwide are published by WHO. Background rates differ from country to country because of differences in national surveillance systems. Understanding the background rates in a specific population is useful for monitoring the sensitivity of the AEFI surveillance system in detecting changes in the frequency of vaccine reactions.

For example, using the background rate in comparison to the observed rate can be helpful to determine the reaction rate of a vaccine (see graphic).

Example: Fever following vaccination



Any increase in the frequency of AEFIs should alert you to consider the quality of the vaccine and whether there are special risks in local populations. In addition, knowing when vaccine reactions may appear (time to onset) is useful for investigating and verifying cases, as Module 4 will describe.



Key point

- Knowing the background rates in your population is essential in detecting changes in the frequency of vaccine reactions and identifying trends of concern, such as rates reported by AEFI surveillance that are higher than expected.

Vaccine safety in immunization programmes

In the pre-vaccine era, morbidity and mortality caused by infectious diseases that are now preventable were high. Obviously, as vaccines did not exist, there were no adverse events to them yet. The pre-vaccine stage in the graph (**STAGE 1**) is the phase before the vaccine gets introduced.

Potential stages in the evolution of an immunization programme

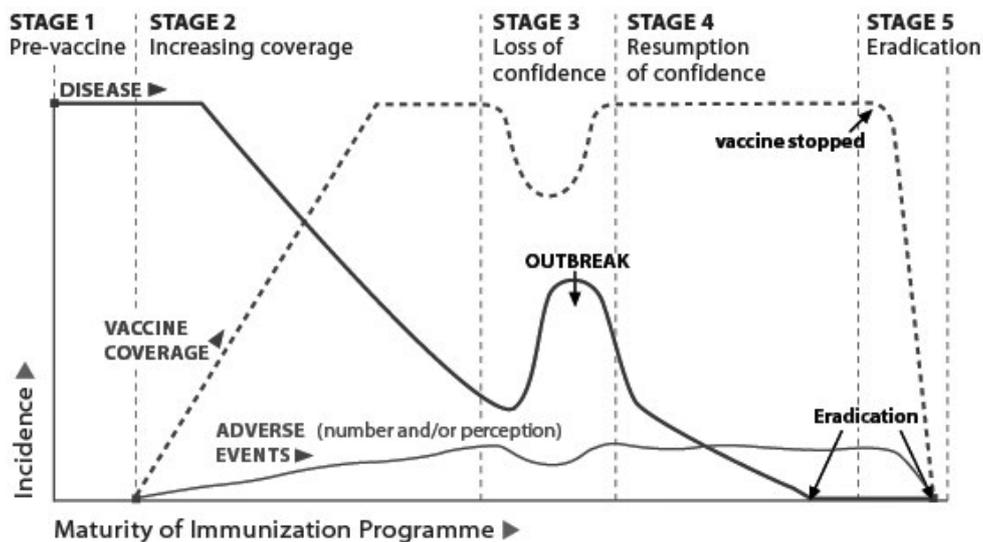


Diagram adapted from Chen RT et al. The Vaccine Adverse Event Reporting System/Vaccine Adverse Event Reporting System (VAERS). *Vaccine*, 1994; 12(6):542–550.

In **STAGE 2**, after an effective vaccine is introduced to prevent a particular disease, an increase in immunization uptake will result in a decrease in disease incidence, but also adverse events (AEFI), real or perceived, may become a major focus. Paradoxically, it is just when vaccine benefits are most apparent and vaccine coverage is highest that vaccine safety concerns are most likely to increase in the general public.

This increased focus on AEFIs, often intensified by media coverage of one or a few case reports, may lead to:

- A loss of confidence in the vaccine by the public,
- A reduction in vaccine coverage,
- A resurgence of the disease to higher or even epidemic levels (**STAGE 3**).

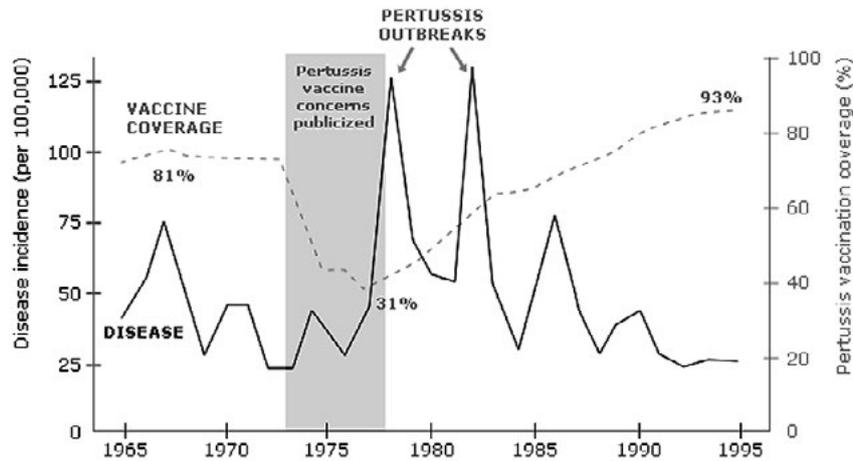
The resurgence of disease or the availability of an alternative vaccine results in renewed public acceptance of vaccination against the disease. Vaccination levels increase and the disease is reduced to earlier low levels (**STAGE 4**).

For vaccine-preventable diseases such as smallpox that can be eradicated, vaccine use can be stopped, thereby removing the risk of any adverse event resulting from its use (**STAGE 5**). To ensure that the cycle displayed in the graph does not repeat, any vaccine safety issue requires timely detection, evaluation, and response efforts to gain and maintain high public confidence.

Pertussis vaccine example

In the mid-1970s in England and Wales, anti-immunization groups caused parents to question the value of pertussis vaccine. As a result, immunization rates fell from 81 to 31% in a span of just a few years. Two epidemics of pertussis (whooping cough) followed, and many children died needlessly. As the population was confronted with the scourge of pertussis returning to their community, immunization coverage rose steadily and even surpassed previous highs.

Pertussis incidence in England and Wales (1965–1995)



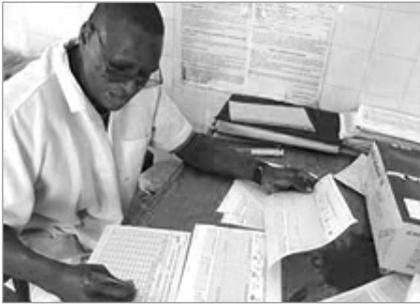
Key point

The more successful a vaccination campaign is, the less visible the prevented disease may become to the public. As the threat of the original disease vanishes in the perception of the public, the attention of the population may focus to the adverse events of the vaccine. A distorted perception of the risk of vaccines and negligence of the much greater health threat by the original disease may lead to decreased acceptance of the vaccine.

To ensure continued public acceptance of vaccines, it is essential to:

- Monitor the incidence of AEFIs,
- Scientifically evaluate the likely associations,
- Respond to newly identified risks from vaccines,
- Communicate the benefits and risks to patients and parents through a trusted health care source in advance of the vaccination visit.

Vaccine regulations



Formal regulation began with vaccine testing, and in response to tragedies associated with vaccine use, more comprehensive regulatory procedures began to be defined.¹¹

In the United States of America, the country with the longest history in vaccine regulation, 20 children became ill and 14 died in 1901 following receipt of an equine-derived diphtheria anti-toxin contaminated with tetanus toxin.

This event stimulated the first legislation to regulate the sale of biologicals, the Biologics Control Act, signed into law in 1902.¹²

Today vaccine regulation includes a range of functions that cover the entire continuum of vaccine development, licensure, and use.

Progress in vaccine regulation globally includes shifts towards strictly defined procedures for vaccine consistency, reliance on Good Manufacturing Practices (GMPs) rather than final product testing and continued vaccine pharmacovigilance and impact surveillance rather than individual, sporadic field studies.

Pre-licensure vaccine safety

Vaccines, like other pharmaceutical products, undergo extensive testing and review for safety, immunogenicity, and efficacy in the laboratory, in animals, and in three phases of clinical trials in human subjects before licensure.

Monitoring adverse vaccine reactions is a major safety component of pre-licensure clinical trials.

In the table below you can see the different steps including clinical trials and further assessment that a vaccine must go through before entering the market. Look at the various sample sizes of the Clinical trial phases and compare them to the classification of frequency of common and rare adverse events on this module's chapter "*Adverse events: Frequency and severity*" on page 21. Note that even trials in Phase III are not generally designed to detect very rare reactions or reactions with vague or delayed onset. Larger studies, often at prohibitive cost and risk to delay vaccine availability, are necessary to detect very rare conditions that might result from vaccination.

! Key point

- Pre-licensure studies often identify common and acute negative reactions that occur with a frequency greater than 1 in 10,000 vaccinations, depending on total sample size of the study.

The sensitivity of detection of uncommon or rare adverse events, or those with delayed onset is, however, low in these trials.

As a result, continuous post-licensure monitoring of vaccine safety is needed to identify and evaluate such adverse events.

Clinical trials and assessment of vaccine safety

	Activity	Sample size (estimates)	Detection of Adverse events	
			Common	Rare
Clinical Trial Phase I ↓	Test the safety and immunogenicity of a vaccine candidate in a few low-risk individuals (usually healthy adults) to determine tolerability.	10–100	+/-	-
Clinical Trial Phase II ↓	Monitor safety, potential side effects, immune response, and determine optimum dosage and schedule.	100–1,000	+	-
Clinical Trial Phase III ↓	Address clinical efficacy in disease prevention and provide further safety information from more heterogeneous populations and longer times of observation.	1,000–10,000	+	-
Submission ↓	The vaccine application is submitted to regulatory authorities for approval to market.			
Introduction	Involves making the vaccine available for use.			

Rotavirus vaccine example

In August 1998 the first rotavirus vaccine, RotaShield®, was licensed in the USA. Pre-licensure literature noted a suspicion of an increased risk of intussusception. After RotaShield® was licensed for routine use by the public (approximately one million children vaccinated within the first nine months licensure) the American vaccine safety surveillance, Vaccine Adverse Event Reporting System (VAERS), began to receive reports of intussusception following administration of the vaccine. About 100 (0.01%) of the one million children vaccinated developed intussusception,¹⁶ a potentially life-threatening bowel obstruction that occurs for unknown reasons in about one child per 10,000, regardless of whether or not they have received a vaccine.¹⁷ Because of the uncertainty about the relationship between RotaShield® and intussusception cases following vaccination, the manufacturer voluntarily took the product off the market in 1999.

This example demonstrates that even if no adverse event is observed in a trial of 10,000 vaccinees (as was the case of RotaShield®’s phase III clinical trial), one can only be reasonably certain that the real incidence of the adverse event is no higher than one in 3,333 vaccinees. Thus to be able to detect a risk of one adverse event per 10,000 vaccinees, a pre-licensure trial of at least 30,000 vaccinees and 30,000 controls is needed.¹⁴

Subsequent rotavirus vaccines were subjected to phase III trials that included at least 60,000 infants.^{18,19} While these trials were adequately powered to detect the problem with intussusception found following RotaShield®, in general, the cost of such large trials might limit the number of vaccine candidates that go through this process in the future.

Post-licensure vaccine safety



Key point

- Spontaneous reporting is the cornerstone of most post-licensure safety monitoring systems because of its relative ease of implementation and ability to capture unexpected events.

Post-licensure surveillance of vaccine safety is critical. The conditions and reasons for safety monitoring change, following licensure and introduction of a new vaccine.

- Vaccines are now in use in the general population and recipients are no longer monitored in clinical trials with narrow inclusion/exclusion criteria,
- Subpopulations commonly excluded in clinical trials (e.g. those with underlying medical conditions, preterm infants) get vaccinated,
- Large numbers of people are being vaccinated, for example, entire birth cohorts receive infant vaccines,
- Other factors that can lead to AEFIs, such as incorrect administration practices, need to be monitored for safety,
- Uncommon and rare vaccine reactions, and reactions with delayed onset may not be detected before vaccines are licensed,
- Health providers should understand that some commonly used vaccines have demonstrated rare and potentially serious adverse events. In these instances, policy-making bodies have judged that the individual and community benefits of vaccination outweigh the risks.

Rotateq® vaccine example

Since the US introduction of RotaTeq® in 2006, the USA's Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) has routinely reviewed post-licensure safety surveillance data recorded through the Vaccine Adverse Event Reporting System (VAERS).

One year following introduction, ACIP reviewed available data to evaluate the rate of reports of intussusception following RotaTeq® vaccination and found that it did not exceed expected background rates in the absence of vaccination. Additionally, active surveillance among a population of insured children did not identify any reports of intussusception within 30 days of more than 28,000 administered doses.²² As a result, the committee has expressed no safety concerns regarding use of this vaccine and reaffirmed its 2006 recommendation for routine administration to all infants in the USA at ages two, four, and six months.²³ Since introduction, the use of second generation rotavirus vaccines in routine immunization has reduced hospitalizations for severe diarrhoea by 70 to 80% and may have prevented illness in unvaccinated children by limiting the infections that spread the virus to others.

Post licensure surveillance options

AEFI surveillance systems are specific to monitoring adverse events associated with vaccine use. In contrast, adverse drug reaction (ADR) surveillance systems are used to monitor suspected adverse reactions associated with medicines.

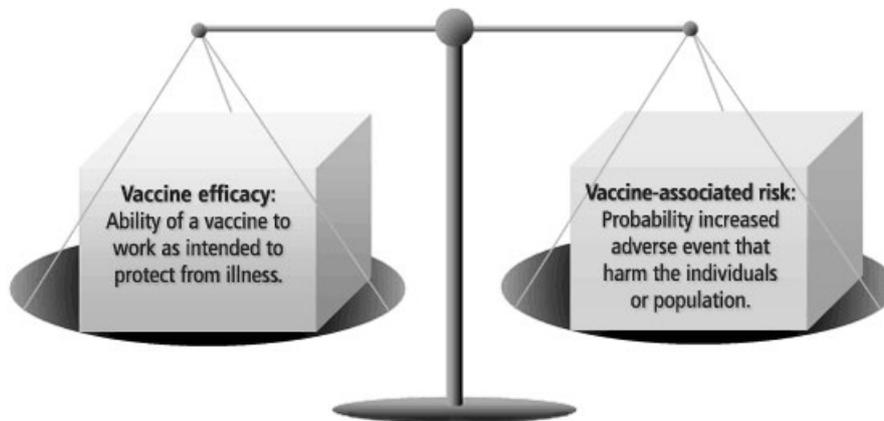
A range of surveillance options can be used to monitor the safety of vaccines and immunizations post-licensure.

Passive surveillance systems	
Passive surveillance systems	<ul style="list-style-type: none"> ■ Passive surveillance systems (or spontaneous reporting systems) are the cornerstone of most post-licensure safety monitoring systems because of their relative ease of implementation, their cost and ability to capture unexpected events. <p>These reporting systems monitor events reported by health care providers and consumers and do not actively seek out and collect data or measure outcomes using study protocols.</p>
Active surveillance systems	
Post-licensure clinical trials and phase IV surveillance studies	<ul style="list-style-type: none"> ■ Vaccines may undergo clinical trials after licensure to assess the effects of changes in vaccine formulation, vaccine strain, age at vaccination, number and timing of vaccine doses, simultaneous administration and interchangeability of vaccines from different manufacturers on vaccine safety and immunogenicity.¹⁴ ■ To improve the ability to detect adverse events that are not detected during pre-licensure trials, some recently licensed vaccines in developed countries have undergone formal phase IV surveillance studies, involving cohorts as large as 100,000 often recruited from health maintenance organizations (HMOs), lasting four to six years.
Large linked databases (LLDBs)	<ul style="list-style-type: none"> ■ LLDBs are large administrative databases from defined populations (such as a single health care provider or HMO) that were created separately from each other and linked to enable the sharing of data across platforms. Such linked databases have become useful to vaccine safety surveillance. ■ Because LLDBs cover enrollee populations numbering from thousands to millions, they can detect very rare adverse events. With denominator data on doses administered and the ready availability of appropriate comparison (i.e. unvaccinated) groups, these large databases provide an economical and rapid means of conducting post-licensure studies of the safety of drugs and vaccines. They also represent powerful tools to allow for testing hypotheses when signals or allegations create suspicions of a possible vaccine safety issue. ■ The Vaccine Safety Datalink (VSD) project is an example of a LLDB between the USA's Centers for Disease Control and Prevention (CDC) and eight HMOs. The VSD project was established in 1990 to monitor immunization safety and to address the gaps in scientific knowledge about rare and serious events following immunization.²⁰
Clinical centers, including the Clinical Immunization Safety Assessment (CISA) centers	<ul style="list-style-type: none"> ■ More recently, tertiary clinical centers have been used to conduct research on immunization-associated health risks. ■ The USA's Clinical Immunization Safety Assessment (CISA) Network is a national network of six medical research centers with expertise in immunization safety conducting clinical research on immunization-associated health risks. Established in 2001 as a collaborative project between the CDC, six medical research centers, and American Health Insurance Plans, CISA conducts clinical research on vaccine adverse events and the role of individual variation.²¹

Balancing efficacy and safety

Vaccine efficacy refers to the ability of a vaccine to bring about the intended beneficial effects on vaccinated individuals in a defined population under ideal conditions of use. The potential benefits of an effective vaccine – e.g. promotion of health and well-being, and protection from illness and its physical, psychological and socioeconomic consequences – must be weighed against the potential risk of an adverse event following immunization (AEFI) with that vaccine. Vaccine-associated risk is the probability of an adverse or unwanted outcome occurring, and the severity of the resulting harm to the health of vaccinated individuals in a defined population, following immunization with a vaccine under ideal conditions of use.

Potential benefits of an effective vaccine must be weighed against potential risk of an AEFI.



Key point

- Public confidence in vaccine safety is increased by clear communication of risk/benefit assessments, comparing the very low vaccine-associated risk with the very significant benefits of vaccination.

An important criterion of vaccine safety that regulatory authorities must establish is the risk/benefit assessment of immunization with a particular vaccine in a defined population. You will learn how to conduct a risk/benefit assessment in Module 4 'Surveillance' and about the actions that follow the identification of an increased or new vaccine risk. Here we introduce you to some basic principles and the issues that regulatory authorities consider when balancing vaccine efficacy and vaccine safety.

Risk evaluation for a specific vaccine requires the collection and analysis of reliable data on:

- The incidence, severity, morbidity and mortality resulting from adverse vaccine reactions,
- Case investigation to determine whether the vaccine presents a new suspected risk,
- The probable mechanism and underlying cause of any vaccine reactions,
- The preventability, predictability and reversibility of the risk of a vaccine reaction occurring,
- The risks associated with alternative vaccines that protect against the same disease,
- The risks associated with not vaccinating, i.e. the risks arising from the infectious disease in unvaccinated individuals. The table below illustrates this point very clearly for measles.

Summarizing the risk/benefit relationship of a vaccine in tables and diagrams is useful to:

- Relate the benefits to the seriousness of the target disease,
- Focus key messages on vaccine efficacy and safety in vaccination campaigns and routine immunization programmes,
- Alert healthcare staff to the dominant risks associated with a vaccine and the probability of an adverse vaccine reaction occurring,
- Encourage consideration of alternative vaccines which may offer greater efficacy and/or safety.

Risk of acquiring illnesses following infection versus risk following vaccination

	Measles infection ^a	Measles vaccine ^b
Otitis	7–9%	0
Pneumonia	1–6%	0
Diarrhoea	6%	0
Post-infectious encephalomyelitis	0.5/1,000	1/100,000 – million
SSPE	1/100,000	0
Anaphylaxis	0	1/100,000 – million
Thrombocytopenia	Not properly quantified ^c	1/30,000 ^d
Death	0.1–1/1,000 (up to 5–15%)	0

- a. Risks after natural measles are calculated in terms of events per number of cases.
- b. Risks after vaccination are calculated in terms of events per number of doses.
- c. Although there have been several reports of thrombocytopenia occurring after measles including bleeding, the risk has not been properly quantified.
- d. This risk has been reported after MMR vaccination and cannot be only attributed to the measles component.

MMR = measles, mumps and rubella; **SSPE** = subacute sclerosing panencephalitis.

P. Duclos, BJ Ward. Measles Vaccines, A Review of Adverse Events, Drug Safety 1998; Dec 19 (6): 435–454



Key point

Risk/benefit assessments should be applied to most situations relating to the efficacy or safety of vaccines to ensure public safety and public health.

Summary

You have now completed the learning for this module. These are the main points that you have learned.

- With the exception of water safety, vaccines have the greatest potential to promote public health. They reduce morbidity and mortality from infectious disease, saving costs as well as lives.
- Public trust in vaccines is easily undermined: there is a lower tolerance for adverse events than for other prescribed drugs.
- The five categories of AEFIs are:
 1. Vaccine product-related reaction,
 2. Vaccine quality defect-related reaction,
 3. Immunization error-related reaction,
 4. Immunization anxiety-related reaction,
 5. Coincidental event.
- Vaccines generate an immune response in the body, and the characteristics of a vaccine that increase the risk of an adverse reaction.
- The four main types of vaccine are live attenuated, inactivated, subunit and toxoid and there are specific vaccines of each antigen type.
- Vaccines are regulated from development, to licensure, to use, and national regulatory authorities play an important role in this process.
- Post-licensure surveillance of a vaccine after its introduction to the market is critical as clinical trials may not detect rare or very rare reactions, or reactions with delayed onset.
- The risks associated with vaccines are very low compared with the risks of the diseases they are designed to prevent.

**You have completed Module 1.
We suggest that you test your knowledge!**

ASSESSMENT 1

Question 1

Which of the following statements is/are correct? Select one or more:

- A. Post-licensure AEFI surveillance is important because vaccine adverse reactions with delayed onset may not be known at the time of vaccine licensure.
- B. Pre-licensure trials do not detect common minor vaccine reactions. These are discovered in Post-licensure AEFI surveillance.
- C. Post-licensure AEFI surveillance is important because subpopulations commonly excluded in clinical trials (e.g. persons with underlying medical conditions, premature infants) are included in immunization programmes and may be at increased risk of AEFIs.
- D. Post-licensure AEFI surveillance of large cohorts may detect uncommon or rare severe vaccine reactions that were not known at the time of vaccine licensure.
- E. Post-licensure clinical trials are not required to assess the effects of changes in vaccine formulation or vaccine strain.
- F. Post-licensure AEFI surveillance does not identify errors in vaccine administration practices.

Question 2

Complete each statement by choosing the correct option from the list below:

1. Transmission of infection by contaminated multidose vial is a _____.
2. An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine is a _____.
3. An adolescent fainting due to a vasovagal syncope during or following vaccination speaks for a _____.
4. A fever occurs at the time of the vaccination (temporal association) but is in fact caused by malaria is a _____.
5. Failure by the manufacturer to completely inactivate a lot of inactivated polio leading to cases of paralytic polio is a _____.

- | | |
|--|--|
| a Immunization anxiety-related reaction | d Vaccine product-related reaction |
| b Coincidental event | e Vaccine quality defect-related reaction |
| c Immunization error-related reaction | |

Question 3

Complete each statement by choosing the correct option from the list below:

1. Exposure to the first dose of naturally-occurring or vaccine _____ triggers a _____ immune response.
2. Vaccination causes the immune system to produce types of protein called _____ and long-lived _____ that confer lasting immunity.
3. The _____ immune response is more rapid and effective than the _____ response and may eliminate the targeted pathogens before symptoms occur.
4. The immune response to immunization with measles _____ mimics the immune response to the _____ of the measles virus.

- | | |
|---------------------|-----------------------|
| a primary | e adjuvants |
| b secondary | f immunity |
| c antibodies | g antigens |
| d vaccine | h memory cells |

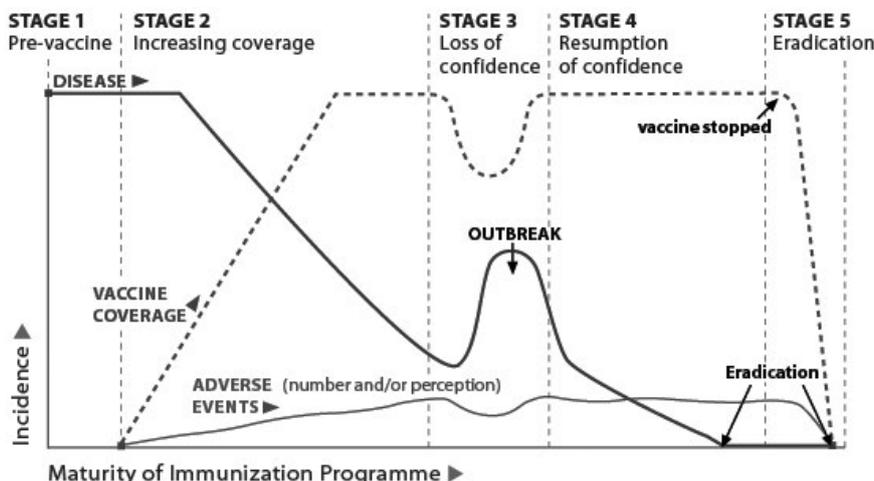
Question 4

Identify how the antigen in each of the following vaccines is prepared by choosing the correct option from the list below:

1. Oral polio vaccine (OPV) _____
2. Whole-cell pertussis vaccine (wP) _____
3. Hepatitis B vaccine (Hep B) _____
4. Tetanus toxoid (TT) _____
5. Rotavirus vaccine _____
6. Acellular pertussis vaccine (aP) _____
7. Measles vaccine _____
8. *Haemophilus influenzae* type b (Hib) _____

- | | |
|-------------------------------------|---------------------------------------|
| a live attenuated | c inactivated toxin |
| b subunit (purified) antigen | d inactivated (killed) antigen |

Question 5



An immunization programme can undergo several stages (Pre-vaccine, Increasing vaccination coverage, Loss of confidence, resumption of confidence, and eradication). Which of the following statements are correct? Select one or more:

- A. Pre-vaccine (STAGE 1): No adverse events occur during the pre-vaccine stage.
- B. Increasing vaccination coverage (STAGE 2): The coverage of vaccination increase, the prevented disease's incidence decreases, adverse events to the vaccine decrease.
- C. Loss of confidence (STAGE 3): The reduced appearance of the prevented illness and the increased focus on AEFIs, often intensified by media coverage lead to a loss of confidence in the vaccine by the public. This leads to a reduction in vaccine coverage, which leads to a resurgence of the disease to higher or even epidemic levels.
- D. Resumption of confidence (STAGE 4): Resurgence of disease and effective communication work by immunization programme officers lead to a regain in public acceptance of the vaccine. Vaccination levels have increased and the disease incidence decreases.
- E. Eradication (STAGE 5): Once a disease is eradicated, vaccine use can be stopped.

You have completed Assessment 1.

Assessment solutions

Question 1

Answers A, C and D are correct.

The key point is that in pre-licensure clinical trials, the sensitivity of detection is low for:

- uncommon or rare adverse reactions, or
- reactions with delayed onset, or
- reactions affecting subgroups excluded from clinical trials.

Continuous post-licensure monitoring of vaccine safety is therefore critical to identify and evaluate such adverse events, particularly when there are changes in vaccine formulation or vaccine strain.

Question 2

The correct choices are:

1. Immunization error-related reaction,
2. Vaccine product-related reaction,
3. Immunization anxiety-related reaction,
4. Coincidental event,
5. Vaccine quality defect-related reaction.

Question 3

The correct answers are:

1. Exposure to the first dose of naturally-occurring or vaccine **antigens** triggers a **primary** immune response.
2. Vaccination causes the immune system to produce types of protein called **antibodies** and long-lived **memory cells** that confer lasting immunity.
3. The **secondary** immune response is more rapid and effective than the **primary** response and may eliminate the targeted pathogens before symptoms occur.
4. The immune response to immunization with measles vaccine mimics the immune response to the **antigens** of the measles virus.

Question 4

The correct choices are:

1. Oral polio vaccine (OPV) – live attenuated,
2. Whole-cell pertussis vaccine (wP) – inactivated (killed) antigen,
3. Hepatitis B vaccine (Hep B) – subunit (purified) antigen,
4. Tetanus toxoid (TT) – inactivated toxin,
5. Rotavirus vaccine – live attenuated,
6. Acellular pertussis vaccine (aP) – subunit (purified) antigen,
7. Measles vaccine – live attenuated,
8. *Haemophilus influenzae* type b (Hib) – subunit (purified) antigen.

Question 5

Answers A, C, D and E are correct.

In the pre-vaccine era, morbidity and mortality caused by infectious diseases that are now preventable were high. Obviously, as vaccines did not exist, there were no adverse events to them yet. The pre-vaccine stage in the graph (**STAGE 1**) is the phase before the vaccine gets introduced.

STAGE 2, after an effective vaccine is introduced to prevent a particular disease, an increase in immunization uptake will result in a decrease in disease incidence, but also adverse events (AEFI), real or perceived, may become a major focus. Paradoxically, it is just when vaccine benefits are most apparent and vaccine coverage is highest that vaccine safety concerns are most likely to increase in the general public.

This increased focus on AEFIs, often intensified by media coverage of one or a few case reports, may lead to:

- A loss of confidence in the vaccine by the public,
- A reduction in vaccine coverage,
- A resurgence of the disease to higher or even epidemic levels (**STAGE 3**).

The resurgence of disease or the availability of an alternative vaccine results in renewed public acceptance of vaccination against the disease. Vaccination levels increase and the disease is reduced to earlier low levels (**STAGE 4**).

For vaccine-preventable diseases, such as smallpox, that have been eradicated, vaccine use can be stopped, thereby removing the risk of any adverse event resulting from its use (**STAGE 5**).

MODULE 2

Types of vaccine and adverse reactions

Overview

There are many types of vaccines. Different types or formulations affect how they are used, how they are stored, and how they are administered. If they are to be safe and effective, it is vital to be familiar with the different types and to know how to handle them.

Different vaccines can cause different adverse reactions, and it is important to recognize what these may be. Can you identify the contraindications for vaccination and know which present an additional risk? What special considerations should you make when immunizing pregnant women or immunocompromised clients?

This module will explain the different types of vaccine and the main routes of administration. You will learn about the main vaccine reactions and the importance of understanding contraindications – as ignoring these could lead to vaccine reactions. Finally, you will look at public concern over vaccines and consider some rumours about vaccine safety that have been disproved by research.

Module outcomes

By the end of this module you should be able to:

- 1 Explain the modes of action of live attenuated vaccines, conjugate vaccines, subunit vaccines, and toxoid vaccines,
- 2 List types of vaccine components, including adjuvants and preservatives, and explain their functions,
- 3 Explain the difference between live attenuated and inactivated vaccines,
- 4 Identify the contraindications for vaccination that may present an additional risk.

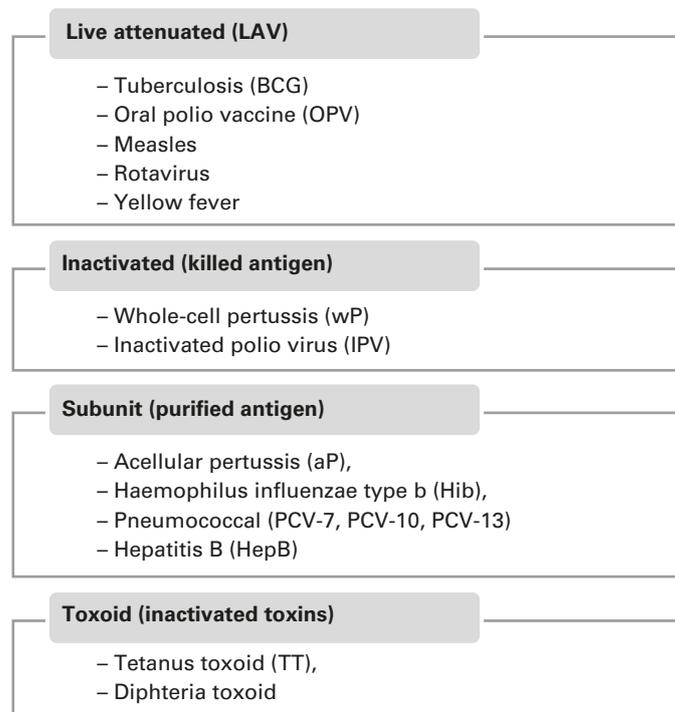
Types of vaccine

In module 1 we have learned that vaccines are used to prevent serious illnesses and that regulatory authorities have strict requirements for safety before they are approved for use.

Vaccines require rigorous follow-up once approved for use to assess types and rates of adverse events. The development of more effective and even safer vaccines as well as developing vaccines for more diseases that are serious is always ongoing.

There are many types of vaccines, categorized by the antigen used in their preparation. Their formulations affect how they are used, how they are stored, and how they are administered. The globally recommended vaccines discussed in this module fall into four main types.

Types of Vaccine



Mono and polyvalent vaccines

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

Combination vaccines

Some of the antigens above can be combined in a single injection that can prevent different diseases or that protect against multiple strains of infectious agents causing the same disease (e.g. combination vaccine DPT combining diphtheria, pertussis and tetanus antigens). Combination vaccines can be useful to overcome logistic constraints of multiple injections, and accommodate for a children's fear of needles and pain.

Live attenuated vaccines

Available since the 1950s, live attenuated vaccines (LAV) are derived from disease-causing pathogens (virus or bacteria) that have been weakened under laboratory conditions. They will grow in a vaccinated individual, but because they are weak, they will cause no or very mild disease.

BACTERIA

Tuberculosis (BCG)

VIRUS

Oral polio vaccine (OPV)

Measles

Rotavirus

Yellow fever

Immune response

LAVs stimulate an excellent immune response that is nearly as good as compared to an infection with the wild-type pathogen.

Live microorganisms provide continual antigenic stimulation giving sufficient time for memory cell production.

In the case of viruses or intracellular microorganisms where cell-mediated immunity is usually desired, attenuated pathogens are capable of replicating within host cells.

Safety and stability

Since LAVs contain living organisms, there is a degree of unpredictability raising some safety and stability concerns.

- Attenuated pathogens have the very rare potential to revert to a pathogenic form and cause disease in vaccinees or their contacts. Examples for this are the very rare, serious adverse events of:
 - vaccine-associated paralytic poliomyelitis (VAPP) and
 - disease-causing vaccine-derived poliovirus (VDPV) associated with oral polio vaccine (OPV).
- Functional immune systems eliminate attenuated pathogens in their immune response. Individuals with compromised immune systems, such as HIV-infected patients may not be able to respond adequately to the attenuated antigens.
- Sustained infection, for example tuberculosis (BCG) vaccination can result in local lymphadenitis or a disseminated infection.
- If the vaccine is grown in a contaminated tissue culture it can be contaminated by other viruses (e.g. retro viruses with measles vaccine).
- As a precaution, LAVs tend not to be administered during pregnancy. However, the actual potential for fetal damage remains theoretical. For example, numerous studies have demonstrated that accidental rubella vaccination during pregnancy did not result in an increased risk of birth defects.
- LAVs can have increased potential for immunization errors:
 - Some LAVs come in lyophilized (powder) form. They must be reconstituted with a specific diluent before administration, which carries the potential for programmatic errors if the wrong diluent or a drug is used.
 - Many LAVs require strict attention to the cold chain for the vaccine to be active and are subject to programme failure when this is not adhered to.

<p>IMMUNE RESPONSE </p> <ul style="list-style-type: none"> ◆ Live microorganisms provide continual antigenic stimulation, giving sufficient time for memory cell production. ◆ Attenuated pathogens are capable of replicating within host cells. <p style="text-align: center;">Excellent immune response</p>	<p>SAFETY AND STABILITY </p> <ul style="list-style-type: none"> ◆ Attenuated pathogens can revert to original form and cause disease. ◆ Potential harm to individuals with compromised immune systems (eg. HIV). ◆ Sustained infection (BCG - local lymphadenitis). ◆ Contamination of tissue culture. ◆ Immunization errors (Reconstitution, cold chain). ◆ Usually not given in pregnancy <p style="text-align: center;">Less safe compared to inactivated vaccines</p>
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Adverse reactions associated with LAVs

Five vaccines that are recommended by WHO are produced using LAV technology which are displayed in the table below:

- Tuberculosis (BCG),
- Oral Polio Vaccine,
- Measles,
- Rotavirus,
- Yellow Fever.

The table lists the rare, more severe adverse reactions of these vaccines. Note the frequency of the adverse reactions to get an idea of how low or high the possibility of an adverse event is. Also read the Comments to understand additional context details on the adverse events.

 **Question 1***

Which of the following statements is correct (Several answers possible see also table on next page):

- A. Febrile seizures are an uncommon reaction to vaccination with measles.
- B. Compared to giving the first dose of measles vaccine, allergic reactions are less likely to occur during the second dose of measles vaccine.
- C. Live vaccines include BCG, Measles, Rotavirus, Pertussis vaccine and Yellow fever vaccine.
- D. Vaccine associated paralytic poliomyelitis occurs very rarely among vaccines (2–4 cases per 1,000,000 vaccinated persons).

* The answer to all questions can be found at the end of this manual (page 202).

Five WHO recommended vaccines using LAV technology

	Vaccine	Rare, more severe adverse reactions	Frequency	Comment
BACTERIA	Tuberculosis (BCG) ²⁸	Fatal dissemination of BCG infection	very rare at 0.000019–0.000159%	Almost exclusively occurs in inadvertently immunized persons with severely compromised cellular immunity.
		BCG osteitis	very rare	In the past BCG osteitis has been reported in connection with certain vaccine batches but now occurs very rarely.
VIRAL	Oral polio vaccine (OPV) ²⁹	Vaccine- associated paralytic poliomyelitis (VAPP) in vaccinees and their contacts	very rare at 0.0002–0.0004%	An essential component of the global polio eradication campaign despite adverse reactions.
	Measles ³¹	Febrile seizures	uncommon at 0.3%	Adverse reactions, with the exception of allergic anaphylactic reactions, are less likely to occur after receipt of the second dose of measles vaccine.
		Thrombocytopenic purpura	very rare at 0.03%	
		Anaphylaxis	very rare at 0.001%	Allergic reactions to vaccine components including neomycin and the stabilizers gelatine or sorbitol, may follow vaccination.
	Rotavirus ⁶¹	None reported to WHO	–	To date, post-licensure surveillance does not indicate any increased risk of intussusception or other serious adverse reaction associated with the use of current rotavirus vaccines.
Yellow fever (YF) ⁶²	Hypersensitivity reactions	very rare	Sensitivity to egg, which is commonly used to stabilize the vaccine, may explain at least some of these cases.	
	Vaccine- associated neurotropic disease (encephalitis)	very rare	Infants seem more susceptible to vaccine-associated neurotropic disease than the YF-vaccinated population at large.	
	Vaccine- associated viscerotropic disease	very rare in children at 0.00001%	The elderly seem more susceptible to reaction (very rare at 0.04–0.05%) than the YF-vaccinated population at large.	

Inactivated whole-cell vaccines

Inactivated vaccines are made from microorganisms (viruses, bacteria, other) that have been killed through physical or chemical processes. These killed organisms cannot cause disease.

BACTERIA
Whole-cell pertussis (wP)

VIRUS
Inactivated polio virus (IPV)

Immune response

- Inactivated whole-cell vaccines may not always induce an immune response and the response may not be long lived.
- Several doses of inactivated whole-cell vaccines may be required to evoke a sufficient immune response.

Safety and stability

- Inactivated whole-cell vaccines have no risk of inducing the disease they are given against as they do not contain live components.
- They are considered more stable than LAV vaccines.

The table lists the rare, more severe adverse reactions of these vaccines. Note the frequency of the adverse reactions to get an idea of how low or high the possibility of an adverse event is. Also read the Comments to understand additional context details on the adverse events.

IMMUNE RESPONSE 	SAFETY AND STABILITY 
<ul style="list-style-type: none"> ◆ May not always induce an immune response at first dose. ◆ Response may not be long-lived, requiring several doses of vaccine. <p>Less strong immune response compared to live vaccines</p>	<ul style="list-style-type: none"> ◆ Have no live components, no risk of inducing the disease. ◆ Safer and more stable than LAVs. <p>Excellent stability profile</p>

Adverse reactions associated with inactivated whole-cell vaccines

	Vaccine	Rare, more severe adverse reactions	Frequency	Comment
BACTERIA	Pertussis (wP) ³⁰	Prolonged crying and seizures are uncommon	less than 1%	Minor adverse reactions such as local redness and swelling, fever and agitation are very common with wP vaccines (10–50%).
		Hypotonic, hypore-sponsive episodes (HHE) are rare	less than 0.1–0.2%	Although mild with no lasting effect, these reactions have affected the acceptance of wP vaccine in some populations. All wP (or DTwP) vaccines contain aluminium salt as adjuvant and in some cases thiomersal as preservative.
VIRAL	Inactivated polio vaccine (IPV) ²⁹	Vaccine-associated paralytic poliomyelitis (VAPP) in vaccinees and their contacts	None known	Many high-income countries have switched from OPV to IPV, as IPV is considered safer. IPV is more expensive than OPV and an injectable vaccine. Many lower- and middle-income countries use OPV.



Question 2*

Which of the following statements is incorrect?

- A. Inactivated whole-cell vaccines contain “killed” pathogens.
- B. Inactivated whole-cell vaccines can be considered safer than live vaccines, particularly when used in vulnerable groups (immunocompromised persons).
- C. Inactivated whole-cell vaccines can be considered more effective compared to live vaccines.
- D. Inactivated whole-cell vaccines should not be seen as ineffective – the immunization schedule foresees repeated doses to ensure adequate immune responses in patients.

Subunit vaccines

Immune response

- Subunit vaccines, like inactivated whole-cell vaccines do not contain live components of the pathogen. They differ from inactivated whole-cell vaccines, by containing only the antigenic parts of the pathogen. These parts are necessary to elicit a protective immune response.
- This precision comes at a cost, as antigenic properties of the various potential subunits of a pathogen must be examined in detail to determine which particular combinations will produce an effective immune response within the correct pathway.
- Often a response can be elicited, but there is no guarantee that immunological memory will be formed in the correct manner.

Protein-based

Polysaccharide

Conjugate

Safety and stability

Like inactivated vaccines, subunit vaccines do not contain live components and are considered as very safe.

<p>IMMUNE RESPONSE </p> <ul style="list-style-type: none"> ◆ Must determine which combination of antigenic properties will produce an effective immune response with the correct pathway. ◆ A response may be elicited, but with no guarantee that memory will form for future responses. <p style="text-align: center;">Less strong immune response compared to LAVs</p>	<p>SAFETY AND STABILITY </p> <ul style="list-style-type: none"> ◆ Have no live components, no risk of inducing the disease. ◆ Safer and more stable than LAVs. <p style="text-align: center;">Excellent stability profile</p>
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* The answer to all questions can be found at the end of this manual (page 202).

Key point

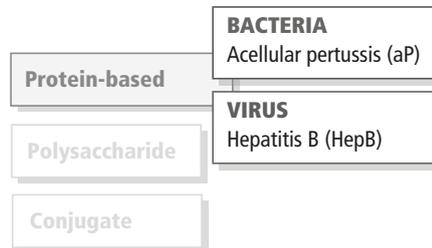
Rather than introducing a whole-cell vaccine (either inactivated or attenuated) to an immune system, a subunit vaccine contains a fragment of the pathogen and elicits an appropriate immune response.

Subunit vaccines can be further categorized into:

- Protein-based subunit vaccines,
- Polysaccharide vaccines,
- Conjugate subunit vaccines.

Protein-based subunit vaccines

Protein based subunit vaccines present an antigen to the immune system without viral particles, using a specific, isolated protein of the pathogen. A weakness of this technique is that isolated proteins, if denatured, may bind to different antibodies than the protein of the pathogen.



Commonly used protein-based subunit vaccines are the following:

- **Acellular pertussis (aP)** vaccines contain inactivated pertussis toxin (protein) and may contain one or more other bacterial components. The pertussis toxin is detoxified either by treatment with a chemical or by using molecular genetic techniques.
- **Hepatitis B** vaccines are composed of the hepatitis B virus surface antigen (HBsAg), a protein produced by hepatitis B virus. Earlier vaccine products were produced using purified plasma of infected individuals. This production method has been replaced by recombinant technology that can produce HBsAg without requiring human plasma increasing the safety of the vaccine by excluding the risk from potential contamination of human plasma.

The table lists the rare, more severe adverse reactions of these vaccines. Note the frequency of the adverse reactions to get an idea of how low or high the possibility of an adverse event is. Also read the Comments to understand additional context details on the adverse events.

Adverse reactions associated with subunit protein-based vaccines

	Vaccine	Rare, more severe adverse reactions	Comment
BACTERIA	Acellular pertussis (aP) ³⁰	Same as tetanus and diphtheria toxoid vaccines.	Acellular pertussis-containing vaccines are less reactogenic in terms of mild-to-moderate reactions than wP-containing vaccines. See “More about Pertussis vaccine”.
VIRAL	Hepatitis B (HepB) ⁶³	Very rare	Reports of severe anaphylactic reactions are very rare.

More about Pertussis vaccine

Both acellular (aP) and whole-cell pertussis (wP) vaccines are safe and effective. In terms of rare, more severe adverse reactions, aP and wP vaccines appear to have the same high level of safety. However, mild-to-moderate adverse reactions are more commonly associated with wP vaccines, and tend to increase with client age and the number of injections. This is why wP vaccines are not recommended for use in adolescents and adults where aP vaccines rather come to use.

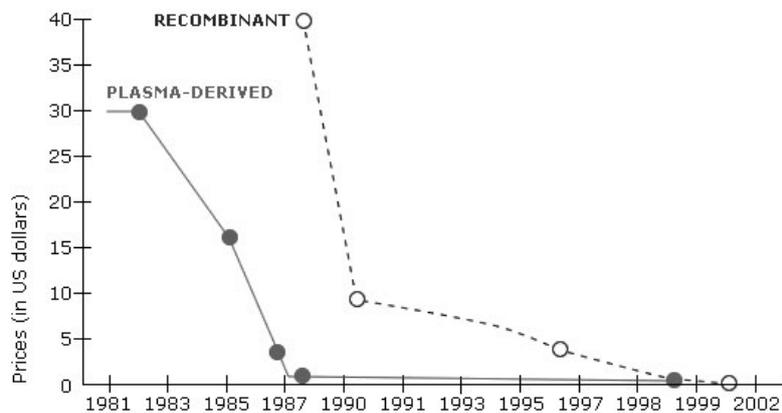
Because the price of wP is considerably less than aP, where resources are limited and the vaccine is well accepted by the local population, wP vaccine remains the vaccine of choice. In countries where a higher rate of adverse reactions after immunization with wP prevents high vaccination coverage, aP is recommended instead, at least for booster injections.³⁰

More about Hepatitis B vaccines

The first available hepatitis B vaccines were plasma-derived, produced by harvesting hepatitis B surface antigen (HBsAg) from the plasma of persons with chronic HBV infection. The particles are highly purified, and any residual infectious particles are inactivated by various combinations of urea, pepsin, formaldehyde and heat. Although concerns about transmission of bloodborne pathogens, including HIV, from plasma-derived vaccines have proven to be unfounded, public concerns over the safety of the plasma-derived vaccine hampered its acceptance in many populations. Therefore increased research efforts were made to develop a recombinant vaccine.

In 1986, a hepatitis B vaccine produced by recombinant technology was licensed, and a second followed in 1989. The recombinant technology expressed HBsAg in other microorganisms and offered the potential to produce unlimited supplies of vaccine.

Although both the plasma-derived and recombinant hepatitis B vaccines are safe and highly effective in protecting against acute hepatitis disease as well as chronic disease, including cirrhosis and liver cancer, competition among the various hepatitis B vaccine producers drove down the price (see figure). When the price of both the plasma-derived and recombinant hepatitis B vaccines was relatively similar, the recombinant gradually replaced the plasma-derived hepatitis B vaccine.



Polysaccharide vaccines

Some bacteria when infecting humans are often protected by a polysaccharide (sugar) capsule that helps the organism evade the human defense systems especially in infants and young children.

Protein-based

Polysaccharide

Conjugate

Polysaccharide vaccines create a response against the molecules in the pathogen’s capsule. These molecules are small, and often not very immunogenic. As a consequence they tend to:

1. Not be effective in infants and young children (under 18–24 months),
2. Induce only short-term immunity (slow immune response, slow rise of antibody levels, no immune memory).

Examples of polysaccharide vaccines include Meningococcal disease caused by *Neisseria meningitidis* groups A, C, W135 and Y, as well as Pneumococcal disease.

Conjugate subunit vaccines

Conjugate subunit vaccines also create a response against the molecules in the pathogen’s capsule. In comparison to plain polysaccharide vaccines, they benefit from a technology that binds the polysaccharide to a carrier protein that can induce a long-term protective response even in infants.

Protein-based

Polysaccharide

Conjugate

BACTERIA
Haemophilus influenzae type b (Hib),
 Pneumococcal
 (PCV-7, PCV-10, PCV-13)

Various protein carriers are used for conjugation, including diphtheria and tetanus toxoid. Conjugate subunit vaccines, can therefore prevent common bacterial infections for which plain polysaccharide vaccines are either ineffective in those most at risk (infants) or provide only short-term protection (everyone else).

The advent of conjugate subunit vaccines heralded a new age for immunization against diseases caused by encapsulated organisms such as meningococcus, *Haemophilus influenzae* type b (Hib) and pneumococcus.

WHO recommends that children receive *Haemophilus influenzae* type b (Hib) and pneumococcal conjugate vaccines. In addition, the meningococcal A vaccine introduced in Africa is also a conjugated subunit vaccine.

Adverse reactions associated with conjugate vaccines

	Vaccine	Rare, more severe adverse reactions	Comment
BACTERIA	<i>Haemophilus influenzae</i> type b conjugate (Hib) ⁶⁵	None known	Hib vaccine has not been associated with any rare, more severe adverse reactions.
	Pneumococcal conjugate, 7-valent (PCV-7), 10-valent (PCV-10), 13-valent (PCV-13) ⁶⁶	None known	PCV conjugate vaccines have not been associated with any rare, more severe adverse reactions. As with the introduction of any new vaccine, continued surveillance for possible unexpected effects is important.

Key point

Conjugate vaccines can prevent common bacterial infections for which plain polysaccharide vaccines are either ineffective in those most at risk (infants) or provide only short-term protection (everyone else).



Question 3*

Which of the following statements is incorrect:

- A. Polysaccharide vaccines provoke an immune response against the polysaccharide capsule.
- B. Conjugate vaccine binds the polysaccharide to a carrier protein.
- C. Polysaccharide vaccines are targeted, but not very immunogenic. They induce only short-term immunity. Polysaccharide vaccines do not provoke a sufficient immune response in infants and young children but can in adults.
- D. Measles vaccine is a typical example for a Conjugate vaccine that provides better protection for infants compared to a Polysaccharide vaccine.
- E. Conjugate vaccine is effective in those most at risk (infants) and provides longer term protection (everyone else).

Toxoid vaccines

Toxoid vaccines are based on the toxin produced by certain bacteria (e.g. tetanus or diphtheria).

<p>BACTERIA Tetanus toxoid (TT) Diphtheria toxoid</p>
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The toxin invades the bloodstream and is largely responsible for the symptoms of the disease. The protein-based toxin is rendered harmless (toxoid) and used as the antigen in the vaccine to elicit immunity.

To increase the immune response, the toxoid is adsorbed to aluminium or calcium salts, which serve as adjuvants.

Safety and stability

Toxoid vaccines are safe because they cannot cause the disease they prevent and there is no possibility of reversion to virulence. The vaccine antigens are not actively multiplying and do not spread to unimmunized individuals. They are stable, as they are less susceptible to changes in temperature, humidity and light.⁷⁶

<p>IMMUNE RESPONSE </p> <ul style="list-style-type: none"> ◆ May require several doses and usually need an adjuvant. <p style="text-align: center;">Not highly immunogenic</p>	<p>SAFETY AND STABILITY </p> <ul style="list-style-type: none"> ◆ Vaccine cannot cause disease it prevents. ◆ Very rare local and systemic reactions. ◆ Usually stable and long lasting. <p style="text-align: center;">Excellent stability profile</p>
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* The answer to all questions can be found at the end of this manual (page 202).

Adverse reactions associated with toxoid vaccines

	Vaccine	Rare, more severe adverse reactions	Comment
BACTERIA	Tetanus toxoid (TT) ⁶⁶	Anaphylaxis (1–6 per million) and brachial neuritis (5–10 per million) are extremely rare	Local and systemic reactions increase with increasing number of doses.
	Diphtheria toxoid (DT and Td) ⁶⁹	None known	No anaphylactic reactions attributable to the diphtheria component have been described.

Combination vaccines

Licensed combination vaccines undergo extensive testing before approval by national regulatory authorities to assure that the products are safe, effective, and of acceptable quality.

Combination vaccines consist of two or more antigens in the same preparation. This approach has been used for over 50 years in many vaccines such as DTwP and MMR. Combination products simplify vaccine administration and allow for the introduction of new vaccines without requiring additional health clinic visit and injections.

Potential advantages of combination vaccines include:

- Reducing the cost of stocking and administering separate vaccines,
- Reducing the cost of extra health care visits,
- Improving timeliness of vaccination (some parents and health-care providers object to administering more than two or three injectable vaccines during a single visit because of a child's fear of needles and pain, and because of concerns regarding safety),
- Facilitating the addition of new vaccines into immunization programmes.

It is very important, however, that combination vaccines are carefully tested before introduction. For instance, adjuvants in a combination vaccine could reduce the activity of one antigen and excessively increase the reactivity of another antigen. There could also be interactions with other vaccine components such as buffers, stabilizers and preservatives.

With all combinations, manufacturers must therefore evaluate the potency of each antigenic component, the effectiveness of the vaccine components when combined to induce immunity, risk of possible reversion to toxicity, and reaction with other vaccine components.

Key point

- No evidence exists that the administration of several antigens in combined vaccines overwhelms the immune system, which has the capability of responding to many millions of antigens at a time. Combining antigens usually does not increase the risk of adverse reactions. In fact, it can lead to an overall reduction in adverse reactions.

With all combinations, manufacturers must, however, evaluate the potency of each antigenic component, the effectiveness of the vaccine components when combined to induce immunity, risk of possible reversion to toxicity, and reaction with other vaccine components.

**Question 4***

Can you identify which five antigens are included in the pentavalent vaccine DTwPHepBHib?

Components of a vaccine

Vaccines include a variety of ingredients including antigens, stabilizers, adjuvants, antibiotics, and preservatives.

They may also contain residual by-products from the production process. Knowing precisely what is in each vaccine can be helpful when investigating adverse events following immunization (AEFIs) and for choosing alternative products for those who have allergies or have had an adverse event known or suspected to be related to a vaccine component.

Antigens

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

You have already learned about antigens on the chapter “Types of vaccine”.

Stabilizers

Stabilizers are used to help the vaccine maintain its effectiveness during storage. Vaccine stability is essential, particularly where the cold chain is unreliable. Instability can cause loss of antigenicity and decreased infectivity of LAV. Factors affecting stability are temperature and acidity or alkalinity of the vaccine (pH). Bacterial vaccines can become unstable due to hydrolysis and aggregation of protein and carbohydrate molecules. Stabilizing agents include $MgCl_2$ (for OPV), $MgSO_4$ (for measles), lactose-sorbitol and sorbitol-gelatine.

Adjuvants

Adjuvants are added to vaccines to stimulate the production of antibodies against the vaccine to make it more effective.

Adjuvants have been used for decades to improve the immune response to vaccine antigens, most often in inactivated (killed) vaccines. In conventional vaccines, adding adjuvants into vaccine formulations is aimed at enhancing, accelerating and prolonging the specific immune response to vaccine antigens. Newly developed purified subunit or synthetic vaccines using biosynthetic, recombinant, and other modern technology are poor vaccine antigens and require adjuvants to provoke the desired immune response.

Chemically, adjuvants are a highly heterogeneous group of compounds with only one thing in common: their ability to enhance the immune response. They are highly variable in terms of how they affect the immune system and how serious their adverse reactions are, due to the resulting hyperactivation of the immune system.

* The answer to all questions can be found at the end of this manual (page 202).

Today there are several hundred different types of adjuvants that are being used or studied in vaccine technology.

Aluminium salts example

Aluminium salts are among the oldest adjuvants that are commonly used. They slow the escape of the antigen from the site of injection thereby lengthening the duration of contact between the antigen and the immune system (i.e. macrophages and other antigen-receptive cells).

Aluminium salts are generally recognized as safe, however, they can cause sterile abscesses and nodules at the site of injection. The formation of a small granuloma is inevitable with alum-precipitated vaccines.

To ensure safe vaccination it is important that aluminium salts are administered intramuscularly and not subcutaneously. Subcutaneous administration can result in necrotic breakdown and cyst and abscess formation. To ensure the proper handling of intramuscular injections, it is critical to ensure that vaccination staff has been well trained.

Antibiotics

Antibiotics (in trace amounts) are used during the manufacturing phase to prevent bacterial contamination of the tissue culture cells in which the viruses are grown. Usually only trace amounts appear in vaccines, 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.

- Used during the manufacturing phase to prevent bacterial contamination of tissue culture cells in which viruses are grown,
- Usually only trace amounts appear in vaccines, for example, MMR and IPV vaccines each contain less than 25 micrograms of neomycin per dose,
- Persons known to be allergic to neomycin should be closely observed after vaccination so any allergic reaction can be immediately treated.

Preservatives

Preservatives are added to multidose vaccines to prevent bacterial and fungal growth. They include a variety of substances, for example Thiomersal, Formaldehyde, or Phenol derivatives.

Thiomersal

- Very commonly used preservative. Thiomersal is an ethyl mercury-containing compound,
- It has been in use since the 1930ies and no harmful effects have been reported for doses used in vaccination except for minor reactions (e.g. redness, swelling at injection site),
- It is used in multidose vials and for single dose vials in many countries as it helps reduce storage requirements/costs,
- Thiomersal has been subjected to intense scrutiny, as it contains ethyl mercury. The Global Advisory Committee on Vaccine Safety continuously review the safety aspects of Thiomersal. So far, there is no evidence of toxicity when exposed to Thiomersal in vaccines. Even trace amounts of thiomersal seem to have no impact on the neurological development of infants.

Formaldehyde

- Used to inactivate viruses (e.g. IPV) and to detoxify bacterial toxins, such as the toxins used to make diphtheria and tetanus vaccines,
- During production, a purification process removes almost all formaldehyde in vaccines,
- The amount of formaldehyde in vaccines is several hundred times lower than the amount known to do harm to humans, even infants. E. g., DTP-HepB + Hib “5-in-1” vaccine contains less than 0.02% formaldehyde per dose, or less than 200 parts per million.



Question 5*

Which of the following answers is incorrect?

- A. Thiomersal prevents bacterial growth and therefore make vaccines more durable, which is particularly helpful for storing and use of multi-dose vials.
- B. Aluminium salts primarily serve to prevent bacterial contamination of tissue culture cells.
- C. Adjuvants serve to enhance the immune response.
- D. Stabilizers make a vaccine more stable towards temporary changes in temperature and pH.

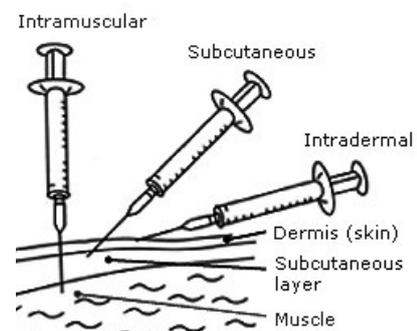
Route of administration

The route of administration is the path by which a vaccine (or drug) is brought into contact with the body. This is a critical factor for success of the immunization. A substance must be transported from the site of entry to the part of the body where its action is desired to take place. Using the body’s transport mechanisms for this purpose, however, is not trivial.

Intramuscular (IM) injection administers the vaccine into the muscle mass. Vaccines containing adjuvants should be injected IM to reduce adverse local effects.

Subcutaneous (SC) injection administers the vaccine into the subcutaneous layer above the muscle and below the skin.

Intradermal (ID) injection administers the vaccine in the top-most layer of the skin. BCG is the only vaccine with this route of administration. Intradermal injection of BCG vaccine reduces the risk of neurovascular injury. Health workers say that BCG is the most difficult vaccine to administer due to the small size of newborns’ arms. A short narrow needle (15 mm, 26 gauge) is needed for BCG vaccine. All other vaccines are given with a longer, wider needle (commonly 25 mm, 23 gauge), either SC or IM.



Oral administration of vaccine makes immunization easier by eliminating the need for a needle and syringe.

Intranasal spray application of a vaccine offers a needle free approach through the nasal mucosa of the vaccinee.

* The answer to all questions can be found at the end of this manual (page 202).

Intranasal flu vaccine

In October 2000, an inactivated intranasal flu vaccine was licensed in Switzerland. Results from a case control study and a case-series analysis indicated a significantly increased risk of Bell's palsy, a one-sided paralysis of facial muscles, developing after intranasal immunization with the vaccine. Following spontaneous reports of Bell's palsy in vaccine recipients, the producer decided not to further market the vaccine.

As a result of the occurrence of Bell's palsy, the Global Advisory Committee on Vaccine Safety (GACVS) recommended additional caution for new intranasal vaccines under development and recommended that the follow-up period in the context of clinical trials should be routinely extended to three months following administration.

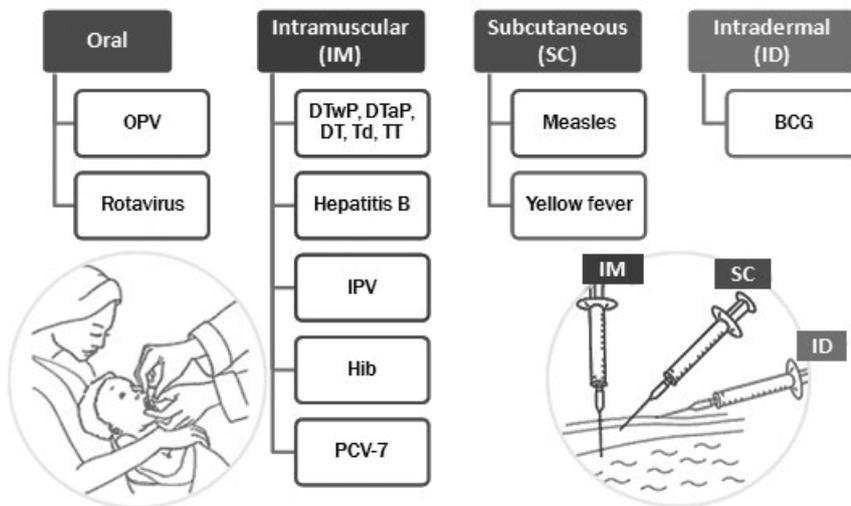
In 2003, a cold attenuated reassortant live intranasal vaccine was licensed in the US. This vaccine differs in formulation and manufacturing from adjuvanted inactivated intranasal vaccine. Bell's palsy was not observed in clinical trials of the cold attenuated reassortant live intranasal vaccine. As of 6 July 2006, with over four million vaccine doses distributed, a total of five Bell's palsy cases have been reported to the adverse event reporting system of the US. A causal association between these reported cases and the vaccine has not been established.

The GACVS continues to review the safety of vaccines administered by the intranasal route.



Bell's palsy (a one-sided paralysis of facial muscles) after intranasal immunization with the vaccine.

Routes of administration vary to maximize effectiveness of vaccine



Key point

- Manufacturers usually recommend the route of administration that limits best adverse reactions of the respective vaccine.

Contraindications

A contraindication to vaccination is a rare condition in a recipient that increases the risk for a serious adverse reaction. Ignoring contraindications can lead to avoidable vaccine reactions. Most contraindications are temporary, and the vaccination can be administered later.

The only contraindication applicable to all vaccines is a history of a severe allergic reaction after a prior dose of vaccine or to a vaccine constituent. Precautions are not contraindications, but are events or conditions to be considered in determining if the benefits of the vaccine outweigh the risks. Precautions stated in product labelling can sometimes be inappropriately used as absolute contraindications, resulting in missed opportunities to vaccinate.

Signs of allergic reactions

Vaccinating health workers should know the signs of allergic reactions and be prepared to take immediate action.

Contraindications to vaccines

Childhood vaccine	Anaphylaxis after previous dose or severe allergy to vaccine component	Pregnancy	Severely immunocompromised*	Comment
BCG ²⁸				Further information available at http://who.int/vaccine_safety/committee/topics/bcg/immunocompromised/Dec_2006/en/
DTwP ³⁰				
DTaP ³⁰				
OPV ²⁹				
IPV ²⁹				CAVEAT: allergy to neomycin.
Measles ³¹				Severe allergy to gelatine is a contraindication to vaccination with MMR vaccine.
HepB ⁶³				
Rotavirus ⁶¹				
Hib ⁶⁵				
PCV-7 ⁶⁶				
Yellow fever ⁶²				CAVEAT: severe allergy to egg. Contraindicated in infants less than 6 months.

* Includes symptomatic HIV/AIDS (but for most LAV vaccines, asymptomatic or properly treated HIV infection is not a contraindication).

Key point

True contraindications are rare. Misconceptions about their frequency can lead to missed opportunities to vaccinate and decrease immunization coverage, or conversely increase the risk of adverse reactions, both of which reduce public confidence in the safety of the vaccine.

Anaphylaxis

Anaphylaxis is a very rare allergic reaction (one in a million vaccinees), unexpected, and can be fatal if not dealt with adequately. Vaccine antigens and components can cause this allergic reaction. These reactions can be local or systemic and can include mild-to-severe anaphylaxis or anaphylactic-like responses (e.g. generalized urticaria or hives, wheezing, swelling of the mouth and throat, breathing difficulties, hypotension and shock). Reports of anaphylaxis are less common in low- and middle-income countries compared to high-income countries, probably because of reduced surveillance sensitivity and as the event may not be recognized (i.e. death attributed to another factor).

The Brighton Collaboration case definition and guidelines for anaphylaxis are available on their website:

 www.brightoncollaboration.org

Misdiagnosis of faints and other common causes of collapse, such as anaphylaxis, can lead to inappropriate treatment (e.g. use of adrenaline and failure to recognize and treat other serious medical conditions).

Anaphylaxis of unknown cause and unrelated to vaccines increases during adolescence, being more common among girls. Vaccinators should be able to distinguish anaphylaxis from fainting and vasovagal syncope (which is also common in adolescents), as well as anxiety and breath-holding spells, which are all common benign adverse events.

WHO's guidelines on recognition and treatment of anaphylaxis is included in Annex C of Mass Measles Immunization Campaigns: Reporting and investigating adverse events following immunization.⁷¹

 vaccine-safety-training.org/tl_files/vs/pdf/AEFI_measles_campaigns.pdf

Distinguishing anaphylaxis from a fainting (vasovagal reaction)

	Fainting	Anaphylaxis
Onset	Usually at the time or soon after injection	Usually some delay between 5–30 minutes after injection
Symptoms		
Skin	Pale, sweaty, cold and clammy	Red, raised, and itchy rash; swollen eyes, face; generalized rash
Respiratory	Normal to deep breaths	Noisy breathing from airways obstruction (wheeze or stridor)
Cardiovascular	Bradycardia	Tachycardia
	Transient hypotension	Hypotension
Gastrointestinal	Nausea/Vomiting	Abdominal cramps
Neurological	Transient loss of consciousness, good response once prone	Loss of consciousness, little response once prone

Using adrenaline to treat anaphylaxis

Adrenaline stimulates the heart and reverses the spasm in the blood vessels and the lung passages, reduces oedema and urticaria, thus countering the anaphylaxis. But this very potent agent can cause irregular heartbeat, heart failure, severe hypertension and tissue necrosis if used inappropriately, although not when treating true anaphylaxis.

The expiry date of adrenaline should be written on the outside of the emergency kit. Adrenaline that has a brown tinge must be discarded.



Key point

- Each vaccinator who is trained in the treatment of anaphylaxis should have rapid access to an emergency kit with adrenaline, and be familiar with its dosage and administration.

Immunizing the immunocompromised

People may be immunocompromised due to HIV/AIDS, congenital immune deficiencies or drug treatments such as chemotherapy for cancer and other conditions and high dose steroids.

Measles vaccination and HIV infection

Measles in children with HIV infection is more often severe and results in higher mortality. Infants born to HIV-infected mothers are at higher risk for measles from 9 months of age.

Measles vaccines, a live attenuated vaccine, are among the most safe and effective vaccines. They should be given routinely to potentially susceptible, asymptomatic, HIV-infected children, adolescents and young adults. Only those with severe clinical symptoms of HIV infection are contraindicated for vaccination. These people often do not develop a protective immune response and are at increased risk of severe complications.

Given the high risk of measles at 9 months of age, WHO recommends that infants infected with HIV receive an early dose of measles vaccine at 6 months of age, followed by a routine dose at 9 months (or according to the routine immunization schedule). Earlier age of vaccination is recommended because HIV-infected infants exhibit a better seroconversion rate at 6 months than at 9 months of age, possibly because of increasing HIV-associated immunodeficiency with age.

HIV-infected infants vaccinated at 6 and 9 months should receive a third measles vaccination (or second opportunity) to prevent the proportion of unprotected children in the population from reaching dangerous levels. Recent studies suggest waning immunity among HIV-infected children, making this recommendation especially important in regions with high HIV prevalence.³¹

The potential risks of live vaccines need to be weighed against the benefits in immunocompromised clients who may be particularly vulnerable to the vaccine-preventable disease. Concerns are that they may not respond adequately to subunit and inactivated vaccination and that LAV vaccines are potentially pathogenic.

Routine childhood vaccinations – except BCG vaccination⁷² – are not contraindicated in children with asymptomatic HIV-infection; however, timing of vaccination may be earlier or more frequent in this subgroup.

In symptomatic HIV/AIDS, LAV vaccines are contraindicated, e.g. measles and yellow fever vaccines should not be given.

BCG vaccination for infants at risk for HIV infection

As in infants symptoms of HIV-infection rarely appear before several months of age, BCG vaccination should be administered to those infants regardless of HIV exposure, especially considering the high endemicity of tuberculosis in populations with high HIV prevalence.

Close follow-up of infants known to be born to HIV-infected mothers and who received BCG at birth is recommended in order to provide early identification and treatment of any BCG-related complication.

In settings with adequate HIV services that could allow for early identification and administration of antiretroviral therapy to HIV-infected children, consideration should be given to delaying BCG vaccination in infants born to mothers known to be infected with HIV until these infants are confirmed to be HIV negative.

Infants who demonstrate signs or reported symptoms of HIV-infection and who are born to women known to have HIV infection should not be vaccinated.

Immunization and pregnancy

Key point

- No evidence exists of risk from vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids.

Influenza



Inactivated influenza vaccine is now recommended for pregnant women in many industrialized countries because of evidence of benefit to the mother and the infant. LAV vaccines pose a theoretical risk to the fetus and are generally contraindicated in pregnant women.

An additional vaccination recommended for pregnant women is seasonal inactivated influenza vaccine. It is considered safe and is recommended for all pregnant women during the influenza season.

This recommendation is motivated not only by the potential severe course of influenza during pregnancy, but also to protect infants against influenza during their vulnerable first months of life⁷³. WHO's Strategic Advisory Committee of WHO (SAGE) has recently discussed seasonal influenza vaccination and recommended pregnant women as the most important risk group for seasonal influenza vaccination. SAGE also supported the recommendation, in no particular order of priority, of vaccination of the following targeted populations:⁷⁷

- Healthcare workers,
- Children 6 to 59 months of age,
- The elderly,
- Those with high-risk conditions.

SAGE Meetings: Information related to influenza immunization:



http://who.int/influenza/vaccines/SAGE_information

Tetanus

Worldwide, all countries are committed to “elimination” of maternal and neonatal tetanus (MNT), i.e. a reduction of neonatal tetanus incidence to below one case per 1000 live births per year in every district. As of 2012, 35 countries have yet to eliminate MNT.

All women of childbearing age, either during pregnancy or outside of pregnancy, should be vaccinated against tetanus to protect themselves and their newborn babies. Neonatal tetanus is almost always fatal and is completely preventable by ensuring that pregnant women are protected through vaccination.

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. This should be assessed on a case-by-case basis.

Tetanus toxoid vaccine example

Tetanus is caused by bacteria that enter the body through open wounds. The bacteria cause an increased tightening of muscles, resulting in spasms, stiffness, and arching of the spine. Ultimately, breathing becomes more difficult, and spasms occur more frequently.

People of all ages can get tetanus. But the disease is particularly common and serious in newborn babies. This is called neonatal tetanus. Most infants who get the disease die. Neonatal tetanus is particularly common in rural areas where most deliveries are at home without adequate sterile procedures. WHO estimated that neonatal tetanus killed about 128,000 babies in 2004.⁷⁴

Tetanus can be prevented by immunizing women of childbearing age with tetanus toxoid, either during pregnancy or before pregnancy. This protects the mother and – through a transfer of tetanus antibodies to the fetus – also her baby.

People who recover from tetanus do not have natural immunity and can be infected again and therefore need to be immunized. To be protected throughout life, an individual should receive three doses of DTP in infancy, followed by a booster containing tetanus toxoid (TT) – at school-entry age (4–7 years), in adolescence (12–15 years), and in early adulthood.

The table below demonstrates the duration of protection against tetanus in women who missed the TT vaccination as infants and then received catch-up immunization during their childbearing years (usually taken to be from 15 to 49 years).

Duration of protection in women after 1–5 doses of TT vaccine

Dose (0.5ml)	When given	Duration of protections
TT1	At first contact with women of childbearing age, or as early as possible in the pregnancy	No protection
TT2	At least 4 weeks after TT1	3 years
TT3	At least 6 months after TT2	5 years
TT4	At least 1 year after TT3	10 years
TT5	At least 1 year after TT4	All childbearing years

Vaccination associations and public concern

Beyond the true vaccine reactions that are well documented and have been illustrated throughout this module, the notion that vaccines could be responsible for serious health problems has led to many allegations and many scientific reviews. Some allegations often based on unfounded rumours or poor science have, at times, profoundly affected the performance of immunization programmes and limited the ability to prevent serious diseases. More on rumours and how to manage can be found in Module 6.



For other health conditions, the scientific evidence available is insufficient to conclude that the association is real, but also insufficient to exclude a link. Systematic study of such conditions can be made difficult as the frequency of a true reaction can be extremely low, or effects would be very mild or they occur many years after vaccination. In recent years, the availability of large computerized databases has allowed testing of many of those potential delayed associations, demonstrating nearly ubiquitously that there is no evidence for a link.

You can learn more about balancing vaccine efficacy and safety of vaccines, and the risks of measles infection versus the risks of the measles vaccine, in Module 1, chapter “*Balancing efficacy and safety*” on page 29.

Summary

You have now completed the learning for this module. These are the main points that you have learned.

- The differences between and the modes of action of live attenuated vaccines, inactivated vaccines, conjugate vaccines, subunit and toxoid vaccines and combined vaccines.
- The correct route of administration for different vaccines.
- The types of vaccine components that exist and their functions.
- The contraindications for vaccination that may present an additional risk.
- The vaccinations that are recommended during pregnancy and the contraindications for pregnant women.
- How to recognize unfounded rumours that affect immunization programmes.

**You have completed Module 2.
We suggest that you test your knowledge!**

ASSESSMENT 2

Question 1

Complete each statement by choosing the correct option from the list below:

1. Live attenuated _____, contains living organisms that have been weakened under laboratory conditions. It stimulates an immune response almost as strong as an infection with _____.
2. Killed antigen vaccines, such as _____, are considered to be very safe and stable and have no risk of _____.
3. Conjugated vaccines such as _____, and pneumococcal conjugate vaccines can provide protection from _____ in infants.
4. Recombinant technology is used to produce protein-based subunit vaccines such as _____, by using other organisms (e.g. yeast cells) to express the desired _____.

- | | |
|---|--|
| a inactivated polio vaccine (IPV) | e wild-type viruses |
| b inducing the disease | f acellular pertussis (aP) vaccines |
| c <i>Haemophilus influenzae</i> type b vaccine (Hib) | g vaccine antigens |
| d common bacterial infections | h measles vaccine |

Question 2

Which of the following statements is correct? Select one or more:

- A. The oral polio vaccine (OPV) never causes paralysis in vaccinated children because the polioviruses in the vaccine have been inactivated.
- B. Live attenuated vaccines may pose a risk to people whose immune system is deficient or suppressed.
- C. Many live attenuated vaccines require strict adherence to the cold chain in order to maintain their efficacy.
- D. Tissue cultures in which live attenuated vaccines are grown may become contaminated with other pathogens.
- E. Live attenuated vaccines induce a weak immune response and therefore always contain adjuvants to enhance the immune response to the vaccine.
- F. Inactivated vaccines are more immunogenic than live attenuated vaccines and a single dose usually produces long-lasting immunity.

Question 3

Which of the following statements is correct? Select one or more:

- A. Live attenuated vaccines include: BCG, OPV, Measles, Rotavirus, whole-cell Pertussis and Yellow fever vaccines.
- B. Osteitis has in the past been reported in connection with certain vaccine batches of BCG vaccines, but now occurs very rarely.
- C. A vaccination with a second dose of a vaccine is contraindicated if a patient previously suffered from anaphylaxis or a severe allergy due to this vaccine or one of its components.
- D. In individuals with symptoms of HIV/AIDS, LAV vaccines are contraindicated.
- E. Conjugate subunit vaccines overcome the problem posed by bacterial pathogens with polysaccharide capsules that protect them from host defences.

Question 4

Complete each statement by choosing the correct option from the list below:

1. Aluminium salts used in vaccines as _____ can occasionally cause a sterile abscess at the injection site.
2. The effectiveness of some live attenuated vaccines can be maintained during storage by the addition of _____.
3. The addition of trace amounts of _____ prevents bacterial contamination of tissue culture cells in which vaccine viruses are grown.
4. Thiomersal is the most common of the _____ used to prevent bacterial and fungal growth in multidose vaccines.
5. The polioviruses used in manufacturing IPV are inactivated by treatment with _____.
6. The immune response to some vaccines is enhanced by the addition of _____.

- | | |
|-----------------------|------------------------|
| a antibiotics | d preservatives |
| b formaldehyde | e stabilizers |
| c adjuvants | |

Question 5

Complete each statement by choosing the correct option from the list below:

1. Vaccines that contain aluminium salts must be administered by _____ injection to reduce the risk of nodule/abscess formation.
2. BCG is the only routine EPI vaccine given to infants by _____ injection.
3. Current rotavirus vaccine should only be given by the _____ route.
4. Combined diphtheria-tetanus-pertussis vaccines should only be given by the _____ route.
5. A needle-free method of giving flu vaccine is administration by _____.
6. Measles vaccine should be injected into the _____ layer.

- | | |
|---------------------------|------------------------|
| a oral | d intradermal |
| b intranasal spray | e intramuscular |
| c subcutaneous | |

You have completed Assessment 2.

Assessment solutions

Question 1

Correct answers:

1. Live attenuated **measles vaccine**, contains living organisms that have been weakened under laboratory conditions. It stimulates an immune response almost as strong as an infection with **wild-type viruses**.
2. Killed antigen vaccines, such as **inactivated polio vaccine (IPV)**, are considered to be very safe and stable and have no risk of **inducing the disease**.
3. Conjugated vaccines such as ***Haemophilus influenzae* type b vaccine (Hib)** and pneumococcal conjugate vaccines can provide protection from **common bacterial infections** in infants.
4. Recombinant technology is used to produce protein-based subunit vaccines such as **acellular pertussis (aP) vaccine**, by using other organisms (e.g. yeast cells) to express the desired **vaccine antigens**.

Question 2

Answers B, C, and D are correct.

Answer A: Polio is among the five vaccines that are recommended by WHO are produced using Live attenuated vaccine technology: Tuberculosis (BCG), Oral Polio Vaccine, Measles, Rotavirus, Yellow Fever.

Answer E: Live attenuated vaccines stimulate an excellent immune response. Adjuvants are therefore not critical elements of them.

(To revise information on Live attenuated vaccines go to the “*Live attenuated vaccines*” on page 41).

Question 3

Answers B, C, D, and E are correct:

Answer A: whole-cell Pertussis is an inactivated vaccine. More information on the “*Inactivated whole-cell vaccines*” on page 44.

Question 4

Correct answers:

1. Aluminium salts used in vaccines as **adjuvants** can occasionally cause a sterile abscess at the injection site.
2. The effectiveness of some live attenuated vaccines can be maintained during storage by the addition of **stabilizers**.
3. The addition of trace amounts of **antibiotics** prevents bacterial contamination of tissue culture cells in which vaccine viruses are grown.
4. Thiomersal is the most common of the **preservatives** used to prevent bacterial and fungal growth in multidose vaccines.
5. The polioviruses used in manufacturing IPV are inactivated by treatment with **formaldehyde**.
6. The immune response to some vaccines is enhanced by the addition of **adjuvants**.

Question 5

Please note that the vaccine must be given by the same route as in the clinical trials that led to its approval.

Correct answers:

1. Vaccines that contain aluminium salts must be administered by **intramuscular** injection to reduce the risk of nodule/abscess formation.
2. BCG is the only routine EPI vaccine given to infants by **intra-dermal** injection.
3. Current rotavirus vaccine should only be given by the **oral** route.
4. Combined diphtheria-tetanus-pertussis vaccines should only be given by the **intramuscular** route.
5. A needle-free method of giving flu vaccine is administration by **intranasal spray**.
6. Measles vaccine should be injected into the **subcutaneous** layer.

MODULE 3

Adverse events following immunization

Overview

Under recommended conditions, all vaccines used in national immunization programmes are safe and effective if used correctly. In practice, however, no vaccine is completely risk-free and adverse events can occasionally result after an immunization.

Adverse events can range from minor side-effects to more severe reactions. They can be a cause of public concerns about vaccine safety. To understand a specific event and to be able to respond appropriately, there are several questions that you need to answer:

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

This module will help you to answer these questions. You will look at the main types of adverse events and the situations in which they may occur. You will also be introduced to the challenges and opportunities of mass vaccination campaigns. Because of the nature of these campaigns, adverse events may be more noticeable.

Module outcomes

By the end of this module you should be able to:

- 1 Define the main types of adverse events following immunization (AEFIs),
- 2 Differentiate between a reaction related to the vaccine itself, to the vaccination procedure (immunization error), or to coincidental events that are not linked to the vaccine,
- 3 Differentiate between minor and severe vaccine reactions,
- 4 Describe potential underlying causes for each type of AEFI, and understand the link between the AEFI and its cause,
- 5 Summarize the expected incidence of the different types of AEFI.

Classification of AEFIs

Although all vaccines used in NIPs are safe and effective if used correctly, no vaccine is completely risk-free and adverse events will occasionally result after an immunization.

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

AEFIs are grouped into five categories.

Vaccine product-related reaction
<p>An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.</p> <p>Example: Extensive limb swelling following DTP vaccination.</p>
Vaccine quality defect-related reaction
<p>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.</p> <p>Example: Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio.</p>
Immunization error-related reaction
<p>An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.</p> <p>Example: Transmission of infection by contaminated multidose vial.</p>
Immunization anxiety-related reaction
<p>An AEFI arising from anxiety about the immunization.</p> <p>Example: Vasovagal syncope in an adolescent during/following vaccination.</p>
Coincidental event
<p>An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.</p> <p>Example: A fever occurs at the time of the vaccination (temporal association) but is in fact caused by malaria.</p> <p>Coincidental events reflect the natural occurrence of health problems in the community with common problems being frequently reported.</p>

Serious event

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 event

Severe is used to describe the intensity of a specific event (as in *mild*, *moderate* or *severe*); the event itself, however, may be of relatively minor medical significance (e.g. Fever is a common relatively minor medical event, but according to its *severity* it can be graded as *mild* fever or *moderate* fever).

Adverse events following immunization (AEFI)

The pandemic influenza A (H1N1) vaccine was an example of where the AEFI classification was used to describe events.

The European Medicines Agency (EMA) publication "Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine" states that there should be "protocols in place [...] to ensure that immunogenicity, effectiveness and safety of the final pandemic vaccine are adequately documented during use in the field (i.e., during the pandemic), since there will be only limited immunogenicity and safety data and no efficacy data at the time of licensing". This publication directed health workers to prioritize reports of the following adverse events:²⁵

- Fatal or life-threatening adverse reactions,
- Serious unexpected adverse reactions. This refers to the classification of AEFIs that is discussed in more detail later in this module,
- AEFI: neuritis, convulsion, anaphylaxis, syncope, encephalitis, thrombocytopenia, vasculitis, Guillain-Barré syndrome and Bell's palsy.

For each of the above AEFI, standard case definitions from the Brighton Collaboration were used if available. This helped compare data from different countries.

The Brighton Collaboration website:

 www.brightoncollaboration.org

! Key point

- It is important to note that 'serious' and 'severe' are often used as interchangeable terms but they are not.

? Question 1*

True or false?

An anaphylactic reaction following immunization that results in the death of the patient is considered a serious event.

* The answer to all questions can be found at the end of this manual (page 202).

Vaccine reactions

- ⊖ Vaccine product-related reaction ⊖
- ⊖ Vaccine quality defect-related reaction ⊖
- ⊖ Immunization error-related reaction ⊖
- ⊖ Immunization anxiety-related reaction ⊖
- ⊖ Coincidental event ⊖

A vaccine reaction is an individual’s response to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly. From the 5 causes for AEFI from the previous page, vaccine reactions comprise *vaccine product-related reactions* and *vaccine quality defect-related reactions*.

Vaccine reactions can be classified into two groups:

<i>Minor reactions</i>	<i>Severe reactions</i>
<ul style="list-style-type: none"> ■ Usually occur within a few hours of injection. ■ Resolve after short period of time and pose little danger. ■ Local (includes pain, swelling or redness at the site of injection). ■ Systemic (includes fever, malaise, muscle pain, headache or loss of appetite). 	<ul style="list-style-type: none"> ■ Usually do not result in long-term problems. ■ Can be disabling. ■ Are rarely life threatening. ■ Include seizures and allergic reactions caused by the body’s reaction to a particular component in a vaccine.

Severe reactions is a term including serious reactions but also including other severe reactions.

! Key point

- There is low public tolerance of vaccine adverse reactions. Vaccines are therefore only licensed when the frequency of severe reactions is very rare and when only minor, self-limiting reactions are reported.

Minor vaccine reactions

Ideally vaccines will cause no, or only minor (i.e. non-severe) adverse reactions.

Vaccination induces immunity by causing the recipient’s immune system to react to antigens contained in the vaccine. Local and systemic reactions such as pain or fever can occur as part of the immune response. In addition, other vaccine components (e.g. adjuvants, stabilizers, and preservatives) can trigger reactions. A successful vaccine keeps even minor reactions to a minimum while producing the best possible immune response.

The frequency of vaccine reactions likely to be observed with some of the most commonly used vaccines, and their treatments, are listed below. These reactions typically occur within a day or two of immunization (except for rash reactions after measles vaccine, which can arise up to 6 to 12 days after immunization) and persist from one to a few days.²⁶



Local reaction: Swelling/redness at the site of injection

Common, minor vaccine reactions and treatment

Vaccine	Local reactions	Systemic reactions	
	(pain, swelling, redness)	Fever > 38°C	Irritability, malaise and systemic symptoms
BCG^a	90–95%	–	–
Hepatitis B	Adults up to 15% Children up to 5%	1–6%	–
Hib	5–15%	2–10%	
Measles/MR/ MMR	~ 10%	5–15%	5% (Rash)
OPV	None	Less than 1%	Less than 1% ^b
Pertussis (DTwP)^c	up to 50%	up to 50%	up to 55%
Pneumococcal conjugate^e	~ 20%	~ 20%	~ 20%
Tetanus/ DT/aTd	~ 10% ^d	~ 10%	~ 25%
Treatment	<ul style="list-style-type: none"> • Cold cloth at injection site • Paracetamol^f 	<ul style="list-style-type: none"> • Give extra oral fluids • Wear cool clothing • Tepid sponge or bath • Paracetamol^f 	<ul style="list-style-type: none"> • Give extra oral fluids

- a. Local reactogenicity varies from one vaccine brand to another, depending on the strain and the number of viable antigen in the vaccine.
- b. Diarrhoea, Headache and/or muscle pains.
- c. When compared with whole cell pertussis (DTwP) vaccine, acellular pertussis (DTaP) vaccine rates are lower.
- d. Rate of local reactions are likely to increase with booster doses, up to 50–85%.
- e. Source: <http://www.cdc.gov/vaccines/hcp/acip-recs/>
- f. Paracetamol dose: up to 15mg/kg every 6–8 hours, maximum of 4 doses in 24 hours.

Severe vaccine reactions

Severe vaccine reactions include among others seizures, thrombocytopenia, hypotonic hyporesponsive episodes (HHE) and prolonged crying, which all need to be reported. Most severe vaccine reactions do not lead to long-term problems. Anaphylaxis, while potentially fatal, is treatable without leaving any long-term effects.

**Key point**

Severe allergic reactions (e.g. anaphylaxis) can be life threatening. Health workers who give vaccinations should know the signs of allergic reactions and be prepared to take immediate action.

Polio vaccine example



A well-documented example of a vaccine-associated adverse reaction is vaccine associated paralytic poliomyelitis (VAPP). This is a very rare event that occurs in about two to four in every million doses of oral polio vaccine (OPV) given.²⁹ A live viral vaccine, OPV contains an attenuated (weakened) version of the disease-causing poliomyelitis virus. The vaccine is given orally and causes a mild infection that creates immunity against the wild poliovirus. However, in very rare instances, OPV can cause paralysis (VAPP), either in the vaccinated child, or in a close contact. VAPP can be proven by a laboratory test that detects vaccine virus in a clinical case of polio.

When there are cases of poliomyelitis in the population, the very rare risk of VAPP is very much less than the risk of acquiring polio by natural infection. However, in countries where there are no longer cases of wild polio, VAPP can become a greater risk than wild polio. In many countries where wild polio has been eliminated, programmes have switched to using inactivated (killed) polio vaccine (IPV), a more expensive vaccine that does not carry the risk of VAPP, but must be injected by a trained health worker.

Severe vaccine reactions, onset interval, and rates associated with selected childhood vaccines

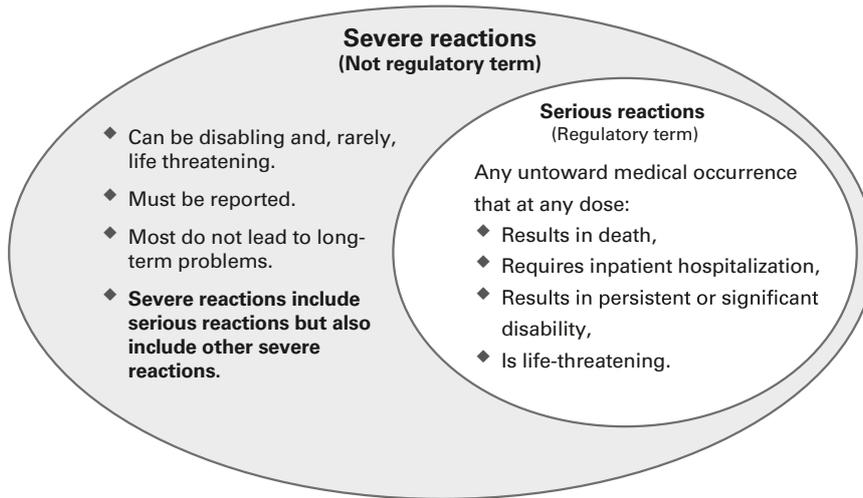
Vaccine	Reaction ^a	Onset interval ²⁶	Frequency per doses given
BCG ²⁸	Fatal dissemination of BCG infection	1–12 months	0.19–1.56/1,000,000
OPV ²⁹	Vaccine associated paralytic poliomyelitis (VAPP) ^b	4–30 days	2–4/1,000,000
DTwP ³⁰	Prolonged crying and seizures ^c	0–24 hours	< 1/100
	HHE	0–24 hours	< 1/1,000–2/1,000
Measles ³¹	Febrile seizures	6–12 days	1/3,000
	Thrombocytopenia	15–35 days	1/30,000
	Anaphylaxis	1 hour	1/100,000

- Reactions (except anaphylaxis) do not occur if already immune (90% of those receiving a second dose); children >6 years unlikely to have febrile seizures.
- VAPP risk higher for first dose (1 in 750,000 compared with 1 in 5.1 million for subsequent doses), and for adults and immunocompromised patients.
- Seizures are mostly febrile. The risk of having a seizure depends on the persons age. The risk is much lower in infants < 4 months of age.

The difference between *serious* and *severe* adverse events

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

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



Immunization error-related reaction

Key point

- Immunization errors often constitute the greatest proportion of AEFIs. They can include deaths associated with the reconstitution of vaccines with an incorrect diluent or a drug (e.g. insulin).

— Vaccine product-related reaction —

— Vaccine quality defect-related reaction —

— **Immunization error-related reaction** —

— Immunization anxiety-related reaction —

— Coincidental event —

Immunization errors result from errors in vaccine preparation, handling, storage or administration. They are preventable and detract from the overall benefit of the immunization programme. The identification and correction of these incorrect immunization practices are of great importance.

Immunization errors can result in a cluster of events, defined as two or more cases of the same adverse event related in time, place or vaccine administered. These clusters are usually associated with a particular provider or health facility, or a vial of vaccine that has been inappropriately prepared or contaminated. Immunization errors can also affect many vials, for example, freezing vaccine during transport may result in an increase in local reactions.

Examples of immunization errors and possible AEFIs

Immunization error	Possible AEFI
<p>Non-sterile injection</p> <ul style="list-style-type: none"> • Reuse of disposable syringe or needle leading to contamination of the vial, especially in multi-dose vials, • Improperly sterilized syringe or needle, • Contaminated vaccine or diluent. 	<ul style="list-style-type: none"> • Local injection site reactions (e.g., abscess, swelling, cellulitis, induration), • Sepsis, • Toxic shock syndrome, • Blood-borne transmission of disease, e.g., hepatitis B, HIV, • Death
<p>Reconstitution error</p> <ul style="list-style-type: none"> • Inadequate shaking of vaccine, • Reconstitution with incorrect diluent, • Drug substituted for vaccine or diluent, • Reuse of reconstituted vaccine at subsequent session. 	<ul style="list-style-type: none"> • Local abscess, • Vaccine ineffective*, • Effect of drug, e.g., insulin, oxytocin, muscle relaxants, • Toxic shock syndrome, • Death.
<p>Injection at incorrect site</p> <ul style="list-style-type: none"> • BCG given subcutaneously, • DTP/DT/TT too superficial, • Injection into buttocks. 	<ul style="list-style-type: none"> • Local reaction or abscess or other local reaction, • Local reaction or abscess or other local reaction, • Sciatic nerve damage.
<p>Vaccine transported/stored incorrectly</p> <ul style="list-style-type: none"> • Freezing vaccine during transport, • Failure to keep vaccine in cold chain, exposing to excessive heat or cold. 	<ul style="list-style-type: none"> • Increased local reaction from frozen vaccine, • Ineffective vaccine*
<p>Contraindication ignored</p> <ul style="list-style-type: none"> • Vaccination staff ignoring or not becoming familiar with contraindications for a vaccine. 	<p>Avoidable severe reaction</p>



Question 2**

What immunization error can most likely occur if vaccines are kept in the same refrigerator as other drugs?

- A. The vaccine could be stored incorrectly.
- B. Contraindication could be ignored.
- C. A reconstitution error might occur.
- D. The injection may be non-sterile.
- E. The injection may occur at the wrong site.

It is vital that health workers or local vaccinators are trained to store and handle vaccines properly, reconstitute and administer vaccinations correctly, and have the right equipment and materials to do their job.

In WHO's Immunization in Practice, Module 6⁵⁸ entitled "Holding an immunization session" includes the correct technique for giving each vaccine.

 http://vaccine-safety-training.org/tl_files/vs/pdf/Module6_IIP.pdf

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

** The answer to all questions can be found at the end of this manual (page 202).

Immunization anxiety-related reactions

- Vaccine product-related reaction
- Vaccine quality defect-related reaction
- Immunization error-related reaction
- **Immunization anxiety-related reaction**
- Coincidental event

Individuals can react in anticipation to and as a result of an injection of any kind. These reactions are not related to the vaccine, but to fear of the injection. There are four reactions you may encounter.²⁶

Fainting

Fainting is relatively common, but usually only affects older children and adults. Fainting does not require any management beyond giving the injection while patients are seated (to avoid injury caused by falling) and placing the patient in a recumbent position after the injection.

Hyperventilation

Hyperventilation as a result of anxiety about immunization can cause light-headedness, dizziness, tingling around the mouth and in the hands.

Vomiting

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

Convulsions

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

Coincidental events

- Vaccine product-related reaction
- Vaccine quality defect-related reaction
- Immunization error-related reaction
- Immunization anxiety-related reaction
- **Coincidental event**

Coincidental events occur after a vaccination has been given but are not caused by the vaccine or its administration.

Vaccinations are normally scheduled in infancy and early childhood, when illnesses are common and congenital or early neurological conditions become apparent. Coincidental events are inevitable when vaccinating children in these age groups, especially

during a mass campaign. Applying the normal incidence of disease and death in these age groups along with the coverage and timing of immunizations allows estimation of the expected numbers of coincidental events after immunization.

Estimates from the WHO Regional Office for the Western Pacific are presented in the table. For example, in Australia, each year there are likely to be 11 coincidental infant deaths the day after immunization.

Influenza A (H1N1) vaccine example

In response to the pandemic influenza A H1N1 strain, many countries had engaged in mass immunization against flu in 2009. Awareness of the expected background rates of possible adverse events was estimated crucial to the assessment of possible vaccine adverse reactions.³⁴

Highly visible health conditions, such as Guillain-Barré syndrome, spontaneous abortion and death, can occur in close proximity to vaccination in substantial numbers when large populations are vaccinated.

For example, for every 10 million individuals vaccinated in the United Kingdom, 21.5 cases of Guillain-Barré syndrome and 5.75 sudden deaths were expected to occur as unrelated coincidental events within 6 weeks of vaccination.³⁴

Careful interpretation of vaccine safety signals was crucial to detect real reactions to vaccine and to ensure that coincidental events were not caused by vaccination and did not affect public confidence in the vaccine. Experts compared background incidence rates of the condition with the rate following a vaccination programme to be able to monitor potential increases of events.

Immediate investigation of a severe adverse event attributed to a vaccine, but not causally related to it, is critical in order to:

- respond to a community's concern about vaccine safety,
- maintain public confidence in immunization.

Calculating the expected rate of an adverse event may be helpful during its investigation. Knowing the background rate of this adverse event enables the investigator to compare expected and post-vaccination rates of the event. An increase or non-increase of the post-vaccination rate may give a clue on whether the event is actually caused by the vaccine. With the background mortality of the AEFI that coincidentally follow vaccination is key when responding to AEFI reports.²⁶ Further information on this subject can be found in this course on the page *Rates of adverse reactions*.⁴⁷

Expected coincidental deaths following DTP vaccination in selected countries²⁶

Country	Infant Mortality Rate per 1000 live births (IMR)	Number of births per year (N)	Number of infant death during year in		
			Month after immunization	Week after immunization	Day after immunization
			$= (IMR \times N / 12) \times nv \times ppv$	$= (IMR \times N / 52) \times nv \times ppv$	$= (IMR \times N / 365) \times nv \times ppv$
Australia	5	267,000	300	69	10
Cambodia	69	361,000	5,605	1,293	185
China	18	18,134,000	73,443	16,948	2,421
Japan	3	1,034,000	698	161	23
Laos	48	170,000	1,836	424	61
New Zealand	5	58,000	65	15	2
Philippines	26	2,236,000	13,081	3,019	431

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

nv = number of immunization doses: assumed here to be three dose schedule; 3.

ppv = proportion of population vaccinated: assumed here to be 90% for each dose; 0.9.

Additional information

To support the analysis of events, WHO is developing vaccine reaction rates information sheets. These include observed rates of vaccine reaction found in scientific literature.

WHO Information sheets on observed rates of vaccine reactions:

 http://vaccine-safety-training.org/tl_files/vs/pdf/VaccRate-Info-sheet-Poster.pdf

? Question 3*

Based on the data in the table, how many infant deaths would you expect to occur coincidentally (i.e. not linked to the vaccine) in China the day after immunization with DTP?

- A. 2,421
- B. 23
- C. 16,948
- D. 185

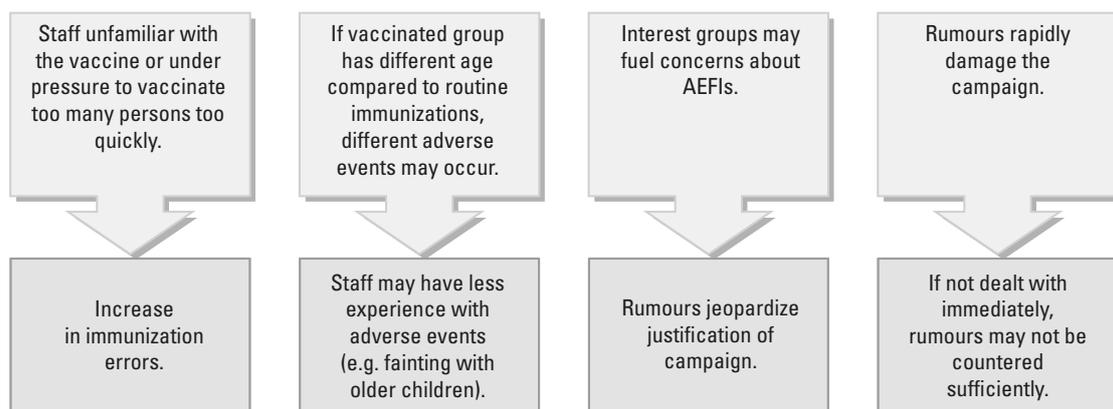
! Key point

Data banks that can provide locally relevant background rates of disease incidence are essential to aid assessment of vaccine safety and to determine whether AEFIs are causally related or coincidental.

Mass vaccination campaigns

A mass vaccination campaign is a particular challenge to AEFI surveillance. It involves administration of vaccine doses to a large population over a short period of time. As a result, adverse events may be more noticeable to staff and to the public.

Common safety issues or concerns in vaccination campaigns include the following points.²⁶



A campaign is an opportunity to strengthen or establish AEFI surveillance. National Immunization Programmes (NIP) are a vital part of surveillance of AEFI, particularly with regards to detection and investigation of AEFI in the field during a mass vaccination campaign.

* The answer to all questions can be found at the end of this manual (page 202).

Example Japanese encephalitis campaign

In 2006, inaccurate media reports about the Japanese encephalitis (JE) vaccine used in India's mass vaccination campaigns nearly derailed an immunization programme that aimed to protect millions of children and adolescents.

The Government of India responded promptly to these unfounded reports. It convened an independent expert committee to investigate AEFIs and address any risks associated with vaccine administration. The expert committee conducted an extensive investigation of 504 adverse events reported through the AEFI system (including 22 deaths) and 29 additional cases identified through active case-finding. It found no link between the vaccine and serious illnesses or deaths. The primary recommendation of the committee's final report states: "No direct causality has been established between the reported illnesses and the JE vaccine. Therefore, no stricture on the further use of the vaccine is warranted."³⁷

The expert committee's findings were presented at key global health events, including the Global Vaccine Research Forum and a meeting of WHO's Global Advisory Committee on Vaccine Safety.³⁸

Understanding background mortality in the context of deaths temporally associated with vaccination is key when responding to AEFI reports: The 22 deaths among children of the required age vaccinated during the campaign was equivalent to a fatality rate of 0.24 deaths per 100,000. The background mortality in the same age group is actually much greater at 8.6 per 100,000. The 22 deaths reported therefore do not reflect an excess mortality caused by the vaccine.

Key point

- A campaign is an opportunity for community outreach and education about local diseases and the vaccinations used to prevent them.

Adverse events and their effects during a campaign can be minimized by proper planning aimed to reduce immunization errors. Components of such planning include thorough training of staff, monitoring and responding to AEFIs, and engaging the community. It can also be helpful to train staff on how to respectfully treat persons being immunized and their family. This may limit the potential for negative publicity from an AEFI.

To assist immunization managers prepare and plan for safety issues associated with immunization campaigns, WHO provides a comprehensive checklist in an aide-memoire:



http://vaccine-safety-training.org/tl_files/vs/pdf/campaigns.pdf

Rates of adverse vaccine reactions

Part of the work of health professionals and regulatory officials in immunization programmes is to:

- Anticipate and/or evaluate AEFIs associated with specific vaccines,
- Compare reported AEFIs in their own jurisdictions with 'expected' adverse events in vaccinated and unvaccinated individuals,
- Facilitate the investigation and response to serious AEFIs.

WHO vaccine reaction rates information sheets:



http://who.int/vaccine_safety/initiative/tools/vaccinfosheets/

However, one of the main challenges in surveillance of AEFIs is to differentiate coincidental events from events that are caused by a reaction to a vaccine or its components.

To help strengthen the capacity to introduce vaccines in Member States, WHO has published *WHO Information Sheets on Observed Rates of Vaccine Reactions* online to provide details on selected vaccines that are relevant to the analysis of reported events. These cover, for example, vaccines such as Anthrax, BCG, Hep A, Hep B, Hib, HPV, Influenza, Pneumococcal, Rabies, Varicella Zoster.

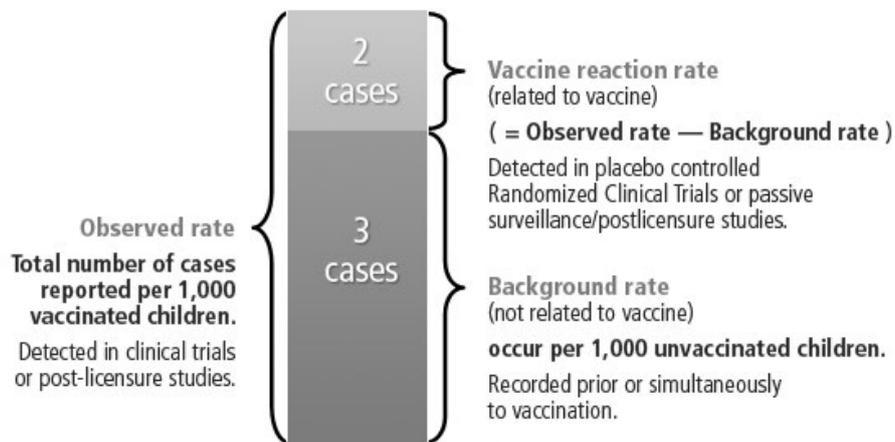


Key point

- Observing the rate of an adverse event in the vaccinated population and comparing it with the rate of this event among the unvaccinated population can help to distinguish genuine vaccine reactions.

The following graphic shows, how comparing the background rate with the observed rate of an event can help to determine the vaccine reaction rate (i.e. the rate of events that are actually caused by the vaccine).

Example: Fever following vaccination



Terminology	How is this measured	Example
Background rate	Background rates can be determined in a population prior to the introduction of a new vaccine or simultaneously in non-vaccinated people.	If we measured the temperatures of a population of 1,000 unvaccinated children during one week, some children would present a fever (defined as >38°C) during the time of observation (e.g., infections). For example, a rate of 2 cases of fever per 1,000 children per week.
Observed (reported) rate	The observed rate can be measured in pre-licensure clinical trials or post-licensure studies.	If we observe the same population of 1,000 children but we now vaccinate all children and measure their temperatures daily there will be greater rate of fever. Thus, the rate of fever may increase to 5/1,000 children per week, with the increase concentrated in the 72 hours that follow vaccination.
Vaccine reaction rate (attributable rate)	Randomized clinical trials which are placebo controlled. Post-licensure studies – passive surveillance.	Thus, the vaccine attributable rate of fever will be 3/1,000 vaccinated children (that is the observed rate minus the background rate).

Comparing observed with “expected” rates of adverse events

If the background rate of a particular adverse event is not known in a community (as is often the case), you will need to compare the observed rate in your population with the ‘expected rate’ published by the vaccine regulatory authorities. For example, this information, from WHO, shows the expected rates of AEFIs following some childhood vaccines:

Expected rates of AEFIs following some childhood vaccines

Vaccine	Estimated rate of severe reactions
BCG	1 in 1,000 to 1 in 50,000 doses
OPV (oral polio vaccine)	1 in 2–3 million doses (or 1 in 750,000 doses for the first dose)
Measles	1 in 1 million doses
DTP	1 in 750,000 doses



Question 4*

Imagine that rumours begin to circulate about a vaccine when cases of convulsions following immunization occur amongst vaccinated infants. The background rate of convulsions in this population is 1:1,000 infants. The observed rate in vaccinated infants is 1.2:1,000. What is the vaccine attributable rate derived from these figures?

- A. 2 additional cases of convulsions in every 1,000 vaccinations, compared with the background rate.
- B. 2 additional cases in every 10,000 vaccinations, compared with the background rate.
- C. 1.2 additional cases in every 1,000 vaccinations, compared with the background rate.
- D. 1.2 additional cases in every 10,000 vaccinations, compared with the background rate.

Other factors to consider when comparing rates of AEFIs

Keep in mind the other confounding factors that may influence the comparison of rates of adverse events.

A confounding factor is anything that is coincidentally associated with an event (in this case, an AEFI), which may mislead the investigator into wrongly concluding that the factor is influencing the rate of an adverse vaccine reaction. Here are some factors to consider when comparing one observed AEFI rate with another.

Vaccines	Although a vaccine may have the same antigens, different manufacturers may produce vaccines (or ‘lots’ of the same vaccine) that differ substantially in their composition, including the presence of an adjuvant or other components. These variations result in vaccines with different reactogenicity (the ability to cause vaccine reactions), which in turn affects the comparison of their vaccine attributable rates.
Age	The same vaccine given to different age groups may result in different vaccine-attributable rates. For example, MMR vaccine given to infants may cause febrile convulsions. This symptom does, however, not occur in adolescents who are given the same vaccine.

* The answer to all questions can be found at the end of this manual (page 202).

Vaccine doses	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 this same vaccine given as a booster dose.
Case definitions	Adverse event may be defined differently in research studies that do not stick to the same case definition. Not using standardized case definitions may consequently affect the estimation of the AEFI rate.
Surveillance methods	The way that surveillance data is collected may alter the rate. For example, surveillance data may be collected actively or passively, using pre- or post-licensure clinical trials, with or without randomization and placebo controls.
Background rate	The background rate of certain events may differ between communities. This can influence the observed rate even though the vaccine attributable rate is the same in both communities. For example, reports of death post-vaccination may be higher in a country that has a higher background rate of deaths due to coincidental infection.

Summary

You have now completed the learning for this module. These are the main points that you have learned.

- The characteristics of the five types of AEFI are Vaccine product-related reaction, Vaccine quality defect-related reaction, Immunization error-related reaction, Immunization anxiety-related reaction, Coincidental event.
- The causes of the five types of AEFI and the practices that can minimize their occurrence.
- Mass vaccination campaigns can lead to an increase in immunization errors, for example, because of staff inexperience in vaccinating a wider age group, and to the spread of unfounded rumours that may damage the campaign.
- The importance of comparing background rates of adverse events with rates of vaccine-attributable reactions and taking account of factors that may confound the results of an AEFI investigation.

**You have completed Module 3.
We suggest that you test your knowledge!**

ASSESSMENT 3

Question 1

**Which of the following AEFIs would be classified as a 'severe reaction'?
Select one or more:**

- A. Vomiting, 5 minutes after receiving a BCG vaccination.
- B. Fainting, 5 minutes after receiving a DTP vaccination.
- C. Anaphylaxis, 5 minutes after receiving an Influenza-A vaccination.
- D. Febrile seizures, 4 days after a measles vaccination.
- E. Loss of appetite, 4 days after BCG vaccination.

Question 2

Which of the following onset intervals of severe adverse events following immunization is probably not due to the given vaccine? Select one or more:

- A. Vaccine-associated paralytic poliomyelitis (VAPP) occurring 4–30 days after OPV.
- B. Febrile seizures occurring 6–12 days following measles vaccination.
- C. Thrombocytopenia occurring 15–35 days after measles vaccine.
- D. Anaphylaxis occurring 2–3 days after MMR vaccination.
- E. Prolonged crying for 0–24 hours after DTP vaccination.

Question 3

For each of the following descriptions of an AEFI, decide what is the most likely cause by choosing the correct option from the list below:

A. The rate of thrombocytopenia following immunization with measles was found to be slightly higher than the background rate in the equivalent unvaccinated population.

B. Several 13-year-old girls reported feeling sick and two fainted soon after being vaccinated against human papilloma virus (HPV) in a mass vaccination campaign at their school. All the affected girls recovered without further ill effects.

C. Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio.

D. Adverse reactions occurred after a nurse in charge of an outreach vaccination clinic used a vial of measles vaccine which she had reconstituted the previous day.

E. A 10-week-old infant developed a high fever within 24 hours of receiving oral polio vaccine (OPV). Malaria was diagnosed in the infant shortly thereafter.

- a Immunization error-related reaction
- b Vaccine product-related reaction
- c Immunization anxiety-related reaction
- d Coincidental event
- e Vaccine quality related reaction

Question 4

Which of the following are common safety issues or concerns in vaccination campaigns? Select one or more:

- A. Staff who are unfamiliar with the given vaccine and are under pressure to vaccinate many children in a short period of time.
- B. Different age groups receiving vaccines.
- C. Rumours spread by anti-vaccine lobbies. Nutritional status of the people/children receiving the vaccine.
- D. The nutritional status of a vaccinee.

Question 5

The country of Rubovia has a population of 60 million and the annual incidence of Guillain Barre syndrome is 2/100,000 individuals.

In an immunization campaign, 5 million adults were immunised with an influenza-A vaccine. In the 8 weeks following immunization 26 of them developed Guillain Barre syndrome.

Calculate the vaccine-attributable rate of Guillain Barre syndrome per 100,000 immunised individuals.

Select one:

- A. 0.2
- B. 26
- C. 10
- D. 16
- E. 1

You have completed Assessment 3.

Assessment solutions

Question 1

Answers C and D are correct.

Minor reactions usually occur within a few hours of injection, resolve after a short period of time and pose little danger. These reactions are often local (including pain, swelling or redness at the site of injection) or systemic (including fever, malaise, muscle pain, headache or loss of appetite).

Severe reactions usually do not result in long-term problems, but can be disabling and, rarely, life threatening. These include, for example, seizures and allergic reactions caused by the body's reaction to a particular component in a vaccine.

Further information go to the chapter "Classification of AEFIs" on page 69.

Question 2

Answer D is incorrect.

Anaphylaxis has an onset interval of up to 1 hour following vaccination.

See the table "Severe vaccine reactions, onset interval, and rates associated with selected childhood vaccines" on page 73.

Question 3

Correct answers:

- A. Vaccine product related reaction.
- B. Immunization anxiety related reaction.
- C. Vaccine quality related reaction.
- D. Immunization error related reaction.
- E. Coincidental event.

Further information go to the chapter "*Classification of AEFIs*" on page 69.

Question 4

Answers A, B and C are correct.

Common safety issues or concerns in vaccination campaigns include the following points:

- A. Staff who are unfamiliar with the given vaccine or mass campaign situations, or who are under pressure to vaccinate many children quickly may cause an increase in adverse events caused by immunization errors.

- B. A wider age group may be targeted than for routine immunizations. Staff may have less experience with adverse events that occur in this age group (e.g. fainting among older children and teenagers).
- C. Some sectors may antagonize against the campaign, for a variety of reasons. This may add fuel to concerns about AEFI during the efforts to justify the vaccination campaign. Rumours may spread rapidly and damage the campaign before there is a chance to counter them.
- D. The nutritional status of a vaccinee is usually not a common issue with mass vaccination campaigns.

For more information go to the chapter “*Mass vaccination campaigns*” on page 78.

Question 5

Answer A is correct.

The expected incidence of Gullain Barre syndrome in a population of 5million people in an 8 week period is:

$$5,000,000 \times 2/100,000 \times 8/50 = 16$$

The number observed is 26, therefore the excess is $26 - 16 = 10$

The excess incidence is $10/5,000,000 = 0.2/100,000$ vaccinated individuals.

The correct answer is: 0.2.

MODULE 4

Surveillance

Overview

Pharmacovigilance is the practice of detecting, assessing, understanding, responding and preventing adverse drug reactions, including reactions to vaccines. It is now an integral part of the regulation of drug and vaccine safety. Surveillance systems exist at national and international levels to ensure effective monitoring and prompt actions in response to AEFIs.

Pharmacovigilance requires that incidents of adverse events are followed up in the correct way. Some adverse events need to be reported and/or investigated, and you will need to know which to report, how and to whom. Causality assessment procedures also need to be carried out effectively.

This module introduces you to the concept of pharmacovigilance and describes national and international surveillance systems. It helps you to assess how to report an AEFI in the correct way and explains the procedure of causality assessment. Finally, you will look at the subject of risk/benefit assessment, including the factors that influence the balance between risks and benefits of vaccines, risk evaluation and options analysis.

Module outcomes

By the end of this module you should be able to:

- 1 Describe the basic principles of pharmacovigilance and the special considerations that apply to vaccination programmes,
- 2 Use AEFI case definitions to evaluate which AEFIs should be detected and reported to the National regulatory authority (NRA) or its equivalent,
- 3 Describe the principles of risk-benefit analysis relative to the protective effect of immunization and the importance of causality assessments to evaluate possible links between AEFIs and a vaccine or vaccine lot,
- 4 Explain how investigation of AEFI reports and vaccine testing can contribute to surveillance that ensures vaccine safety.

Pharmacovigilance

Definition

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, response and prevention of adverse drug reactions (ADRs) and other potential medicine-related problems – including adverse events following immunization.

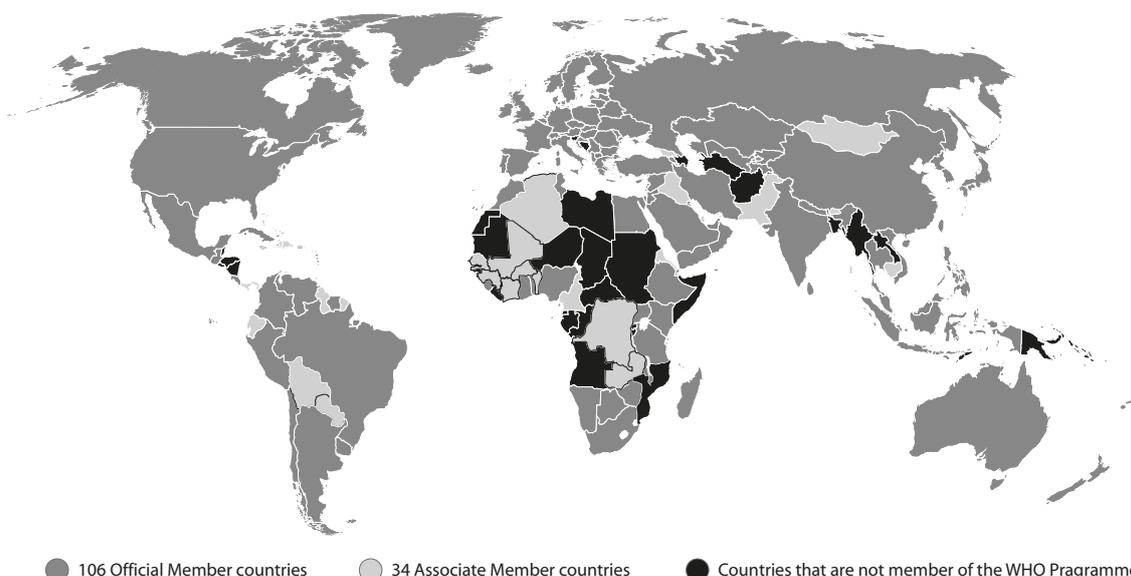
The specific aims of pharmacovigilance are to:⁴⁶

- Improve patient care and safety in relation to the use of medicines in medical and paramedical interventions,
- including vaccination,
- Improve public health and safety in relation to the use of all medicines,
- Contribute to the assessment of benefit, harm, effectiveness and risk of medicines,
- Encourage the safe, rational and effective (including cost-effective) use of medicines,
- Promote understanding, education and clinical training in pharmacovigilance and effective communication of its surveillance role to the public.

Origins of pharmacovigilance

The WHO Programme for International Drug Monitoring (PIDM)⁸² was established in 1968 in response to the thalidomide disaster in which thousands of infants were born with congenital deformations following fetal exposure to thalidomide, a medicine that had been used to treat morning sickness in pregnancy.

The PIDM, now coordinated through the Uppsala Monitoring Center (UMC)⁸³ in Sweden, developed an international system for detecting previously unknown or poorly understood adverse drug reactions (ADRs). National regulatory authorities (NRAs) are responsible for reporting ADRs, particularly rare ones or new signals, to the UMC so that they can be monitored within the global population.⁴⁶



In many countries, National pharmacovigilance centres are established or existing entities are designated to serve this function on behalf of the NRA. Such centres collect information about AEFI using standardized methodologies. They analyse this information and communicate regularly with NRAs to update the safety profiles of the products used in a country. You will learn more about vaccine safety institutions and reporting mechanisms in Module 5.

NRA's role in the regulation of drug safety

National regulatory authorities (NRAs) are responsible for ensuring that every pharmaceutical product – including vaccines – used within the country is:

- Of good quality,
- Of known potency,
- Safe for the purpose or purposes for which it is proposed.

Whereas the first two criteria must be met before any consideration can be given to approval for medical use, the issue of safety is more challenging.

There is a possibility that rare yet severe adverse events (such as those occurring with a frequency of one in several thousand) may not be detected in the pre-licensure development of a drug. It is therefore generally accepted that part of the process of evaluating drug or vaccine safety must happen post-licensure (post-marketing).

Pharmacovigilance is often conducted by national pharmacovigilance centres on behalf of/in collaboration with NRAs. Pharmacovigilance centres have a significant role in post-licensure surveillance of ADRs. They may conduct:

- Post-licensure surveillance of ADRs,
- Data collection on AEFIs using standardized methodologies,
- Data analysis,
- Regular communications with NRA to update safety profiles.

Example for collaboration among institutions: Canada

Canada's national regulatory authority (NRA) is Health Canada. The Public Health Agency of Canada (PHAC) conducts pharmacovigilance for vaccines in collaboration with public health authorities in the provinces and territories, and maintains the national database of reports of adverse events following immunization (AEFI).

During the 2009 influenza pandemic, PHAC used the vaccine safety monitoring system to identify a higher than normal rate of anaphylaxis linked to one particular lot (Lot 7A) of a newly released adjuvanted H1N1 flu vaccine.

In close collaboration between PHAC and Health Canada, and following further investigation of serious adverse event reports linked to Lot 7A, unused vaccines from this lot were withdrawn from use during the investigation.

Adverse Drug Reaction (ADR) surveillance

ADR surveillance is responsible for detecting and responding to adverse events associated with drugs. Although vaccines represent less than 1% of all drug products, their use and purpose is very specific and requires a modified ADR system able to detect and respond adequately and rapidly to occurring adverse events. The following pages of this module will look into why vaccines are different and what the specific needs and expectations are towards vaccine surveillance.

Post-licensure ADR surveillance is mainly conducted by national pharmacovigilance centres. In collaboration with WHO's Uppsala Monitoring Center (UMC), they have achieved a great deal in:

- Collecting and analyzing case reports of ADRs,
- Distinguishing signals from background 'noise' (or coincidental occurrences),
- Supporting regulatory decisions based on strengthened signals,
- Alerting prescribers, manufacturers and the public to new risks of ADRs.

The number of National pharmacovigilance centres participating in WHO's PIDM has increased from 10 in 1968 (when the programme started) to 108 as of June 2012.⁴² The centres vary considerably in size, resources, support structure and scope of activities. Collecting spontaneous reports of suspected ADRs remains their core activity.

The stronger the national system of pharmacovigilance and ADR surveillance, the more likely it is that evidence-based regulatory decisions will be made for the early release of new drugs with the promise of therapeutic advances. Legislation governing the regulatory process in most countries allows for conditions to be placed on approvals, such as the requirement that there should be detailed pharmacovigilance in the early years after a drug's release.

In many countries, pharmacovigilance and NRA approvals are linked by an ADR advisory committee appointed by, and directly reporting to, the NRA. An ADR committee may include independent experts in clinical medicine, epidemiology, paediatrics, toxicology, clinical pharmacology and other disciplines. Such an arrangement inspires confidence amongst health personnel and can make a substantial contribution to public health.

Immunization safety requires a modified surveillance system

Vaccines are considered drugs but require different "immunization safety" surveillance systems to monitor adverse events.

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,
- management of waste.

The skills and infrastructure to deal with genuine vaccine adverse reactions are essential to public safety, as well as to prevent or manage fear caused by false or unproven signals from patients and health workers. Some of the key differences between vaccines and drugs, which lead to the need for specific AEFI surveillance, are listed in the table below.

VACCINES	OTHER DRUGS
Who gets them?	
Usually, healthy people including infants.	Usually, sick people.
Often most of the population, birth cohort, or group at high risk for disease or complications.	
Why?	
To prevent disease.	Usually to treat disease.
How do they get them?	
Vaccines are often administered through public health programmes.	Often administered by a medical doctor or pharmacist.
In some countries, vaccination may be a prerequisite for enrolment in school.	
When do they get them?	
Most childhood vaccines are administered at specific ages, or in relation to special circumstances such as outbreaks or travel.	Normally at time of illness.
The age at the time of vaccination may coincide with the emergence of certain age-related diseases (e.g. neurodevelopmental disorders).	
What about adverse events?	
Low acceptance of risk.	
Intensive investigation of severe AEFIs, even if rare, is necessary.	Acceptance of adverse events often depends on the severity of illness being treated and the availability of alternative treatment options.
Minor AEFIs also should be carefully monitored because they may suggest a potentially larger problem with the vaccine or immunization, or have an impact on the acceptability of immunization in general.	
How many?	
8–15 Childhood vaccines globally recommended.	Thousands of drugs are available.



Question 1*

When parents bring their children for immunization, why may they have a low tolerance for any adverse events that follow?

* The answer to all questions can be found at the end of this manual (page 202).

Vaccine pharmacovigilance

Definition

According to the CIOMS/WHO Working Group on Vaccine Pharmacovigilance, Vaccine pharmacovigilance is defined as

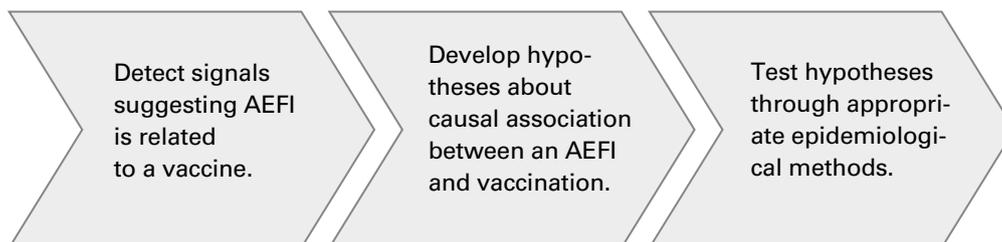
“the science and activities relating to the

- *Detection,*
- *Assessment,*
- *Understanding and*
- *Communication*

*of adverse events following immunization and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization”.*⁷⁸

Like drug pharmacovigilance, vaccine pharmacovigilance aims to detect adverse events early to trigger accurate risk assessment and appropriate response (risk-management) to the problem. This ensures the minimization of negative effects to individuals. Another goal of vaccine pharmacovigilance is to lessen the potential negative impact on immunization programmes.⁴⁹

Vaccine pharmacovigilance relies on three steps:³⁹



Rotavirus vaccine example

In August 1998 the first rotavirus vaccine, RotaShield®, was licensed in the USA. Pre-licensure literature noted a possible increased risk of intussusception, a potentially life-threatening bowel obstruction that occurs for unknown reasons in about one young child in every 10,000 regardless of vaccination history. The manufacturer noted intussusception as a possible adverse reaction in the package insert and post-licensure surveillance for intussusception was recommended by the United States' vaccine safety surveillance Advisory Committee on Immunization Practices (ACIP).⁵¹

After RotaShield® was in routine use by the public (approximately one million children vaccinated within the first 9 months following licensure) VAERS began to receive reports of intussusception following administration of the vaccine. Intussusception was confirmed in 98 cases after vaccination with rotavirus vaccine and reported to VAERS, approximately 0.01% of the one million children vaccinated. The passive surveillance system, relying primarily on spontaneous reports from health workers, indicated at least a fourfold increase over the expected number of intussusception cases occurring within a week of receipt of rotavirus vaccine. As a result, additional studies were conducted to better understand the relationship between rotavirus vaccine and intussusception. In light of these studies, the rotavirus vaccine manufacturer voluntarily removed its product from the market less than a year after it had been introduced, and the recommendation for routine use of rotavirus vaccine among infants in the USA was withdrawn.⁵¹

A different Rotavirus vaccine is now being used in the USA, after better understanding and appropriate recommendation for its use.



Question 2*

In Module 1 you were introduced to the rotavirus vaccine case. Take a look at the additional information in the *Rotavirus vaccine example* given in this question.

What hypothesis was developed as a result of the post-licensure surveillance of RotaShield® vaccine to explain why the original clinical trial (on 10,000 vaccinees) did not detect the incidence of intussusception?

Special considerations for AEFI surveillance

Three major factors need to be given special consideration because they could affect the type of AEFI surveillance and its outcomes.

Training for health workers

Health workers administering vaccinations are on the frontlines and are usually the first responders to an AEFI. They need to be trained how to detect, report, and respond to adverse events, including stabilizing the patient (for example, in a case of anaphylaxis) and communicating with parents, the community and the media.

Determining causality

Difficulties in determining causation between events that are linked in time are common to all drug and vaccine safety monitoring systems. This is particularly challenging in the case of vaccines, because:

- Information on “dechallenge and rechallenge” is usually missing,
- Vaccines are given to most of the country’s birth cohort at an age when coincidental disease are likely,
- Several vaccines are likely to be administered at the same immunization visit,
- Vaccine storage, handling, transport and administration must adhere to specific conditions. Any of these, if not done correctly, can result in an adverse event. The possibility of immunization errors therefore must be investigated.

Independent review is needed

There is a need for independent review of adverse events, separate from the immunization programme. Causality assessment requires a team of investigators, including an immunologist or other experts, depending on the nature of the adverse event. The team usually does not directly include officials from the NIP. They may be perceived to have a conflict of interest as they are responsible for investigating adverse events related to administration of a vaccine.

* The answer to all questions can be found at the end of this manual (page 202).

Interactions between AEFI and ADR surveillance systems

The National Regulatory Authority is usually the only agency with the mandate to ensure the safety, efficacy and quality of vaccines. While AEFI surveillance is a key function of National Regulatory Authorities, monitoring the safety of vaccines requires the involvement of both the National Immunization Programme and the National Regulatory Authority. Their good collaboration should be supported by clearly distinguishing their roles and responsibilities.

The most critical function necessary for meeting the National regulatory authority responsibility to ensure vaccine safety is a strong AEFI surveillance system closely integrated with the system of vaccination delivery.

Because the NRA may have limited knowledge of the structure and management of the National immunization programme, it is essential that the immunization programme manager be involved in AEFI surveillance and the roles of the two parties in this process must be clearly established.

	NRA		NIP
Monitoring safety of vaccines	✓	↔	✓
Integrating AEFI surveillance with system of vaccine delivery	✓	↔	✓
Clear distribution of roles in reporting and detection	✓	↔	✓

There have been several instances where NIPs and NRAs have failed to work with each other when developing national AEFI or ADR surveillance systems. This has often resulted in duplication of effort and a failure to capture all relevant data in one central repository. In addition, potential crises may go undetected through such confusion and the health-care providers may see this as an additional barrier to reporting AEFIs and ADRs.

! Key point

■ A good collaboration between National Regulatory Authority and National Immunization Programme are usually critical components of a strong AEFI surveillance system.

In some countries where the NRA is not in a position to execute the aforementioned tasks, the National immunization programme may have taken over part of the activities of the NRA.

AEFI surveillance components

This section describes the objectives of AEFI surveillance, which adverse events should be reported and by whom. Next we discuss how AEFI reports are generated, and how AEFI reports from health workers lead to investigation and action at the highest levels of responsibility in the National regulatory authority (NRA), the ministry of health and international organizations such as WHO and UNICEF.

The objectives for an effective AEFI surveillance system are to:

- Identify problems with vaccine lots or brands leading to vaccine reactions caused by the inherent properties of a vaccine,
- Detect, correct and prevent immunization errors caused by errors in vaccine preparation, handling, storage or administration,
- Prevent false blame arising from coincidental adverse events following immunization, which may have a known or unknown cause unrelated to the immunization,
- Reduce the incidence of injection reactions caused by anxiety or pain associated with immunization, by educating and reassuring vaccinees, parents/guardians and the general public about vaccine safety,
- Maintain confidence by properly responding to parent/community concerns, while increasing awareness (public and professional) about vaccine risks,
- Generate new hypotheses about vaccine reactions that are specific to the population of your country/region,
- Estimate rates of occurrence of AEFIs in the local population compared with trial and international data, particularly for new vaccines that are being introduced.

The following pages describe the following components of AEFI surveillance:

- Detection and reporting,
- Investigation,
- Causality assessment of AEFIs,
- Risk/benefit assessment.

You will be introduced to the stakeholders involved in these processes, and their respective responsibilities.

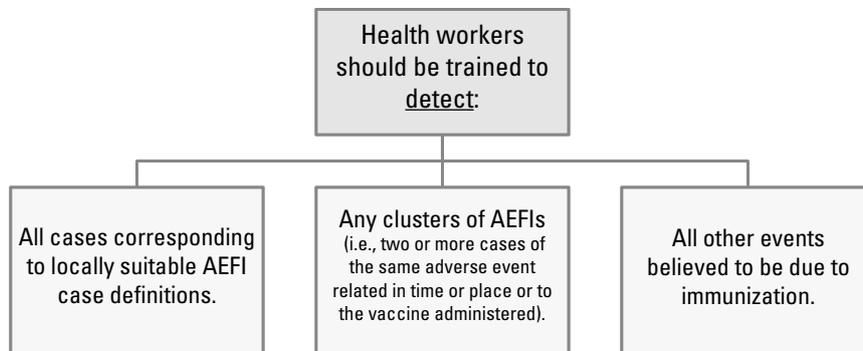
Detection and reporting

Stakeholders



Parents of immunized infants/children, health workers at immunization facilities and staff of accident and emergency rooms in hospitals are most likely to recognize or detect AEFIs when they first occur.

Health workers have the responsibility to detect AEFIs and report AEFIs when appropriate. They also have the responsibility to treat or refer patients for treatment. All immunization staff must be able to identify and report adverse events. Detection requires effective staff training and education to ensure accurate diagnosis of AEFIs based on clear case definitions, which can be included on the AEFI reporting form and in the national AEFI guidelines.

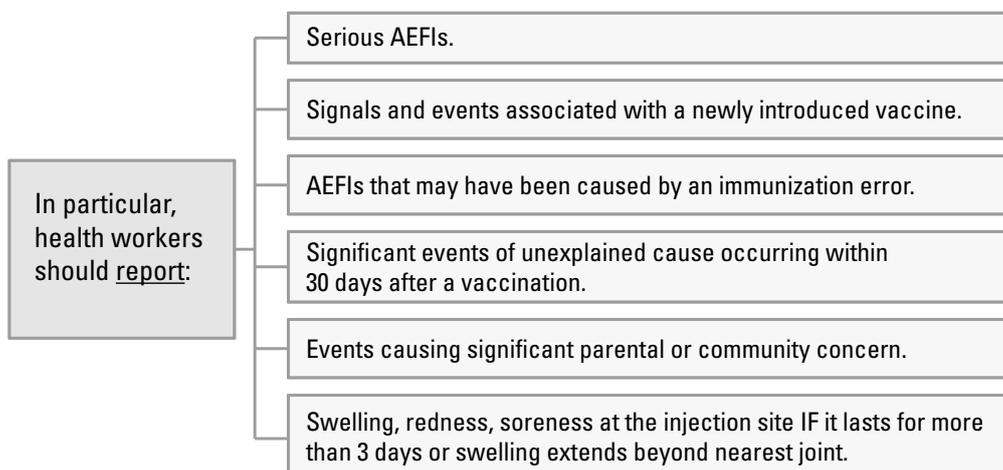


Immunization programme managers should establish appropriate criteria for detecting AEFIs by identifying adverse events of importance to the programme in their country.

Which AEFIs should be reported?

! Key point

Any AEFI that is of concern to the parents or to the healthcare worker should be reported.



In addition to deciding which adverse events should be reported, it is essential that immunization programme managers define the roles and responsibilities of stakeholders, clarify on the process of reporting, and how to ensure/encourage reporting. The following questions should guide the immunization programme manager when setting up and maintaining a detection and reporting mechanism.

Who should make the AEFI report and to whom?	Make sure that health workers are aware of their responsibility to report AEFI.
How should reporting occur?	Reporting should be as standardized as possible, best done through an unambiguous and standardized reporting form.
What should the route of reporting be?	This may depend on the local context. Keep in mind that with unclear responsibilities among stakeholders, there is the danger of double-reporting or under-reporting. Make sure that reporting lines are simple and direct and clear to all stakeholders involved.
When should AEFIs be reported?	Any AEFI that is of concern to the parents or to the healthcare worker should be reported. See above for a list of events that must be reported.
How to improve/encourage reporting?	Health workers may be afraid of getting penalized for reporting. It is important that reporting health workers understand that adverse events following immunization – related to the vaccine or not – must be expected and can happen independent of the health worker's action.

Question 3*

Case definitions support reporting of standardized diagnoses, which provides investigators with data that is comparable. Which of the following statements has or have not been reported in line with the examples of standard case definitions of the Brighton collaboration provided and may therefore lead to misinterpretation of data? Select one or more:

- A. “Child developed high fever” (temperature measured was 41 degree Celsius).
- B. “The child suffered from afebrile seizures” (body temperature was normal).
- C. “A severe local reaction occurred at the injection site” (the occurred swelling extended beyond the nearest joint and lasted for 3 days).
- D. “Patient developed symptoms of encephalopathy due to vaccination with DTP given 4 weeks before occurrence of symptoms”.

* The answer to all questions can be found at the end of this manual (page 202).

Investigation

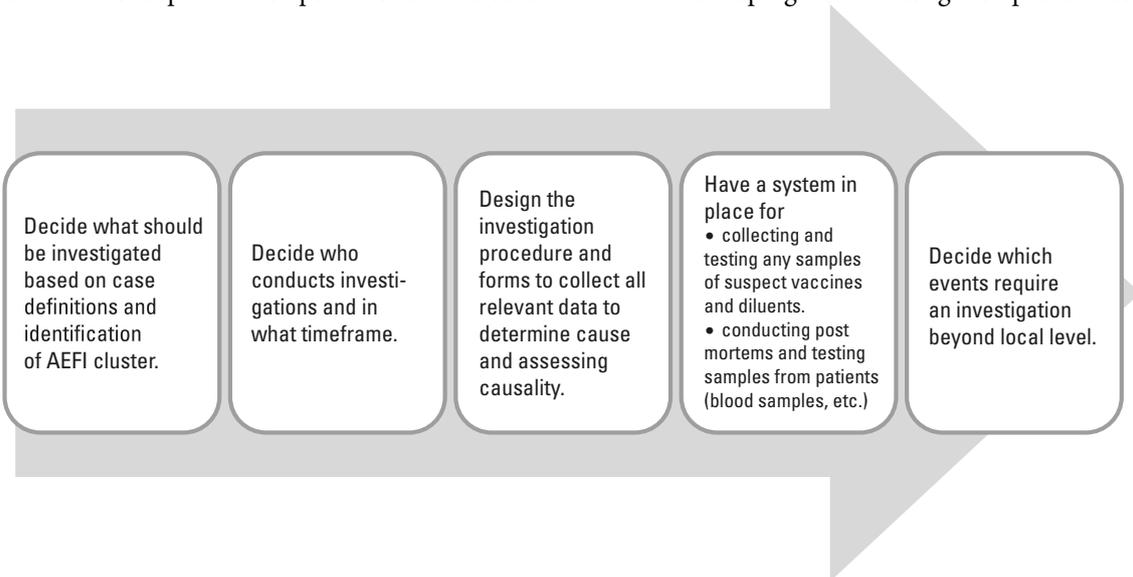
Conducting an AEFI investigation

Some AEFI reports will need further investigation. The purpose of an AEFI investigation is to:

- Confirm the diagnosis (or propose other diagnoses) and determine the outcome of the adverse event,
- Identify specifications of implicated vaccine(s) used to immunize patient(s),
- Examine operational aspects of the immunization programme, which may have led to immunization errors,
- Justify the search for other AEFI cases/clustering,
- Compare background risk of adverse event (occurring in unimmunized people) to the reported rate in the vaccinated population.



A key instrument to organize an AEFI investigation is WHO’s “Aide-Memoire on AEFI Investigation”. Look at the Aide-Memoire to find out more about key definitions, guidance to prepare for an investigation, as well as a checklist providing useful information for each step of an investigation. See the graphic below to view a list of practical steps that should be considered when developing AEFI investigation procedures.



Practical issues for developing your AEFI investigation procedures

- Decide what should be investigated (develop the reporting system around these events), based on case definitions and identification of AEFI clusters (see below for cluster investigation).
- Decide who should conduct investigations and in what timeframe.
- Design the investigation procedure and forms to collect all relevant information for determining cause and assessing causality.
- Have a system in place for collecting and testing any samples of suspect vaccines and diluents.
- Have a system in place to conduct post mortems and test samples from patients (blood samples, etc.)
- Decide which events require high-level versus lower-level investigation.

AEFI reports to be investigated

Not all AEFI reports will need investigation. Reported events requiring the initiation of an investigation are:

- Serious AEFIs, i.e. adverse events or reactions that result in death, hospitalization (or prolongation of existing hospital stay), persistent or significant disability or incapacity (e.g. paralysis), or are potentially life-threatening,
- Clusters of minor AEFIs,
- Signals and events associated with newly introduced vaccines,
- Other AEFIs as recommended by WHO:
 - AEFIs that may have been caused by immunization error (e.g. bacterial abscess, severe local reaction, high fever or sepsis, BCG lymphadenitis, toxic shock syndrome, clusters of AEFIs),
 - Significant events of unexplained cause occurring within 30 days after a vaccination,
 - Events causing significant parental or community concern.

AEFI cluster investigations

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

Examples of AEFI clusters

Example 1

An outbreak of lymphadenitis 3 months after BCG immunization was traced to a switch to a different strain of vaccine. The investigation also highlighted a number of immunization errors (vaccines not properly reconstituted, and injections not given intradermally).

Cause: vaccine reaction compounded by immunization errors.



Illustration 2

Four children died and a fifth was hospitalized after receiving measles vaccine from the same vial. The vaccine was not refrigerated, and was transported from house to house for immunization. Reactions began 4-5 hours after vaccination, with vomiting, unconsciousness, and meningeal irritation. *Staphylococcus aureus* bacteria were cultivated from the incriminated vial.

Cause: sepsis caused by inappropriate vaccine handling.

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

1. Identify the immunization history of the cluster cases including details of when, where and which vaccines were given, by collecting and recording:
 - Detailed data on each patient,
 - Programme-related data (storage and handling, etc.),
 - Immunization practices and the associated health workers' practices.

2. Identify any common exposures among the cases, for example:
 - All data on vaccine(s) used (name, lot number, etc.),
 - Data on other people in the area (also non-exposed).

Including vaccine testing in an AEFI investigation

If it is appropriate to the working hypothesis on the possible cause of the vaccine reaction, collecting and testing a vaccine specimen may confirm or rule out a suspected vaccine-associated cause of the AEFI.

For vaccine testing, collect a vial of the residual vaccine (if possible) from the health facility. Retain adequate samples from the same site of unopened vaccine and diluent vials if the vaccine was reconstituted. The samples should be maintained under correct storage conditions until a decision on testing is made.

If a vaccine is implicated in an AEFI case or cluster, it is rarely necessary to test the vaccine quality, which should already be part of the national regulatory protocols. Potency testing is of little value and is only useful to determine reasons for lack of vaccine efficacy.

If a decision is made to test the vaccine (and where appropriate, the diluent), the test(s) chosen depend on the nature of the adverse event and the working hypotheses on the possible causes. One or more of the following tests may be carried out:

- Visual test for clarity, presence of foreign matter, turbulence or discoloration,
- Sterility testing (vaccine and/or injection equipment) if an infectious cause is suspected,
- Chemical composition analysis: preservatives, adjuvant level, etc. (e.g. aluminium content); abnormal components (e.g. suspect drug used instead of vaccine or diluent),
- Biological tests for foreign substances or toxins if abnormal toxicity is suspected (note: OPV-neurovirulence testing is expensive and adequate samples are not usually available),
- Additional field performance information should be obtained from the vaccine manufacturer.

Causality assessment of AEFIs

Most countries have AEFI systems and attach great importance to reports of suspected adverse events. These systems have been successful in identifying severe AEFIs after vaccines are licensed. Follow-up studies are usually needed to further investigate causality of AEFIs.

Although the most reliable way to determine whether an adverse event is causally related to vaccination is through a randomized clinical trial, such trials are limited to the clinical development phase of vaccines. Once a vaccine is licensed, controlled trials are no longer an option owing to ethical reasons (withholding vaccination).

Causality assessment is the systematic review of data about an AEFI case. It determines the likelihood of a causal association between the event and the vaccine(s) received. Causality assessment helps determine:

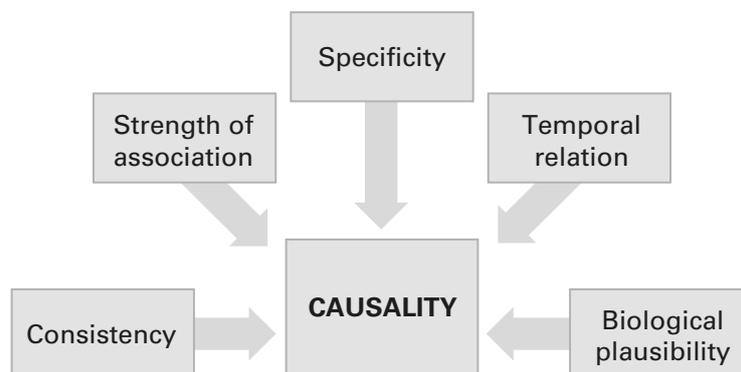
- If an AEFI is attributable to the vaccine or the vaccination programme,
- What steps – if any – need to be taken to address the event.

Causality assessment outcomes help raise awareness of vaccine associated risks among healthcare workers. This, combined with knowledge of benefits of immunization, forms the basis of vaccine information for parents and/or vaccinees.

The quality of a causality assessment depends on:

- Quality of AEFI case report,
- Effectiveness of AEFI reporting system,
- Quality of the causality review process.

There are five principles that underpin the causality assessment of vaccine adverse events.³⁵



Consistency: The association of a purported AEFI with the administration of a vaccine should be consistent. The findings should be replicable in different localities, by different investigators not unduly influencing one another, and by different methods of investigation, all leading to the same conclusion(s).

Strength of association: The association between the AEFI and the vaccine should be strong in terms of magnitude and also in the dose-response relationship of the vaccine with the adverse event.

GACVS report “Causality assessment of adverse events following immunization” that includes other conditions and provisions that should be applied in evaluating causality in the field of vaccine safety.

 vaccine-safety-training.org/tl_files/vs/pdf/GACVS_causality.pdf

The WHO Aide-Memoire on causality assessment serves as a guide to a systematic, standardized causality assessment process for serious adverse events following immunization (including clusters).³⁶

 who.int/vaccine_safety/initiative/investigation/New_aide_mem_causal_assmt.pdf

Specificity: The association should be distinctive. The adverse event should be linked uniquely or specifically with the vaccine concerned rather than occurring frequently, spontaneously or commonly in association with other external stimuli or conditions.

Temporal relation: There should be a temporal relationship between the vaccine and the adverse event. For example, that receipt of the vaccine should precede the earliest manifestation of the event.

Biological plausibility: The association should be coherent, that is, plausible and explicable according to known facts in the natural history and biology of the disease.

Risk/benefit assessment

Continuous evaluation of risks and benefits of vaccines is required to strengthen the confidence in immunization programmes. In Module 1 you looked at the need to *balance vaccine efficacy and vaccine safety* (page 29) by conducting risk/benefit assessments.

On this page, let us look at how risk/benefit assessments are conducted and acted upon. A risk/benefit assessment should:

- Address the population at risk (not the individual at risk),
- Take into account contextual issues (economics, availability of alternative vaccines, sociopolitical and cultural factors),
- Be prompted by a newly identified risk, but must remain holistic (e.g. take into account the entire safety profile of a vaccine, not only the specific information relating to the event that was detected),
- Run in parallel to active enquiry, cooperation and exchange of information.

The need for urgent action should be weighed against the need for further investigation; the question below illustrates this principle.

Question 4*

Think about this example:

During a mass measles campaign for 7.5 million children aged from 9 months to 14 years, a 7-year-old child developed encephalopathy, convulsions and died.

Should the measles campaign be suspended?

Does the need for action to protect children from possible vaccine-related harm in this situation outweigh the need for further investigation, or vice versa?

Benefit evaluation begins with an understanding of the epidemiology and natural history of a vaccine-preventable disease in the unvaccinated population. It involves evaluating the size of the reduction in risk of morbidity and mortality from the disease in the vaccinated population, which is dependent on the efficacy of the vaccine used.

The following table may help to break down some of the various aspects when evaluating the benefits versus the risks.

* The answer to all questions can be found at the end of this manual (page 202).

BENEFIT EVALUATION	RISK EVALUATION
<ul style="list-style-type: none"> • Description of implicated vaccine and lots (incl. brand, manufacturer, lot, international use). • Indications for use (e.g. reduce risk of morbidity and mortality associated with measles or rotavirus cases by 80%). • Identification of alternative modalities (if any, e.g. vitamin A supplementation, behaviour modification etc). • Brief description of safety of vaccine. • Epidemiology and natural history of disease (e.g. morbidity and mortality of rotavirus disease). • Known efficacy of vaccine used. 	<ul style="list-style-type: none"> • Weight of evidence for suspected risk (e.g. frequency, severity, mortality of anaphylaxis). • Detailed presentation and analysis of data on new suspected risk (results of case investigation, incidence in campaign). • Probable and possible explanations. • Preventability, predictability and reversibility of new risk (e.g. is it the same as known risk of measles vaccine?). • Risks of alternative vaccines. • Review of complete safety profile of vaccine. • Estimation of excess incidence of any AEFI common to alternatives. • Highlighting of important differences between alternatives.

Considering the options for action

As a result of the risk/benefit assessment, an options analysis should list all appropriate options for follow-up action.

EXAMPLE

Options for action could include discontinuing the immunization campaign, withdrawing a vaccine batch, and improving staff training and communication.

The options analysis should describe the advantages and disadvantages of each option and the likely consequences.

EXAMPLE

Withdrawing a vaccine lot:

- **Advantages:** reduces fear of vaccine, renews confidence in the vaccine or the campaign,
- **Disadvantages:** cost, potential compromise of the campaign, loss of confidence in vaccine quality.

Finally, the options analysis should outline plans or suggestions of studies that could help to determine the best course of action.

EXAMPLE

Audit injection practices of health workers to identify possible sources of immunization errors; investigate the need for improved training and education.

It is essential to indicate the quality and quantity of any future evidence necessary to trigger reconsideration of the issue, and how the outcomes of any actions will be monitored and assessed.

Summary

You have now completed the learning for this module. These are the main points that you have learned.

- The basic principles of pharmacovigilance, and the special conditions that apply to immunization programmes.
- The interaction and differences between the ADR and the AEFI reporting system.
- The different components of AEFI surveillance detection, investigation and causality assessment.
- The conducting of risks/benefit assessments for a vaccine.

**You have completed Module 4.
We suggest that you test your knowledge!**

ASSESSMENT 4

Question 1

Vaccines are considered drugs but require different surveillance systems to monitor adverse events. Below is a list of differences between vaccines and drugs, which lead to the need for specific 'immunization safety', or AEFI surveillance.

Vaccines usually differ from drugs in terms of:

Select one or more.

- A. Recipient's age.
- B. Recipient's health-status.
- C. Registration processes in National Regulatory Authorities.
- D. Staff administrating the vaccine/drug.
- E. Expectations towards substance's safety.

Question 2

Effective detection and reporting of adverse events are a cornerstone of efficient AEFI surveillance. Parents of immunized infants/children, health workers at immunization facilities and staff of accident and emergency rooms in hospitals are most likely to recognize or detect AEFIs when they first occur.

Which of the following statements is not correct?

Select one or more.

- A. Health workers have the responsibility to detect AEFIs and report AEFIs when they first occur.
- B. Health workers should be able to detect all cases corresponding to locally suitable AEFI case definitions.
- C. Health workers should be trained to detect clusters of AEFI and all other events believed to be due to immunization.
- D. Health workers must report serious AEFIs only.
- E. To support reporting in their countries, immunization programme managers should establish appropriate criteria for detecting AEFIs by identifying adverse events of importance to the programme in their country.

Question 3

Some AEFI reports will need further investigation, some do not.

Which of the following statements are correct? Select one or more:

- A. Two or more cases of the same, minor adverse event, if related in time, place or the vaccine administered should be investigated.
- B. Investigation is limited to the follow-up of serious adverse events following immunization.
- C. Signals and events associated with newly introduced vaccines should be investigated.
- D. Investigation is recommended when the events are causing significant parental or community concern.
- E. Following the reporting of an adverse event following immunization, vaccine testing should be an integral part of its investigations.

Question 4

According to the WHO Aide-memoire on Causality Assessment, which of the following is **not** one of the five principles underpinning the causality assessment of vaccine adverse events? Select one or more.

- A. Consistency
- B. Strength of association
- C. Risk-benefit balance
- D. Temporal relation
- E. Biological plausibility

Question 5

During a national immunization programme against measles, if four deaths occur in children within one week of vaccination then the programme must be suspended, until further investigations have taken place.

Is this statement true or false? Select one.

- True
- False

You have completed Assessment 4.

Assessment solutions

Question 1

Answers A, B, D and E are correct.

Key differences between vaccines and drugs see table on page 93.

Question 2

Answer D is incorrect.

Any AEFI that is of concern to the parents or to the healthcare worker should be reported.

In particular, health workers **must report**:

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

Question 3

Answers A, C and D are correct.

Answers A – D

Reported events requiring the initiation of an investigation are:

- Serious AEFIs, i.e. adverse events or reactions that result in death, hospitalization (or prolongation of existing hospital stay), persistent or significant disability or incapacity (e.g. paralysis), or are potentially life-threatening,
- Clusters of minor AEFIs,
- Signals and events associated with newly introduced vaccines,
- Other AEFIs recommended by WHO:
 - AEFIs that may have been caused by immunization error (e.g. bacterial abscess, severe local reaction, high fever or sepsis, BCG lymphadenitis, toxic shock syndrome, clusters of AEFIs),
 - Significant events of unexplained cause occurring within 30 days after a vaccination,
 - Events causing significant parental or community concern.

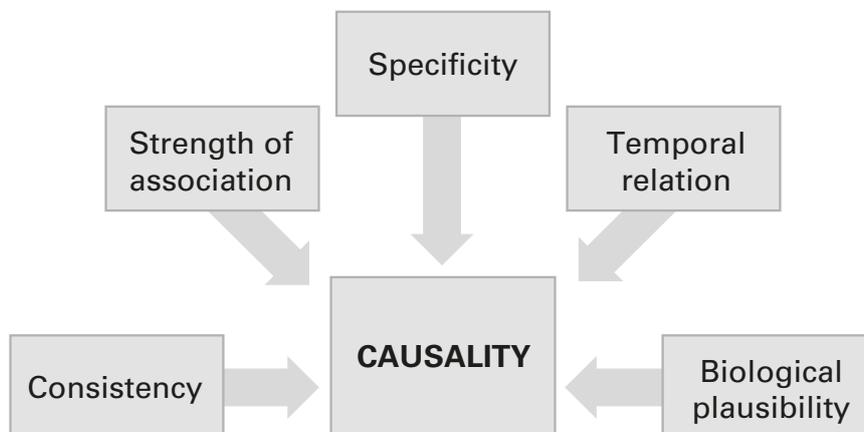
Answer E

Vaccine testing is not an integral part of an investigation. It is only appropriate if the working hypothesis about the possible causes of an AEFI suggests there may be a problem with vaccine quality, e.g. bacterial contamination, damage due to inadequate maintenance of the cold chain, a reconstitution error, etc.

Question 4

Answer C is incorrect.

The five principles that underpin the causality assessment of vaccine adverse events are:



Question 5

The correct answer is 'False'.

Before suspending a programme, it must be established that the deaths are genuinely related to the vaccination, and that the number of deaths is higher than expected.

Even if a causal relationship is established between the deaths and the vaccination, a risk/benefit calculation should be made, to determine if the danger of death from the disease is greater than the risk of the vaccination. Once this is established, there is a rational basis for deciding whether to suspend the campaign or not.

Keep in mind that during a national campaign a very large number of persons will be vaccinated and some deaths may occur coincidentally in vaccinated individuals.

MODULE 5

Vaccine safety institutions and mechanisms

Overview

The general principles for the surveillance of adverse events following immunization (AEFIs) are similar in all countries. However, approaches may differ due to factors such as how immunization services are organized and the level of resources available.

The first half of the Module describes the central role of the national regulatory authority (NRA) and the national immunization programme (NIP) along with the role of the AEFI review committee; other participants are also briefly introduced.

In the second half of the Module you will look into the international services available to support vaccine safety in countries. You will understand how national and international agencies work together and how information flows between countries and them.

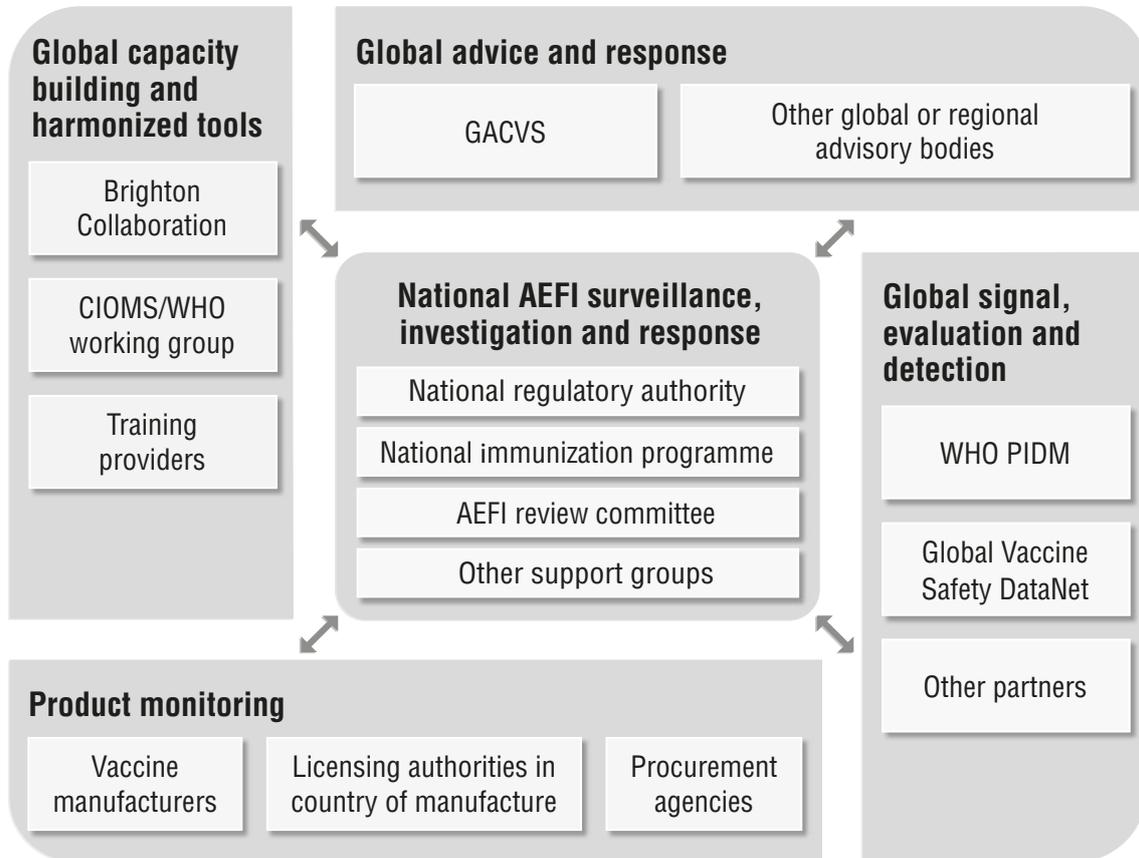
Module outcomes

By the end of this module you should be able to:

- 1** List the main functions or services for vaccine safety, including national and international bodies, as well as manufacturers,
- 2** Describe the relevant areas of responsibility and (if applicable) the areas of collaboration between the National regulatory authority and immunization programmes within your own country,
- 3** Identify the mechanisms by which an AEFI seen in a clinic can be reported to the national regulatory authority,
- 4** Summarize information flows between institutions at national level (immunization clinics, NRAs, etc.) and international bodies.

Overview of functions

Components of a 21st Century global vaccine safety monitoring, investigation, and response system.



There are many different organizations serving different purposes in vaccine safety and in the monitoring and support of national responses to adverse events.

In this module we will first focus on the national institutions displayed in the middle of the graphic. Following this, we will introduce the various international stakeholders and the services they provide to the national level.

NATIONAL LEVEL

National AEFI surveillance systems

The national regulatory authority (NRA) and the national immunization programme (NIP) are responsible for developing and maintaining a national AEFI surveillance system. Often an AEFI review committee and other support groups such as academic institutions and technical agencies are linked to the AEFI surveillance system. In countries that produce their own vaccines, vaccine manufacturers and national control laboratories may be part of the national AEFI surveillance system.



AEFI surveillance addresses the needs of immunization programmes and National regulatory authorities. The general principles of AEFI surveillance are:²⁴

- Detection, correction and prevention of immunization errors,
- Identification of potential problems with specific vaccine lots,
- Prevention of false blame from coincidental events,
- Maintenance of confidence in the programme by properly responding to parent/community concerns,
- Identification of signals for unexpected adverse events and generation of hypotheses to be tested by controlled studies,
- Estimation of AEFI rates in local populations,
- Support to formulate and adjust contraindications, risk/benefit equations, and provider and patient information.

Mass vaccination campaigns

An area of specific need are mass vaccination campaigns. During campaigns, a large number of doses are administered over a short period. There is a high probability of coincidental adverse events. Immunization errors may occur if vaccines are not being given by those who regularly administer vaccine. During campaigns there is also often increased awareness towards an apparent rise in reported adverse events, which can undermine the confidence in the vaccine being used and can have a major impact on the success of the campaign.

Key point

- General principles of AEFI surveillance are similar in all countries. However, approaches may differ because of factors such as the organizational structure of immunization services and the amount of resources available.

National AEFI surveillance should be carried out in close collaboration with the NIP, NRA, AEFI review committee, and other support groups (i.e. technical agencies and academic institutions). In countries that produce their own vaccines, vaccine manufacturers, and national control laboratories should be involved in AEFI surveillance.

National regulatory authority

! Key point

- The safety of vaccines is under the mandate of the National regulatory authority (NRA).

Note: The NIP is also involved in securing the safety of vaccines and their use. Both the role of the NRA and the NIP should therefore be clearly defined.

All countries should have a National regulatory authority to ensure that all medicines, including vaccines, used within the country are safe, effective and of good quality. NRAs function within the framework of national medicines policy and overall health policy, and as with any public entity, must abide by principles of transparency, fairness and accountability.

After licensure and introduction of a vaccine, the NRA's responsibility to ensure vaccine safety must be met by a strong AEFI surveillance. It is important to ensure exchange of information between the NRA and the system of vaccination delivery or the national immunization programme.

Because the NRA may have limited knowledge of the structure and management of the NIP, it is essential that the immunization programme manager is involved in AEFI surveillance and that everyone's role in monitoring and responding to vaccine safety issues is clear.

National AEFI surveillance, investigation and response

National regulatory authority

National immunization programme

AEFI review committee

Other support groups

Core functions specific to vaccines

The NRA is usually the main institution mandated to regulate drugs, including vaccines. It has the aim of ensuring the quality, efficacy and safety of the product. NRAs function within the framework of national medicines policy and overall health policy. As with any public body, NRAs must have principles of transparency, fairness and accountability.

Strengthening NRAs

In 1997, WHO launched an initiative to strengthen the capacity of national regulatory systems. These include institutions such as NRAs, national control laboratories and NIPs, and must operate in close collaboration with the vaccine manufacturers. The ultimate objective of this initiative was for all countries to have a reliable, properly functioning NRA. To achieve its objectives, the initiative undertakes a five-step process of capacity development that is customized to the requirements of each individual country.⁶³

1. Define and regularly update benchmarks and other tools used to assess whether a national regulatory system is capable of ensuring that the vaccines used or made in its country are of the required standards of quality, efficacy and safety.
2. Use benchmark indicators and other tools to assess the national regulatory system.
3. Work with the country's regulators and other health officials in drawing up an institutional development plan to deal with any shortcomings in the country's regulatory system, and to build on the existing regulatory strengths in the country.
4. Implement the institutional development plan, which may involve technical support or staff training to perform regulatory functions.
5. Re-assess the NRA within 2 years to evaluate progress.

When the initiative started in 1997, only 37 (19%) of WHO's 190 Member States had reliable, fully functioning NRAs. By the end of 2010, the number had risen to 60 (31.5%). Priority countries for the initiative are those that have vaccine manufacturers and thus contribute to the world's vaccine supply. In 1997, 20 (38%) of the 52 vaccine-producing countries had a reliable, functioning NRA. By the end of 2010, the numbers had risen to 34 (77%) of 44 vaccine-producing countries.

NRA functions relating to vaccines²

FUNCTION 1 Marketing authorization and licensing activities	Issuing a market authorization, and licensing vaccine production facilities and vaccine distribution facilities.
FUNCTION 2 Post-marketing surveillance (including AEFI surveillance)	Ensuring that post-marketing surveillance is carried out, with a focus on detecting, investigating, and responding to unexpected AEFIs.
FUNCTION 3 Vaccine lot release	Verifying consistency of the safety and quality of different batches of vaccine coming off the production line (lot release).
FUNCTION 4 Laboratory access	Accessing, as needed, a national control laboratory in order to test vaccine samples.
FUNCTION 5 Regulatory inspections	Inspecting vaccine manufacturing sites and distribution channels.
FUNCTION 6 Oversight of clinical trials	Authorizing and monitoring clinical trials to be held in the country.

Functions depending on the source of vaccines

Of the six core functions, all NRAs are responsible for Function 1 (licensing vaccines) and Function 2 (AEFI surveillance). Both these functions should be coordinated with the National Immunization Programme.^{2,54}

The NRA's can be responsible for Functions 3–6 depending on how its respective country obtains vaccines. Countries may:

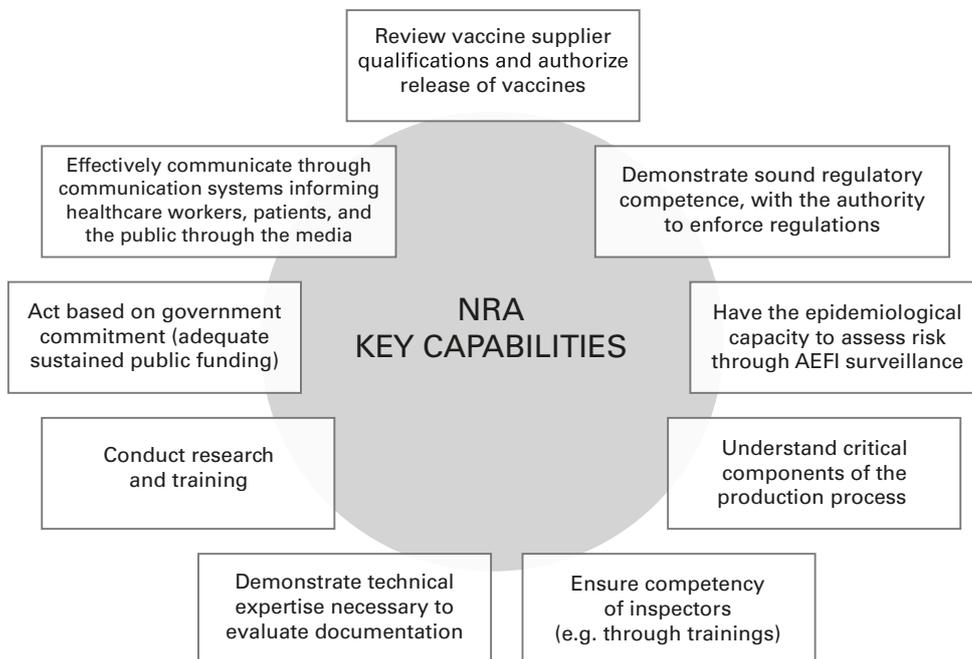
- Obtain vaccines through United Nations procurement agencies, i.e. United Nations Children's Fund (UNICEF), WHO, or Pan-American Health Organization (PAHO) Revolving Fund for Vaccine Procurement,
- Procure vaccines directly on the domestic or the international market,
- Manufacture their own vaccines.

The table below shows which responsibilities are taken up by the NRA depending on the source of the vaccine.

NRA functions depending on source of vaccines

Vaccine-specific NRA functions needed	Areas of activity by NRA (or WHO) depending on source of vaccines		
	Vaccine procured by United Nations agency	Vaccine procured by NRA	Vaccine manufactured in country
FUNCTION 1 Marketing authorization and licensing activities	✓	✓	✓
FUNCTION 2 AEFI surveillance	✓	✓	✓
FUNCTION 3 NRA lot release		✓	✓
FUNCTION 4 Laboratory access	NRA functions undertaken by WHO on behalf of United Nations agencies or producing countries.	✓	✓
FUNCTION 5 Regulatory inspections		NRA functions undertaken by producing country.	✓
FUNCTION 6 Oversight of clinical trials			✓

The graphic below shows some of the key capabilities enabling a NRA to implement the 6 core functions listed in the table above.



Vaccine procurement and lot release

There are only about 30 different vaccine types (but many more product formulations) compared with approximately 20,000 drugs.⁵⁵ Accordingly, there are relatively few vaccine manufacturers and a limited number of countries where vaccines are produced. Most countries use vaccines that are imported from elsewhere.

To support countries with limited national regulatory (NRA) capacity, WHO provides a system of vaccine prequalification that has been adopted as a standard for procurement by United Nations agencies and some countries. Alternatively, countries can procure their vaccines directly on the domestic or international market.

Regardless of how a country obtains vaccines, NRAs are responsible for licensing them i.e. approving their use within the country. Appropriate licensing of vaccines ensures that quality products are used in immunization programmes by determining that the manufacturer can provide a safe and effective vaccine.

Because vaccines are biological products and quality can vary from lot to lot, NRAs should conduct tests before a vaccine lot is released for public use. NRAs often delegate testing to a national control laboratory. NRAs are not responsible for testing vaccine lots when the vaccine is procured through a United Nations organization i.e. prequalified, which takes responsibility for the testing.

Diversification of vaccine manufacture

Over the past decade, there has been substantial diversification in the manufacture of vaccines, including the growing importance of prequalified vaccines produced by manufacturers in low- or middle-income countries. In addition to producing vaccines for their own countries, these manufacturers can often provide large volumes at low prices on the international market and now represent an increasing proportion of the vaccines procured by UNICEF and the Pan-American Health Organization (PAHO) Revolving Fund for Vaccine Procurement. At the end of 2008, there were 83 different vaccine products prequalified by WHO, of which 37 were manufactured in low- or middle-income countries.

Testing of every batch is not done for other drug products. The lot release system is perhaps the greatest difference between the NRA vaccine functions and NRA functions for other medicines.

Once the NRA releases a vaccine lot, the national immunization programme (NIP) takes responsibility for its proper storage and handling until it can be administered safely to the target population. Storage and handling, including maintenance of the cold chain (continuous refrigeration) involves many steps, and presents opportunities for immunization errors that could result in AEFIs.

Key point

Unlike other drugs, NRAs should test every vaccine lot before public use, unless this is done by WHO on behalf of United Nations agencies or producing countries. The system of lot release is probably the greatest difference between vaccines and other medicines.

Once the NRA releases a vaccine lot, the responsibility to keep the vaccine safe and effective is passed to the NIP.

Regulation of drug safety

NRAs are responsible for ensuring that every pharmaceutical, including vaccines, used within the country is:

1. Of sufficient quality,
2. Effective,
3. Safe for the purpose or purposes for which it is proposed.

There is a possibility that rare, yet severe, adverse events (such as those occurring with a frequency of one in several thousand) may not be detected during drug development before licensing, because the number of recipients in the trials is relatively small. It is therefore generally accepted that part of the process of evaluating drug safety must happen after licensing and marketing. The acceptability of a vaccine shall be based on its benefit-risk ratio.

Pharmacovigilance is often conducted by national pharmacovigilance centres on behalf of NRAs. These centres, in collaboration with NRAs, have a significant role in the surveillance of adverse drug reactions after licensing, including for vaccines and have to be staffed with persons with experience in vaccinology or training in vaccine vigilance.

Influenza A (H1N1) vaccine example

Canada’s national regulatory authority (NRA) is Health Canada. The Public Health Agency of Canada conducts pharmacovigilance for vaccines in collaboration with public health authorities in the provinces and territories and maintains the national database of reports of AEFIs.

Through the vaccine-safety monitoring system, the Public Health Agency of Canada identified a higher than normal rate of anaphylaxis linked to one particular lot (Lot 7A) of a newly released adjuvanted H1N1 flu vaccine. In collaboration with Health Canada and pending further investigation of serious adverse event reports linked to Lot 7A, unused vaccines from this lot were withdrawn from use during the investigation.

This document shows an example of an AEFI reporting form that would be used for investigation. This one is from the Public Health Agency of Canada; the form for your own country may be different. This demonstrates the importance of clearly defined roles and close coordination between organizations responsible for pharmacovigilance and NRAs.

Example AEFI reporting form:

 vaccine-safety-training.org/tl_files/vs/pdf/aeфи_report_form_canada.pdf

National immunization programmes (NIP)

A national immunization programme (NIP) is the organizational component of Ministries of Health charged with preventing disease, disability, and death from vaccine-preventable diseases in children and adults. A NIP is a government programme that operate within the framework of overall health policy.

The national immunization programme is used interchangeably with the Expanded Programme on Immunization (EPI) that originally focused on preventing vaccine-preventable diseases in children. All countries have a national immunization programme to protect the population against vaccine-preventable diseases.

National AEFI surveillance, investigation and response

National regulatory authority

National immunization programme

AEFI review committee

Other support groups

Key point

- Like the NRA, the NIP is responsible for the delivery to the population of safe, effective vaccines of high quality.

The NRA releases vaccines for public use (lot release). The NIP assumes responsibility for the safe storage, handling, delivery and administration of these vaccines. In countries where the NRA does not have the capacity to act on vaccine safety issues, the NIP may factually have taken over some of the responsibilities of the NRA.

Core functions specific to vaccine safety

When an adverse event following immunization (AEFI) happens, it is the health staff administering vaccines that often are the first responders. They assess and treat the adverse event, reporting it, and may be called to contribute to an AEFI investigation. The national immunization programme is responsible for assuring that health staff respond to adverse events, and act to minimize the risk of AEFIs in the future.

Given the central role of the national immunization programme in ensuring the safe delivery and administration of vaccines, it is imperative that it works closely with the NRA and other groups or committees involved in AEFI surveillance.

The national immunization programme NIP should also work in collaboration with national pharmacovigilance centres on the collection and assessment of AEFI data.



Safety of vaccine administration



NRAs and vaccine manufacturers provide guidance on how to prepare and administer vaccines correctly. The national immunization programme, as part of the national health delivery system, is responsible for ensuring that health workers and local vaccinators are trained to prepare and administer vaccine correctly.

It is vital that health workers or local vaccinators are trained to store and handle vaccines properly, reconstitute and administer vaccinations correctly, and have the right equipment and materials to do their job.

The correct technique for preparing and administering a vaccine must be followed to ensure that it is effective and does not result in an AEFI caused by immunization errors. Given that immunizations are often administered to a large segment of the healthy population, and often are delivered in remote underserved areas, immunization errors are always a concern. To read more about immunization errors, go to Module 3, chapter “*Immunization error-related reaction*” on page 74.

In WHO’s *Immunization in Practice*⁵⁷, Module 4 discusses practices that health workers should follow to deliver immunization injections safely. Read the document “Ensuring safe injections”:

 vaccine-safety-training.org/tl_files/vs/pdf/Module4_IIP.pdf

The following steps should be taken by the national immunization programme to avoid immunization errors:

- Train immunization workers adequately, provide refresher updates and ensure close supervision so that proper procedures are being followed.
- Do not store other drugs or substances in the refrigerator of the immunization centre. This will avoid mix-up between vaccine vials and other drug containers and minimize immunization errors. If stored together, a drug risks being given instead of a vaccine or an inappropriate diluent.
- Use sterile, preferably single-use, auto-disable syringes for all injections. If only multi-use syringes are available, sterilize them adequately after each use.
- Reconstitute vaccines only with its specific diluent supplied by its manufacturer.
- Discard Reconstituted vaccines within 6 hours or at the end of each immunization session (whichever comes sooner).

- Carefully conduct epidemiological investigation of an AEFI to pinpoint the cause and how to improve immunization practices where necessary.
- Monitor persons receiving vaccines for 20 minutes after vaccination.

AEFI Review Committee

Every country should establish an AEFI Review Committee to:

- Review individual serious and unusual AEFIs and other AEFIs referred to it by expert groups (e.g. the national immunization technical advisory groups) and/or national pharmacovigilance centres,
- Assess potential causal links between AEFIs and a vaccine (or vaccine lot),
- Monitor reported AEFI data for potential signals of previously unrecognized vaccine-related adverse events,
- Provide recommendations for further investigation, education, corrective action and communication with interested parties, including the media,
- Record its deliberations and decisions and feedback on each reviewed case to all relevant stakeholders.

National AEFI surveillance, investigation and response

National regulatory authority

National immunization programme

AEFI review committee

Other support groups

An AEFI Review Committee should be composed of members that are independent of the immunization programme. It should represent a wide range of specialists whose expertise may add to the task of reviewing the AEFIs. Areas of expertise would include paediatrics, neurology, internist, forensic physician, pathology, microbiology, immunology and epidemiology. Medical experts in particular should be invited for the analysis of special clinical events.

To avoid conflict of interest, the national EPI manager, vaccine laboratory scientists, representatives of the National vaccine regulatory authority, and regional/district EPI officers should not be included as members in the committee, however, should be available to support it in its functions.

Other support groups

Support for the development, implementation and communication of vaccine safety policies and procedures is available to immunization programmes from a range of other national, regional and local organizations.

These include National immunization technical advisory groups, and pharmacovigilance centres.

Pharmacovigilance centres

The AEFI surveillance functions of pharmacovigilance centres relate to the reporting and investigation of adverse events associated with vaccines as well as medicinal drugs. Many countries now operate a decentralized pharmacovigilance system, with a national pharmacovigilance centre functioning as the

National AEFI surveillance, investigation and response

National regulatory authority

National immunization programme

AEFI review committee

Other support groups

focal point for a network of regional and/or local centres. These may be located in a range of organizations, including relevant government departments, hospitals, academic environments, or hosted by a professional body such as a national medical association.

The provision of a high-quality information service to health workers is a basic task of pharmacovigilance centres. Continuous and appropriate educational activities improves knowledge, and stimulates and encourages health workers to report AEFIs.

National immunization technical advisory groups (NITAGs)

The general objective of NITAGs is to guide national governments and policy-makers to develop and implement evidence-based, locally relevant immunization policies and strategies that reflect national priorities. They support national authorities and empower them to address issues associated with:

- Vaccine quality and safety,
- The introduction of new vaccines and immunization technologies.

NITAGs also serve to:

- Reinforce the credibility of national vaccine and immunization policies,
- Help governments and national immunization authorities to resist pressure from vested interest groups,
- Enhance the ability to secure government or donor funding for immunization programmes,
- Encourage a more comprehensive approach to immunization policy that:
 - Considers the health of vulnerable populations,
 - Integrates various pre-existing vaccine-specific task forces.

Evidence-based information is accessible to NITAGs via the online NITAG Resource Centre. It provides four dedicated services.

 NITAG Resource Centre
www.nitag-resource.org

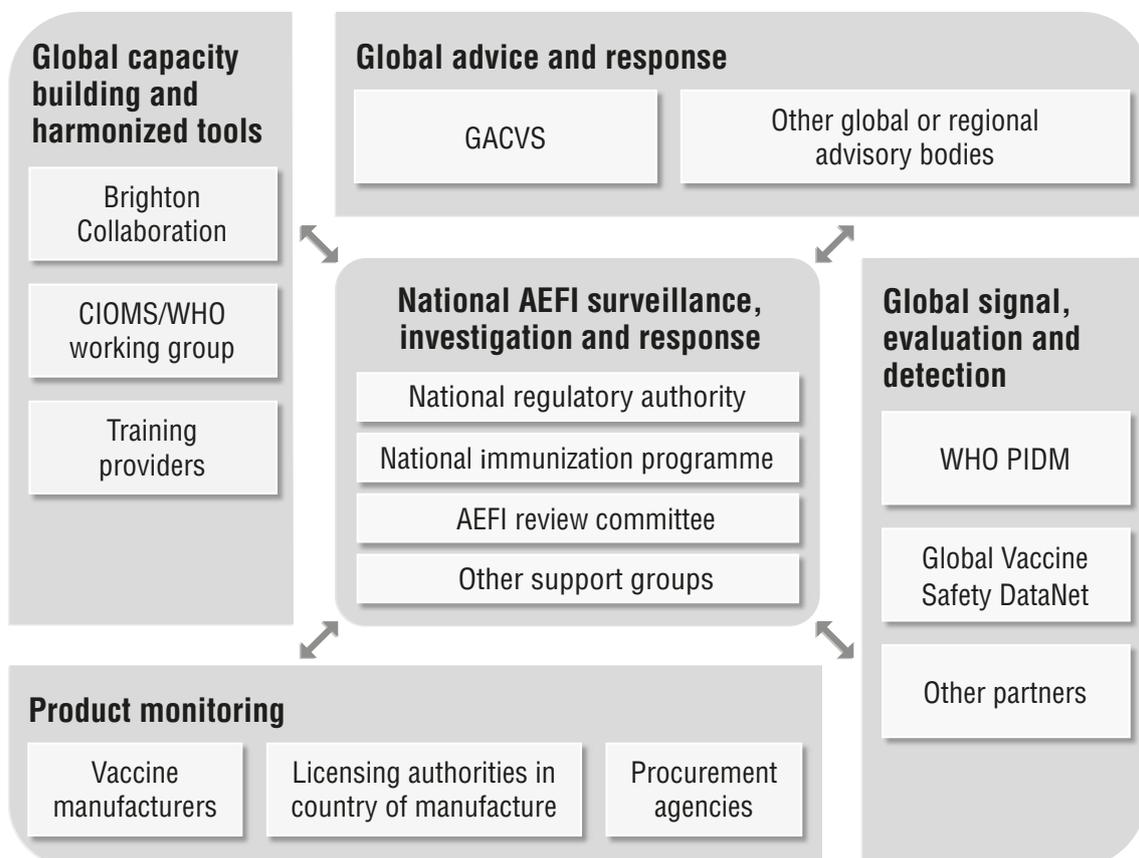
INTERNATIONAL LEVEL

Global vaccine safety stakeholders and services

International collaboration is essential to maintain the significant achievements of immunization to date and to prevent the spread of misinformation about safety concerns from paralysing and damaging immunization programmes. Vaccine safety is both a priority and a challenge to countries. Examples of challenges that countries need to address in differing priorities depending on their local contexts include:

- Continued prevalence of unsafe injections and injection practices,
- Mishandling of rumours and adverse events,
- Lack of access to new, safer technologies such as auto-disable syringes,
- Growing anti-immunization movements, including anti-vaccination websites,
- Inadequate AEFI surveillance,
- Globalization and the internet (greater impact of misinformation raising public concerns about harm from vaccines).

WHO and other partners are supporting various global initiatives that aim to strengthen and support national AEFI surveillance, investigation and response. The following graphic shows some of the initiatives at global level that support countries on vaccine safety issues. Move your mouse over each group to find out about its overall role.



Components of 21st century global vaccine systems³⁹

GACVS

The Global Advisory Committee on Vaccine Safety (GACVS), established in 1999 under WHO's Immunization Safety Priority Project, advises WHO on vaccine-related safety issues and enables WHO to respond promptly, efficiently and with scientific rigour to issues of vaccine safety with potential global importance.

WHO and partners

Many partners support drug safety activities at global or regional levels, in particular non-governmental organizations, such as academic, clinical care and public-health institutions.

Brighton collaboration

The Brighton Collaboration, an international voluntary collaboration launched in 2000, provides globally accepted standard case definitions for assessing AEFIs so that safety data across trials and surveillance systems can be compared.

Council for International Organizations of Medical Sciences CIOMS/WHO working group

The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by WHO and the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949. CIOMS includes technical working groups (e.g. vaccine pharmacovigilance).

WHO Programme for International Drug Monitoring (PIDM)

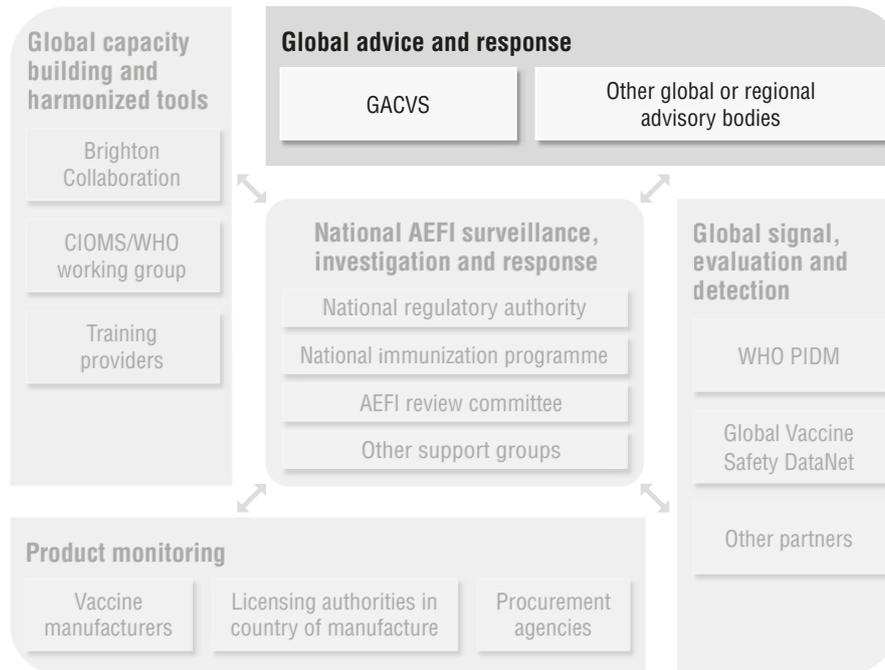
The WHO Programme for International Drug Monitoring (PIDM), established in 1968, consists of a network of national pharmacovigilance centres, WHO headquarters in Geneva, and the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, Sweden.

Other support groups

Depending on the countries, other groups such as academic institutions or technical agencies (e.g. national immunization technical advice groups, NITAGs) provide significant support to drug safety activities.

On the following pages we will introduce some of these initiatives and their respective areas of activity. Following this, we will introduce the Global Vaccine Safety Initiative, an implementation support mechanism that envisions effective vaccine pharmacovigilance systems to be established in all countries.

Global analysis and response



Global Advisory Committee on Vaccine Safety (GACVS)

Established in 1999 under WHO's Immunization Safety Priority Project, the Global Advisory Committee on Vaccine Safety (GACVS)⁸⁴ advises WHO on vaccine-related safety issues and enables WHO to respond promptly, efficiently and with scientific rigour to vaccine safety issues of potential global importance. Outcomes of the deliberations of the GACVS are reported routinely in WHO's Weekly Epidemiological Record (www.who.int/wer).



The Committee takes under consideration or makes recommendations regarding all aspects of vaccine safety that might be of interest and importance to Member States and to WHO, and that are of sufficient importance to affect WHO or national policies.

The Global Advisory Committee on Vaccine Safety has 14 members.⁴³ They represent a broad range of disciplines covering immunization activities. These members:

- **Are independent and unbiased:** They take decisions free of vested interests, including the interests of WHO itself or of other organizations. Each committee member signs a declaration of interest accordingly.
- **Offer broad expertise:** They have the expertise to evaluate and make decisions in the field of vaccine safety. They are familiar with drug regulatory processes, with special reference to the needs of the low-income countries.
- **Take decisions with scientific rigour:** All decisions of the Committee are based on the best available scientific evidence and expertise. It is authoritative, defensible and explicable in terms of fact, scientific evidence and process.

Since its establishment, GACVS has discussed a broad range of vaccine safety issues either causing, or with a potential to cause, public concern. These include general issues relevant to all vaccines, such as the safety of adjuvants, as well as vaccine-specific issues relating to long-standing vaccines and to new vaccines and vaccines under development.

GACVS example

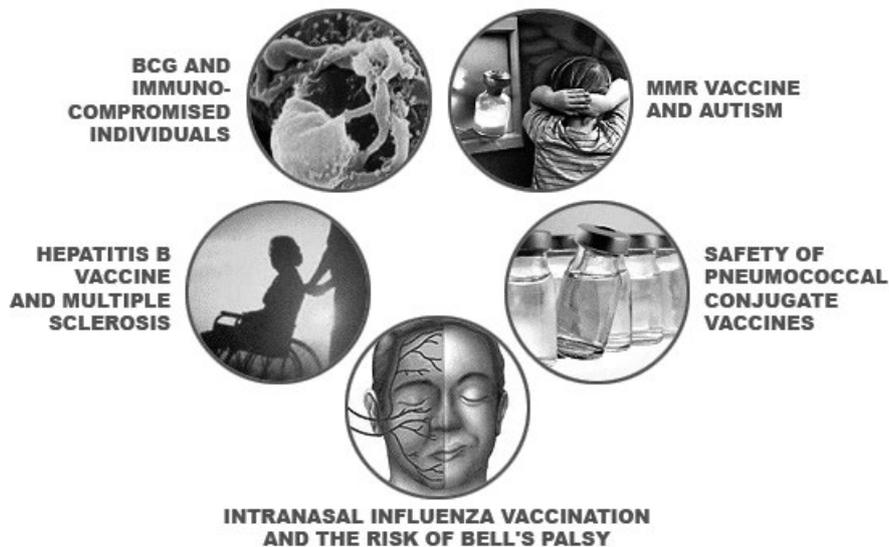
The Global Advisory Committee on Vaccine Safety (GACVS) reviewed data from Argentina and South America confirming in 2007 the significantly high risk of disseminated BCG (dBCG) disease in HIV-positive infants, with rates approaching 1%. GACVS took into consideration other studies showing that infection with HIV severely impairs the BCG-specific T-cell responses during the first year of life.

Based on evidence available, and considering the significant risk of BCG disease, GACVS advised that routine BCG vaccination shall no longer be recommended for infants known to be HIV-infected with or without symptoms of HIV infection.

For infants whose HIV status is unknown*, GACVS recommended that BCG vaccination should be administered regardless of HIV exposure, especially considering the high endemicity of tuberculosis in populations with high HIV prevalence. Close follow up of infants known to be born to HIV-infected mothers and who received BCG at birth was also recommended to provide early identification and treatment of any BCG-related complication. In settings with adequate HIV services that could allow for early identification and administration of antiretroviral therapy to HIV-infected children, consideration should be given to delaying BCG vaccination in infants born to mothers known to be infected with HIV until these infants are confirmed to be HIV negative. Infants who demonstrate signs or reported symptoms of HIV-infection and who are born to women known to have HIV infection should not be vaccinated.

Interactive exercise

Seek advice on the vaccine-specific concerns addressed by GACVS by visiting the GACVS topic list: www.who.int/vaccine_safety/committee/topics.



* in infants symptoms of HIV-infection rarely appear before several months of age.

? Question 1*

Based on the information provided in the *GACVS example*, define, which of the following statements is correct:

- A. Infants known to be HIV infected, with or without signs and symptoms should be immunized with BCG vaccine.
- B. Infants with unknown HIV status who have signs and symptoms of infection should be immunized.
- C. Infants born to women of unknown HIV status should be immunized.
- D. Infants whose HIV status is unknown and who demonstrate no signs or reported symptoms suggestive of HIV infection should not be immunized.

! Key point

- It is essential that concerns about vaccine-related adverse events are responded to in a prompt and efficient manner. The GACVS is the main global advisory body to provide such advice with necessary scientific rigour.

Good information practices – Vaccine Safety Net

The internet is a mine of useful information on various topics, but also contains websites of dubious quality. Although many quality websites offer science-based information about vaccine safety, other sites provide unbalanced and misleading information.

This can lead to undue fears, particularly among parents and patients.

Global advice and response

GACVS

Other global or regional advisory bodies

To assist readers in identifying websites providing information on vaccine safety that comply with good information practices, the Global Advisory Committee on Vaccine Safety (GACVS) recommended a list of criteria that sites providing information on vaccine safety should adhere to.⁴⁵ The recommended criteria fall into four categories:

- Essential criteria, i.e. with respect to credibility,
- Important criteria, i.e. with respect to content,
- Practical criteria, i.e. with respect to accessibility,
- Desired criteria, i.e. with respect to design.

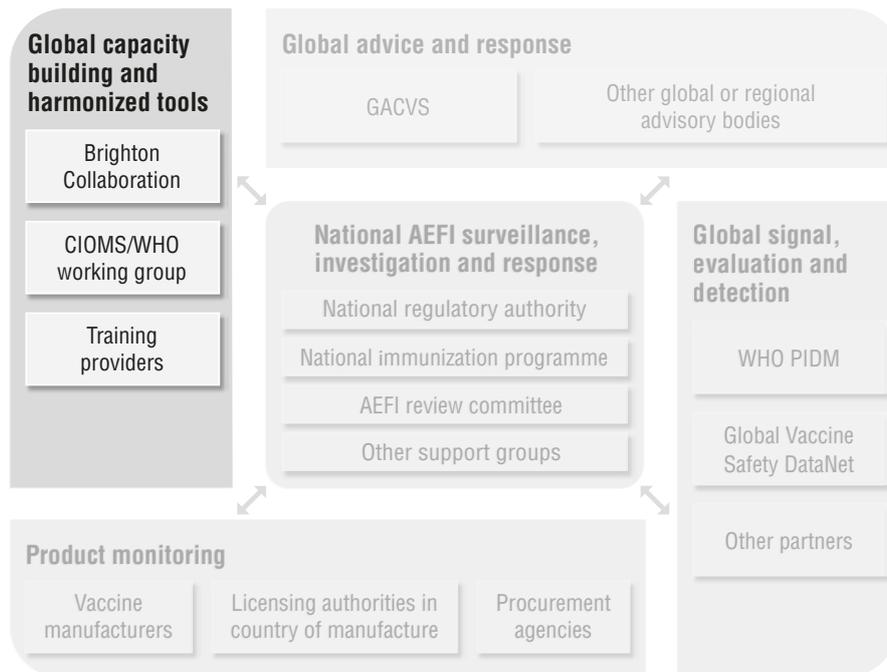
WHO has reviewed a number of sites for adherence to the credibility and content criteria noted above. Vaccine websites not listed may not appear because:

- They have not been reviewed,
- They are currently under review,
- They have been reviewed and do not meet the credibility and content criteria,
- Commercial sites i.e. those supported by vaccine manufacturers are not listed as a matter of policy.

* The answer to all questions can be found at the end of this manual (page 202).

From March 2010, more than 30 websites successfully met the GACVS criteria and are listed on the WHO website. Listed sites are re-evaluated for their adherence to the credibility and content criteria every two years. Evaluation dates are included within each site description.⁴⁵

Global Capacity building and harmonized tools

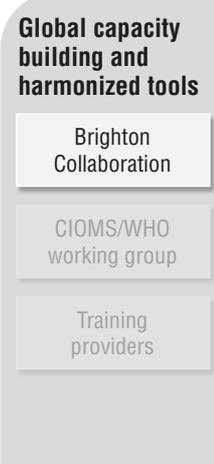


Brighton Collaboration – setting standards in vaccine safety

The Brighton Collaboration⁸⁵ is an international voluntary collaboration of scientific experts, launched in 2000. It facilitates the development, evaluation and dissemination of high-quality information about the safety of human vaccines.

The main objectives of the collaboration are.⁴⁰

- To raise **global awareness** of the availability of standardized case definitions and guidelines for data collection, analysis and presentation, and to educate about the benefit of and monitor their global use and to facilitate access,
- To develop single **standardized case definitions**⁸⁶ for specific AEFIs,
- To prepare guidelines for **data collection**, analysis and **presentation** for global use,
- To develop and implement **study protocols for evaluation** of case definitions and guidelines in clinical trials and surveillance systems.



Case definitions

In Module 4, chapter “*AEFI surveillance: Detection and reporting*” (page 99) you have learnt about the use of standard case definitions and guidelines. Without globally accepted standard case definitions for assessing AEFIs, it is difficult, if not impossible, to compare safety data across trials with any validity. Standard case definitions serve to define the levels of diagnostic certainty or specificity of the reported AEFI. They also indicate if the AEFI was diagnosed solely on clinical signs and symptoms (lower specificity) or confirmed by laboratory test (higher specificity).



Key point

- The Brighton Collaboration provides globally accepted, standard case definitions for assessing AEFIs so that safety data across trials and surveillance systems can be compared.

CIOMS/WHO working group

The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949 to serve the scientific interests of the international biomedical community.

The Council for the International Organizations of Medical Sciences (CIOMS) and WHO established a joint working group on vaccine pharmacovigilance in 2005, recognizing that vaccines represent a special group of medicinal products with issues specific to the monitoring and assessment of vaccine safety.

- To propose standardized definitions relevant to the monitoring of safety of vaccines intended for the prevention of infectious diseases during clinical trials and for the purposes of vaccine pharmacovigilance after licensing,
- To contribute to the development, review, evaluation and approval of AEFI case definitions as developed by the Brighton Collaboration process, and to contribute to their dissemination, including their translation into additional languages,
- To collaborate with other CIOMS Working Groups, especially that on Standardized MedDRA Queries (MedDRA is the Medical Dictionary for Regulatory Activities) and the CIOMS Working Group VIII on Signal Detection on issues relevant to vaccine safety.

The purpose of developing standardized definitions and terminology, or other guidance documents relevant to vaccine safety, is to contribute to the harmonization of vaccine pharmacovigilance among different stakeholder groups and bodies. The principal stakeholders are represented among the 22 Joint Working Group members from the vaccine industry, regulatory agencies, national and international public health agencies (including WHO and CIOMS) and academia.

A number of subgroups have also been established to carry out specific assigned work.

Additional activities that the CIOMS/WHO Working Group on Vaccine Pharmacovigilance has engaged in, although not formally incorporated in its terms of reference, have included providing consultations and expert inputs to other vaccine pharmacovigilance initiatives, such as the Global Vaccine Safety Blueprint project led by WHO (discussed later in this module), and the development of a vaccine dictionary by the Uppsala Monitoring Centre.

Global capacity building and harmonized tools

Brighton Collaboration

CIOMS/WHO working group

Training providers

CIOMS/WHO Report on Vaccine Pharmacovigilance:



vaccine-safety-training.org/tl_files/vs/pdf/report-of-cioms-who-working-group.pdf

Vaccine safety training opportunities

Global Vaccine Safety Resource Centre

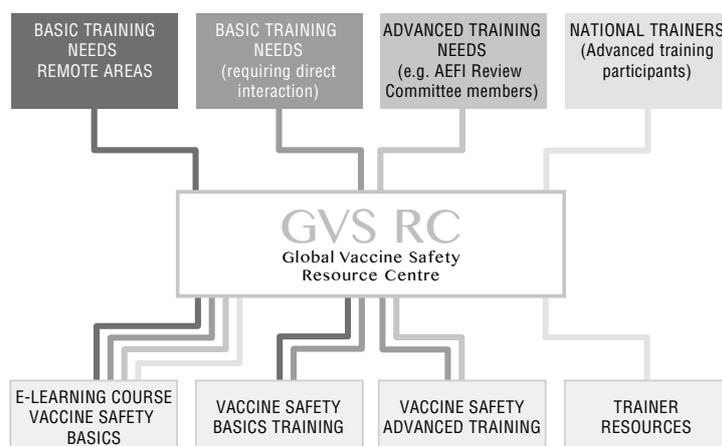


The Global Vaccine Safety Resource Centre (GVS RC)⁸⁷ is an online platform through which WHO provides learning resources for capacity strengthening both in form of workshops and online courses. The GVS RC offers learning opportunities to national public health officials, immunization programme managers, vaccination staff.

Among the resources available are:

- This E-learning course on Vaccine Safety Basics, which complements WHO workshops on Vaccine Safety,
- Workshops to build minimal capacity for vaccine pharmacovigilance in countries,
- Advanced level workshops that focus on causality assessment in particular and mainly aim at building investigational capacity, for example among members of national AEFI Review Committees,
- Access to training material for national staff that has passed WHO workshops and wishes to train staff at country level.

Overview of vaccine safety training opportunities for different target groups



Go to www.who.int/vaccine_safety/initiative/tech_support to access more information on the Global Vaccine Safety Resource Centre.

Global signal evaluation and detection



WHO Programme for International Drug Monitoring

Established in 1968, The WHO Programme for International Drug Monitoring (PIDM)⁸² provides a forum for WHO Member States to collaborate in the monitoring of drug safety, and notably, the identification and analysis of new adverse reaction signals from data submitted to the WHO global individual case safety report (ICSR) database by member countries.

The programme consists of a three-part network:⁴²

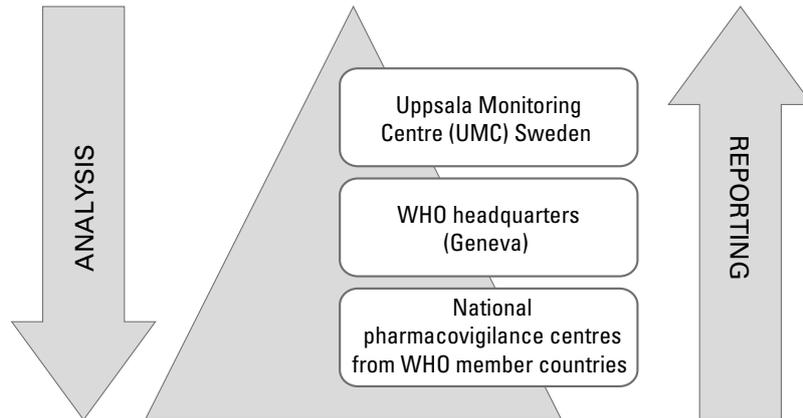
- National pharmacovigilance centres from WHO member countries are responsible for case reports sent to the WHO ICSR database (managed by the Uppsala Monitoring Centre (UMC)⁸³ in Sweden),
- UMC oversees the WHO programme operations, including:
 - Collecting, assessing and communicating information from member countries about the benefits, harm, effectiveness and risks of drugs,
 - Collaborating with member countries in the development and practice of pharmacovigilance,
 - Alerting NRAs of member countries about potential drug safety problems via the WHO signal process.
- WHO headquarters in Geneva, Switzerland is responsible for policy issues.

Global signal, evaluation and detection

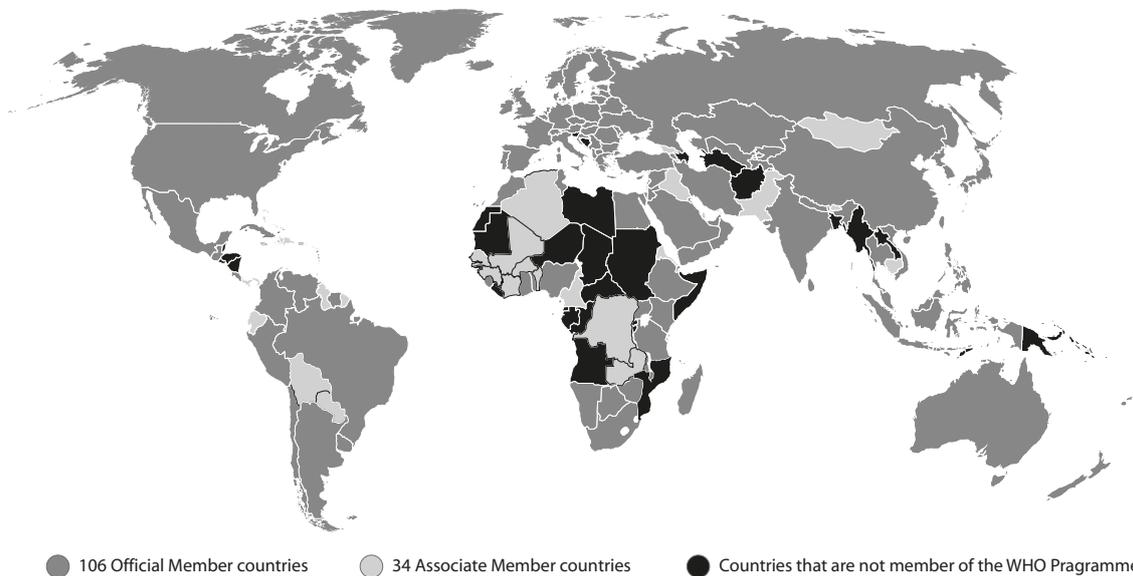
WHO PIDM

Global Vaccine Safety DataNet

Other partners



As of June 2012, more than 100 countries had joined the programme, and more than 30 associate members were awaiting compatibility between the national and international reporting formats. Member countries are shown on the map below.⁴²



Global Vaccine Safety DataNet (GVSD)

In 2007, an international meeting was held in France to discuss the establishment of a Global Vaccine Safety DataNet (GVSD). It was attended by:

- Experts from developed and developing countries that currently, or will soon, collect computerized information on vaccine exposure and clinical outcomes,
- Representatives of public health agencies,
- Pharmaceutical companies.

The goals of the meeting were to:

- Assess current capabilities and interest in establishing a global vaccine safety data network,

Global signal, evaluation and detection

- WHO PIDM
- Global Vaccine Safety DataNet
- Other partners

- Explore the infrastructure and funding required to bring such a project to fruition,
- Define how to best implement this project.

Several considerations prompted the urgent need for a global approach to monitoring vaccine safety:

- Vaccine manufacturing is becoming globalized. Many countries outside North America and Europe are now producing vaccines,
- An increasing number of new vaccines will be first introduced in developing countries that have a limited infrastructure for monitoring vaccine safety,
- Future vaccines, such as those against HIV or malaria, will probably make use of newer technologies with limited safety information, such as DNA vaccines, live virus vectors and new adjuvants.



A globally accessible computerized database for evaluating vaccine safety would allow rapid identification of possible vaccine safety issues, based on vaccine exposure information, standardized terminology, and case definitions. Such a database would allow comparison or combination of data from different sites in collaborating countries.

For example, if a vaccine safety issue is identified and validated in one site or country, the information can be rapidly communicated via the database to other countries using the same vaccine. Global collaborations would also enable the experience and expertise of the high-income countries to be extended to immunization programmes in the low-income countries, for example:

- Training in data management, data sharing, data governance and data protection,
- Developing ethical policies and procedures in collecting and reporting data, including guarding against conflicts of interest,
- Sharing protocols, agreements and methods for evaluating local vaccine signals at global level.

The Global Vaccine Safety DataNet GVSD would also enable collaborative studies to be conducted across several countries and allow results obtained in one geographical area to be tested in different populations with a different balance of vaccine risk and immunization benefit.

Question 2*

Think back to the *example of the introduction of rotavirus vaccines* (page 26) and detection of the post-licensure incidence of intussusception. How could the pooling of AEFI data from several countries via a global database have influenced the outcomes of surveillance in this example?

- A. Pooling of data would have increased the statistical power for identifying intussusception following rotavirus vaccination.
- B. The time to establish a causal association between the AEFI and the vaccine would have increased.
- C. Pooling of data would have decreased the statistical power for identifying intussusception following rotavirus vaccination.
- D. The time to establish a causal association between the AEFI and the vaccine would have decreased.

* The answer to all questions can be found at the end of this manual (page 202).

Product monitoring

Procurement agencies

A country that does not produce its own vaccines acquires them from providers outside. It is strongly recommended that governments buy their vaccines through a competent procurement body that observes well-established, internationally recognized procurement procedures, whether the vaccines are imported or locally produced. International organizations supporting countries' procurement efforts are:

- UNICEF Supply division – Copenhagen, Denmark,
- WHO.

In addition, WHO provides courses in strengthening vaccine procurement skills, which can be accessed at the [Global Learning Opportunities for Vaccine Quality⁸⁸](#) website.



Licensing authorities in countries of manufacture

All vaccines used within a national immunization programme must meet WHO prequalification requirements for quality and safety. To assure the quality and safety of vaccines, a country must have a competent and functioning independent National regulatory authority (NRA) that supervises:

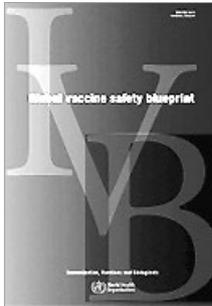
- Licensing the product and product facilities,
- Surveillance for the vaccine performance in field conditions,
- Lot release,
- Laboratory testing,
- Regular inspection,
- Compliance with Good Manufacturing Practice (GMP),
- Evaluation of clinical trial data in licensing decisions.

Prequalification requirements are rigorous and standardized. Before prequalification is granted, the WHO conducts quality assurance tests on individual vaccine batches, rigorously inspects manufacturing sites and evaluates the National regulatory authority of the country where the vaccine will be produced.

Vaccine manufacturers

Marketing authorisation (MA) holders are expected to provide summary of relevant new safety information together with a critical evaluation of the risk-benefit balance of the product, in form of periodic benefit-risk evaluation report (PBRER). The evaluation of such reports should ascertain whether further investigations need to be carried out or if changes to the marketing authorisation or product information has to be made.

Global Vaccine Safety Initiative



Hundreds of millions of doses of vaccine are used every year in developing countries. However, assessments of regulatory authorities conducted by WHO demonstrate that few of these countries' programmes have the ability to monitor and assure the safe use of vaccines.

By studying the current performance of vaccine pharmacovigilance systems in low- and middle-income countries, and of existing inter-country and global support mechanisms, WHO has developed a Global Vaccine Safety Blueprint Strategy⁹⁷ in an inclusive drafting process.



Key point

Global Vaccine Safety Blueprint is a strategic framework aiming at the establishment of effective vaccine pharmacovigilance systems in all countries.

It defines indicators of a minimal capacity for ensuring vaccine safety and proposes a strategic plan for enhancing global vaccine safety activities by combining the efforts of major pharmacovigilance stakeholders.

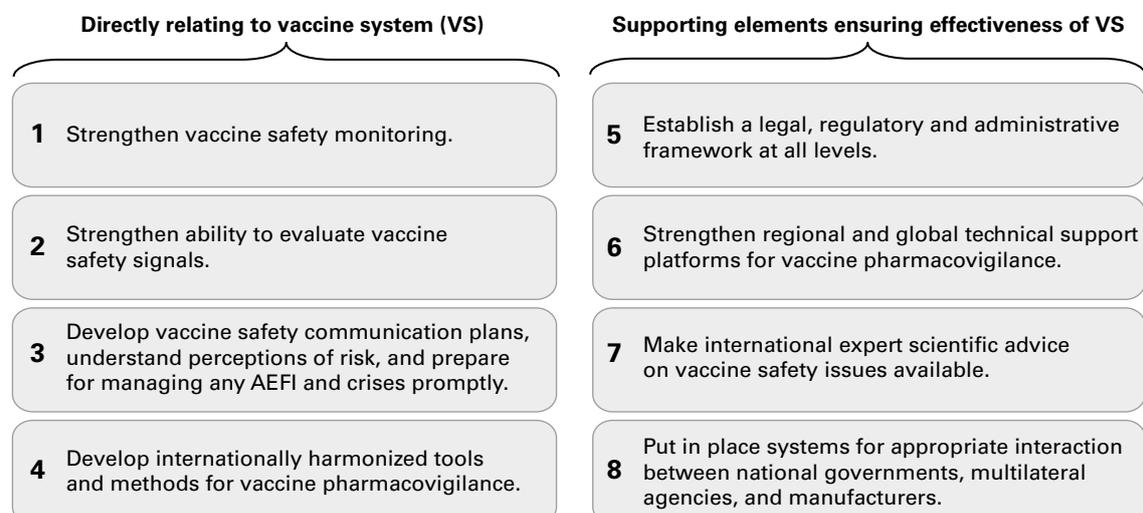
The Global Vaccine Safety Blueprint has three main goals:

- The first goal aims at assisting low- and middle-income countries to have at least minimal capacity for vaccine safety activities,
- The second goal aims to enhance capacity for vaccine safety assessment in countries; that introduce newly developed vaccines; that introduce vaccines in settings with novel characteristics; that both manufacture and use prequalified vaccines,
- The third goal looks to establish a global vaccine safety support structure so that countries can benefit from international collaboration, training and information exchange.

To implement the Global Vaccine Safety Blueprint strategy, a Global Vaccine Safety Initiative project has been initiated.

 www.who.int/vaccine_safety/initiative

The 3 main goals run through 8 Strategic Objectives which relate directly to vaccine systems, or are supporting elements to the effectiveness of vaccine safety systems:



Summary

You have now completed the learning for this module. These are the main points that you have learned.

- The main functions and services that are present for vaccine safety, including national and international bodies, and manufacturers.
- The relevant areas that the NRA and NIP in your own country are responsible for, and (if applicable) the areas of collaboration between them.
- The main actors providing support on vaccine safety to countries at global level, as well as their areas support:
 1. Global capacity building and harmonized tools,
 2. Global analysis and response,
 3. Global signal evaluation and detection,
 4. Product monitoring.
- The Global Vaccine Safety Blueprint as the main strategic framework aiming at the establishment of effective vaccine pharmacovigilance systems in all countries.

**You have completed Module 5.
We suggest that you test your knowledge!**

ASSESSMENT 5

Question 1

National regulatory authorities are responsible for licensing vaccines and AEFI surveillance, whereas National Immunization Programmes assume responsibility for the safe storage, handling, delivery and administration of these vaccines. Both are responsible for the delivery to the population of safe, effective vaccines of high quality.

Is this statement true or false? Select one:

- True
- False

Question 2

Every country should establish an AEFI Review Committee to review individual serious and unusual AEFIs and other AEFIs referred to it by expert groups, to assess potential causal links between AEFIs and a vaccine (or vaccine lot). Furthermore, the AEFI Review Committee should monitor reported AEFI data for potential signals of previously unrecognized vaccine-related adverse events, and provide recommendations for further investigation, education, corrective action and communication with interested parties, including the media.

**Which of these people are suitable as members of a national AEFI review committee?
Select one or more:**

- A. National EPI Manager.
- B. A university professor of epidemiology.
- C. The director of the National Regulatory Authority.
- D. A senior investigator in immunology from the national research laboratory.
- E. A forensic physician.
- F. The transport manager of the company that distributes the vaccine.

Question 3

Reporting lines for AEFIs:

Identify one person or organization who should receive information from you, if you have been alerted to an AEFI, or a cluster of causally related AEFIs, assuming that you are:

- A. A pharmacovigilance officer in the NRA _____
- B. A person working in a vaccination centre _____
- C. A Regional Health Officer _____

- a Immunization programme manager
- b The National Regulatory Authority
- c The vaccine manufacturer

Question 4

Link the organizations listed below to the corresponding areas of expertise.

1. Global Advisory Committee on Vaccine Safety (GACVS)

2. Vaccine manufacturers

3. National advisory body responsible for strengthening evidence-based, locally-relevant policy and strategy decisions on issues of vaccine quality and safety, including the introduction of, or need for, new vaccines and immunization technologies.

4. Brighton collaboration

5. Global Vaccine Safety Data Link

- a Global signal detection and evaluation
- b National Immunization Technical Advisory Groups (NITAGs)
- c Product monitoring
- d Global capacity building and harmonized tools
- e Global analysis and response

Question 5

The Global Advisory Committee on Vaccine Safety (GACVS) is the main advisory body to WHO on vaccine-related safety issues. Which of the following actions are in the remit of this committee? Select one or more:

- A. Providing advice on vaccine safety alerts that may have a potential to cause, public concern.
- B. Develop standard case definitions for specific Adverse Events Following Immunization.
- C. Providing scientific advice on vaccine safety issues of potential global importance, for example on the use of BCG vaccine in immunocompromised individuals.
- D. Review key tools of WHO that support the investigation of adverse events following immunization, for example the WHO Information Sheets on Observed Rates of Reactions of specific vaccines.
- E. Identify and analyse new adverse reaction signals from data submitted to the WHO global individual case safety report (ICSR) database.

You have completed Assessment 5.

Assessment solutions

Question 1

The correct answer is 'True'.

National regulatory authorities are responsible for licensing vaccines and AEFI surveillance. The NRA is usually the main institution mandated to regulate drugs, including vaccines. It has the aim of ensuring the quality, efficacy and safety of the product.

A nates in children and adults. A NIP is a government programme that operate within the framework of overall health policy. National Immunization Programmes assume responsibility for the safe storage, handling, delivery and administration of vaccines.

Question 2

Answers B, D and E are correct.

An AEFI Review Committee should be composed of members that are independent of the immunization programme. It should represent a wide range of specialists whose expertise may add to the task of reviewing the AEFIs. Areas of expertise would include paediatrics, neurology, internist, forensic physician, pathology, microbiology, immunology and epidemiology. Medical experts in particular should be invited for the analysis of special clinical events.

To avoid conflict of interest, the national EPI manager, vaccine laboratory scientists, representatives of the national vaccine regulatory authority, and regional/district EPI officers should not be included as members in the Committee, however, should be available to support it in its functions.

Question 3

Correct answers:

- A. The vaccine manufacturer,
- B. Immunization programme manager,
- C. The National Regulatory Authority.

The National Immunization Programme is a national organisation within Ministry of Health responsible for protecting children and adults from vaccine-preventable diseases through the correct storage, handling, preparation and administration of safe, effective and high quality vaccines.

The Global Advisory Committee on Vaccine Safety (GACVS) is the multidisciplinary body responsible for advising WHO on global vaccine safety issues and the prompt, efficient and scientifically rigorous response to issues of vaccine safety with potential global importance.

The National Regulatory Authority (NRA), is a national institution responsible for the regulatory procedures governing vaccine lot release and subsequent confirmatory testing, to ensure that all vaccines released for use within a country are safe, effective and of good quality.

National Immunization Technical Advisory Groups (NITAGs) are national advisory bodies responsible for strengthening evidence-based, locally-relevant policy and strategy decisions on issues of vaccine quality and safety, including the introduction of, or need for, new vaccines and immunization technologies.

Question 4

Correct answers:

1. Global analysis and response,
2. Product monitoring,
3. National Immunization Technical Advisory Groups (NITAGs),
4. Global capacity building and harmonized tools,
5. Global signal detection and evaluation.

Question 5

Answers A, C and D are correct.

Established in 1999 under WHO's Immunization Safety Priority Project, the **Global Advisory Committee on Vaccine Safety (GACVS)** advises WHO on vaccine-related safety issues and enables WHO to respond promptly, efficiently and with scientific rigour to vaccine safety issues of potential global importance. (http://www.who.int/vaccine_safety)

Answer B

The **Brighton Collaboration** develops of single standardized case definitions for specific AEFIs. It is an international voluntary collaboration of scientific experts, launched in 2000. It facilitates the development, evaluation and dissemination of high-quality information about the safety of human vaccines. (<https://brightoncollaboration.org/public>)

Answer E

The **WHO Programme for International Drug Monitoring (PIDM)** provides a forum for WHO Member States to collaborate in the monitoring of drug safety, and notably, the identification and analysis of new adverse reaction signals from data submitted to the WHO global individual case safety report (ICSR) database by member countries.

(www.who.int/medicines/areas/quality_safety/safety_efficacy/National_PV_Centres_Map)

MODULE 6

Communication

Overview

Every year, billions of doses of vaccine are given in immunization programmes around the world. Vaccines are designed to provoke an immune response in the body, and it is inevitable that this reaction carries a small attributable risk to the health of a tiny minority of recipients. This risk is hugely outweighed by the very significant benefits of immunization in terms of protection from vaccine-preventable diseases and their wide-ranging consequences.

Explaining risks and benefits of vaccines clearly to parents, guardians and vaccine recipients requires effective communication and interpersonal skills from trained health professionals in immunization programmes and educators such as school teachers.

This module will help you to understand public fear and concerns, and how you can improve your communication skills on the subject of vaccine safety.

Module outcomes

By the end of this module you should be able to:

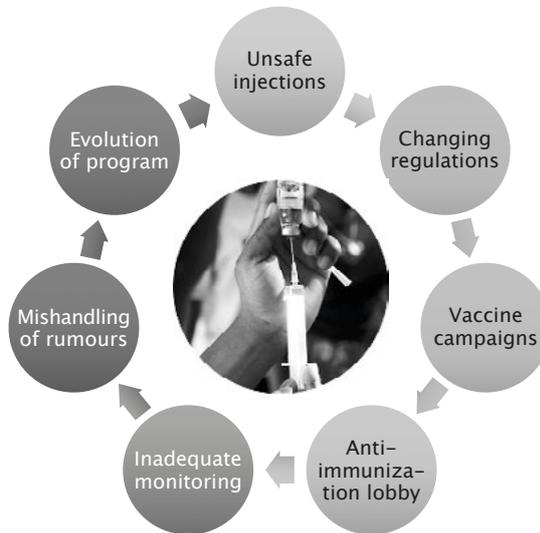
- 1 Understand the need for improved communication on vaccine safety,
- 2 Critically evaluate and assess new information about vaccines before communicating to the target audience,
- 3 Gather information about the various target audiences, who they are, how they perceive vaccine risk and their knowledge about vaccines and safety,
- 4 Outline the fears and concerns of different groups associated with, or likely to be affected by, an immunization programme,
- 5 Design, simple, clear and tailor-made messages to communicate information about vaccine safety to your target audience (e.g. parent, vaccinee, clinic staff, media, health professional, drug regulatory authority, health minister, etc),
- 6 Identify the most suitable means and channels of communication to convey information to different target groups,
- 7 Understand the media as being an important ally in vaccine safety.

Risk communication

Need for improved communication

Concerns are frequently raised about vaccines and immunization protocols by members of the general public and in the media. These concerns can be serious and are often misplaced. See the graphic below for some factors that may trigger public concerns.

We need to improve the quantity, quality and targeting of communication about vaccine safety if we are to increase acceptance of vaccination through improved awareness of the risks and benefits.



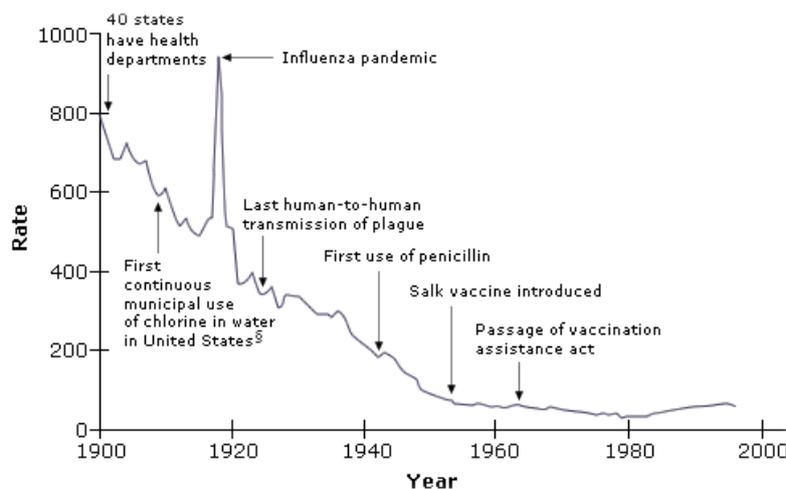
Challenges to effective communication

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

Decline of childhood infections in high-income countries

The impressive decline in the rates and severity of childhood infections in high-income, industrialized countries during the twentieth century (see diagram) has effectively faded memories of the threats to health and life posed by once-common diseases such as measles, polio, pertussis, diphtheria and tetanus. The benefits of vaccination are no longer being reinforced by direct experience of the diseases that vaccines prevent.

Crude death rate* for infectious diseases – United States, 1900 – 1996**



§ American Water Works Association. Water chlorination principles and practices: AWWA manual M20. Denver, Colorado: American Water Works Association, 1973.

* Per 100,000 population per year.

** Adapted from Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. JAMA 1999;281: 61–6.

Parents view that infectious disease is a thing of the past

Some parents in countries such as the USA and western Europe may feel that exposing a child to even a small potential risk from vaccination is unnecessary because they assume that infectious diseases are ‘a thing of the past’. Parents have to be made aware of the consequences of their decisions not to vaccinate their children – if herd immunity falls, the disease may re-emerge and spread through the population. This is what happened when concerns about the safety of the vaccine against measles, mumps and rubella (MMR) in the 1990s led to a sharp decline in vaccine uptake in the UK, followed by an increase in cases of measles, mumps and rubella.

Introduction of new vaccines

New vaccines are being introduced and a wider range of ages is being targeted for routine immunization. For example, teenagers in some countries are offered vaccines against human papillomavirus and bacterial meningitis. Likewise, elderly people are encouraged to seek vaccination against influenza. In the developing world, women of childbearing age are targeted for vaccination with at least two doses of tetanus toxoid to protect themselves and their newborns from the disease.

Communication with different age groups requires different skills and the use of age-appropriate language. Staff needs to be prepared and trained to deal with the different target groups and to expect different adverse events (e.g. immunization anxiety may occur at a different frequency in different age groups).

Transparency and accountability

Finally, good communication to all relevant stakeholders is essential to keep the trust of the public towards a transparent and accountable immunization service.

Communicate only reliable information

Before beginning a consultation or leading a training/education session, all health workers must carefully evaluate the reliability and validity of the information they give to clients, patients or professional colleagues.



The national AEFI coordinator is responsible for ensuring that a critical review of the vaccine literature is available to health workers.

Ensuring that the literature, library or database is accurate, and up to date, supports effective communication in several ways:

- It ensures that up-to-date vaccination policies and procedures are applied at national level,
- It facilitates effective management of rumours and community concerns arising from poor science or misleading reports in the media,
- It supports the detection, investigation and decision-making about actions needed in response to new safety concerns. These may originate from other places/countries or may occur during the introduction of new vaccines.

Before acting on new information about vaccine safety in the scientific literature, ensure that you critically review the published material yourself if this is within your expertise.

You can also seek advice from an expert who is qualified and trained to conduct an evaluation. Such experts can be persons from the National immunization programme (NIP) or the National regulatory authority (NRA). If appropriate expertise is limited or inaccessible, obtain guidance from international

sources, such as the Global Advisory Committee on Vaccine Safety (GACVS) or WHO’s Vaccine Safety Net. The WHO evaluation of whether MMR vaccine increases the incidence of autism is a good example of an expert evaluation by the Global Advisory Committee on Vaccine Safety, responding to information needs of the public.

WHO evaluation of whether MMR vaccine increases the incidence of autism

In 1998, a researcher claimed that MMR vaccine increases the incidence of autism. Parents expressed their concerns and media reported widely on this statement. Global scientific advice on this issue was needed for professional staff to take informed decision on this issue.

WHO, based on the recommendation of its advisory body the Global Advisory Committee on Vaccine Safety (GACVS) (who.int/vaccine_safety/committee), commissioned a literature review by an independent researcher of the risk of autism associated with MMR vaccine. The existing studies did not show evidence of an association between the risk of autism or autistic disorders and MMR vaccine.

Based on the extensive review presented, GACVS concluded that no evidence existed of a causal association between MMR vaccine and autism or autistic disorders. The Committee expressed its belief that the matter would likely be clarified by an improved understanding of the causes of autism.

GACVS also concluded that there was no evidence to support the routine use of monovalent vaccines against measles, mumps and rubella vaccines over the combined vaccine, a strategy which would put children at increased risk of incomplete immunization.

GACVS recommended that there should be no change in current vaccination practices with MMR.

Simplified and key messages



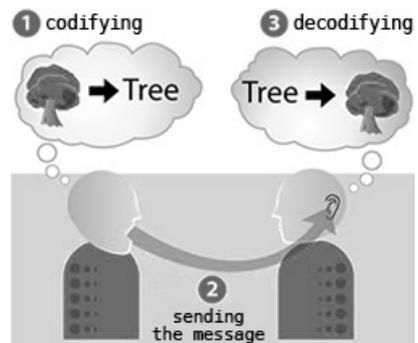
Photo credit: WHO/Christopher Black

In earlier modules and in the previous case study, we described and illustrated how you communicate complex detailed information about AEFIs accurately and systematically, using the approved procedures for reporting adverse events to higher levels (e.g. the NRA). The focus of this module is to support your ability to communicate appropriately targeted and simplified messages about vaccine safety to relevant audiences.

It is important to be clear about key messages and simple messages. To frame your communication simply and clearly, while covering all the essential points, you first need to know:

- Who is your intended audience?
- What is their background knowledge, attitudes and beliefs about vaccination?

Encoding communication.



Source: wikipedia.org

KEY MESSAGES 	SIMPLE MESSAGES 
<ul style="list-style-type: none"> ◆ Key messages give the most important information that you want the public to know. One or two sentences get to the heart of the matter. ◆ Key messages help you to take charge of a situation that requires firm, unambiguous communication, e.g. to refute a misleading rumour or inaccurate report in the media. 	<ul style="list-style-type: none"> ◆ Simple messages are "jargon free" and easy for the general public to understand. ◆ They "translate" complex concepts and information into readily accessible ideas and examples. ◆ They may be short (e.g. slogans used in a campaign poster), or much longer (e.g. an article in a magazine or on a website).

Question 1*

Example key messages of a statement developed to respond to a public concern about a cluster of fatal AEFIs:

- Three children died after immunization with measles vaccine at a Central Clinic,
- Investigations found the cause of death is not due to the vaccine, but to problems arising from unsterile needles,
- Measles causes 750,000 deaths and debilitating disease in children worldwide every year,
- The measles vaccine is the only effective measure in the world for the control of measles,
- Staff training in injection safety and infection control will be prioritized to prevent similar adverse events from occurring.

Look at the example key messages. Which of the five categories of AEFI that you have learnt in Module 1 is the cause of the problem here?

Refrain from over-simplifying or withholding information

Vaccination clinic staff may fear that raising the topic of vaccine-associated risks with members of the public may cause alarm and generate concerns about vaccination where none existed previously. Some health workers may also be tempted to omit certain information about vaccine safety to parents, guardians or vaccinees, assuming a lack of understanding on their part. In particular, health workers may believe that members of the public cannot absorb complex scientific information, for example, about how the immune system responds to a vaccine and why vaccine reactions sometimes occur. For the same reason, health workers may be hesitant to explain the risks and benefits of a vaccine using the background rate of an adverse event, the rate of the same event in the vaccinated population, and how the population risk relates to the risk of an AEFI occurring in a vaccinated individual.

* The answer to all questions can be found at the end of this manual (page 202).

<p>+ DO</p> <p>Inform vaccinees or their families. They deserve to know the details about the vaccine:</p> <ol style="list-style-type: none"> 1. Name of the vaccine, 2. What the vaccine protects against, 3. Expected or potential adverse events, 4. What to do if they or their child experience an adverse event. <p>As a Healthcare provider, communicate this information in understandable terms, ideally in written form ahead of the time of vaccination.</p>	<p>— DO NOT</p> <p>Do not leave the vaccinees or their families uninformed. It is unethical to conduct an invasive procedure without informed consent.</p> <p>Do not assume parents or the public will not understand information about vaccine safety.</p>
---	---

! **Key point**

It is important to emphasize that it is unethical to conduct an invasive procedure such as immunization without first obtaining informed consent from the vaccinee or from a responsible adult in the case of a child.

True consent cannot be given unless the essential information has been communicated to the target audience in simple, accessible language that enables the listener to reach an informed decision.

Risk perception

Health experts do not view the risks associated with a medical procedure (such as vaccination) in the same way as members of the public (parents, patients and vaccinees).

Experts understand risks in terms of numerical values and rates: for example, this table compares the risks of death due to three vaccine-preventable diseases and the risks of adverse events following immunization with the approved vaccines.

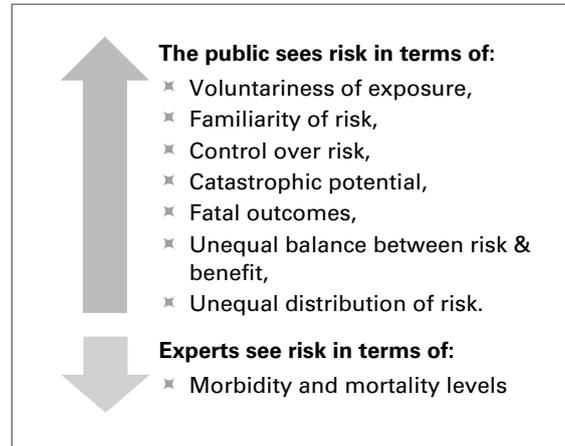


Risks of illnesses and risks associated to the corresponding vaccines

Measles	Death: <ul style="list-style-type: none"> • 1 in 3,000 cases in high income industrialized countries. • As much as 1 in 5 cases during outbreaks in low- to middle-income countries.
Diphtheria	Death: 1 in 20 cases.
Tetanus	Death: 25–70 in 100 cases overall. (10–20 in 100 cases with good intensive care management.)
Measles vaccine	Encephalitis or severe allergic reaction: 1 in 1,000,000 cases.
DTP vaccine	Continuous crying, then full recovery: 1 in 100 cases.
Tetanus toxoid vaccine	<ul style="list-style-type: none"> • Convulsions or shock (full recovery): 1 in 1,750 cases. • Acute encephalopathy: 0–10.5 in 1,000,000 cases.

Public perception

In contrast to the perception of experts, parents, guardians and vaccinees rather want to know whether they or their child could be the “one in a million” who develops encephalitis following immunization with measles vaccine.



Other factors that may influence the way public tends to see risk, include:

Negligence of the danger of the disease

Most adults in high-income countries with high vaccination coverage have never seen a case of measles or any of the other vaccine-preventable childhood diseases. As a consequence, they may underestimate the probability of harm if the disease does develop.

Influence by individual context

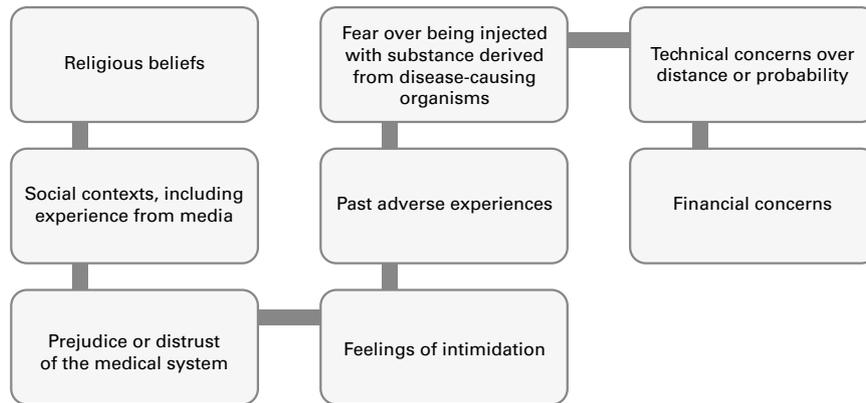
The public is likely to perceive risk in broad religious, social or personal contexts. For example, some will distrust the medical system due to a personal prejudice against “experts” and a desire not to be influenced by them; others will uncritically accept all instructions from health workers because they feel intimidated or inferior.

Aversion to medicine

Adverse personal experiences from the past (e.g. the memory of a painful injection or a sore/swollen arm) may also negatively influence attitudes to vaccine-associated risk. The thought of being injected with a foreign substance derived from disease-causing organisms can induce fear and dread. Clients may feel reluctant to come to a clinic or other health facility, or to bring their children if the environment feels intimidating and the health workers are not reassuring or welcoming.

For all these reasons, it is important to understand the concerns of your target audience and the different approaches required to communicate effectively with persons planning to receive a vaccine, the public and your expert colleagues.

Personal perspectives influence perception



Concerns of the target audience

There are some common misconceptions about vaccination that are often cited by concerned parents as reasons not to get their children vaccinated. If staff can respond to these with accurate rebuttals perhaps they may not only ease parents’ minds but discourage them from taking other anti-vaccine “facts” at face value.

Sources of information

Lack of information, or inadequate or misleading information about vaccine safety increases the risk of the erosion of trust and confidence in health experts, immunization programmes and governments. Ultimately it can result in lost opportunities to protect health. WHO estimates that two million additional lives could be saved every year by the effective use of readily available vaccines.

Be aware of the different sources of information in your country. Even in remote rural locations in developing countries, the knowledge, attitudes and beliefs of the population towards vaccine safety are influenced by an increasingly wide range of information sources. Roll your mouse over the images to see what the main information sources might be.





Question 2*

Select from the below sources of online information that may help you as immunization manager to powerfully share information with colleagues and the public on the safety of vaccines and immunization?

- | | | |
|-----------------------------------|------------------------------------|--------------------------------------|
| <input type="checkbox"/> Facebook | <input type="checkbox"/> Blogs | <input type="checkbox"/> Website |
| <input type="checkbox"/> Twitter | <input type="checkbox"/> Wikipedia | <input type="checkbox"/> Newsletters |

The World Wide Web is a mine of useful information on various topics, but also contains websites of dubious quality. Many quality websites contain science-based information about vaccine safety. Others provide unbalanced and misleading information, which can lead to undue fears, particularly among parents and patients. At WHO's Vaccine Safety Net website (www.who.int/vaccine_safety/initiative/communication/network/vaccine_safety_websites/) you can find Websites providing information on vaccine safety which adhere to good information practices.

Should you be seeking information on vaccine safety that you want to communicate in your country or region, consider the advice of the Global Advisory Committee on Vaccine Safety (GACVS) on how to identify good information practices for vaccine safety websites.⁸⁹

Communicating in public

The most effective method of communicating an important message depends on many factors – including how the communicator gets the message across. Some people are gifted at presenting a message verbally to a large audience (e.g. in a lecture or meeting). Others may find large audiences intimidating, but may be excellent communicators in small groups or one-to-one interviews.

Whatever the setting or means of communication you choose, there are some general principles to keep in mind. These apply both when the communication is with one (interpersonal communication) or with many people:

Target audience

Gather as much information as possible about your target audience to ensure you design messages they will hear.

- Reflect on the capabilities and concerns of your target audience – what do they need to understand to make informed decisions?

FOR EXAMPLE

Providing reassurance to concerned parents, differs from communicating newly available evidence to experts at a conference.

- Consider the age range of your audience.

FOR EXAMPLE

Informing teenagers learning about papilloma virus and HPV vaccination at school versus talking to elderly people learning about influenza and flu vaccination at a community centre.

- Take into account differing educational levels.

* The answer to all questions can be found at the end of this manual (page 202).

FOR EXAMPLE

Talking to preschool children versus qualified nurses at an immunization clinic.

- Mind language problems.

FOR EXAMPLE

Speaking to someone with the same local language versus speaking to someone who has difficulties understanding your language.

- Respect gender differences.

FOR EXAMPLE

Talking to female patients may differ from communicating to a male audience depending on your cultural contexts.

- Take differing religious contexts into account.

Communication objective

- What is your single overarching communications objective?
- What key messages are necessary to achieve that objective and consider the best ways to communicate them (for example, verbally, in writing or in pictures).

Structured communication

- Communicate in a logical sequence.
- Sum up the key points at the end.

Interactive communication

- Encourage the audience to ask questions.
- Thank the target audience for its attention.

? Question 3*

Imagine that during an immunization campaign you have to communicate information in your country about vaccine safety and the benefits of immunization to either nervous parents and their child, or to teachers in a secondary school. Which of the following statements is correct? Several answers possible.

- A. Conduct an interview with a nervous young mother with her first baby choosing a quiet room to enable an atmosphere of trust.
- B. Be aware of your time schedule when interviewing concerned parents. You should not take more than a few minutes to look into their concerns.
- C. When communicating to teachers at a large secondary school, group them to get your message across to them at the same time and allow time for discussion to resolve potential information gaps in your audience.
- D. Provide information material (posters, videos, slides) to target audiences that supports your key messages and provides additional information.

* The answer to all questions can be found at the end of this manual (page 202).

Responding to vaccine safety crises

Rumours and crises

Allegations regarding vaccine-related adverse events that are not rapidly and effectively dealt with can undermine confidence in a vaccine and ultimately have dramatic consequences for immunization coverage and disease incidence.

Some situations that encourage rumour include:

- Serious social conflict,
- Economic and political uncertainty,
- Social transition and clashes of culture and beliefs,
- A history of discrimination and manipulation,
- Lack of transparency in a distant or authoritarian organization.

What is a vaccine safety crisis?

You may not be able to define it, but you certainly know when you are in one!

Crises in vaccine safety are characterized by an unexpected series of events that initially seem to be out of control. The outcome is usually uncertain when the crisis is first identified, and there is a threat to the success of a vaccine or immunization programme.

A crisis may have a “real” basis arising from genuine vaccine reactions or immunization errors, or it may have no foundation in reality and be triggered entirely by mistaken rumours. Often a crisis in vaccine safety originates in the identification of AEFIs, but is aggravated by negative rumours.

Whether a rumour triggers a series of events that build into a crisis depends on the nature of the rumour, how fast it spreads and whether prompt and effective action is taken to address it.

When approaching a crisis, keep in mind that this may not only be a challenge, but also an opportunity to improve the communication on immunization issues. You have the opportunity to dispel negative rumours, to take action to upgrade policies and procedures if required, and to correct any errors or lapses in best practice.

<p>CRISIS CAN ENTAIL: </p> <ul style="list-style-type: none"> ◆ Unexpected series of event. ◆ Events are out of control. ◆ The outcome is uncertain. ◆ Threat to existing situation. 	<p>EVERY CRISIS IS ALSO AN OPPORTUNITY TO: </p> <ul style="list-style-type: none"> ◆ Improve communication. ◆ Dispel negative rumours. ◆ Take any required action to upgrade policies and procedures. ◆ Correct any errors or lapses in best practice.
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Question 4*

Consider the following scenarios. A new vaccine is introduced in a country and a cluster of serious AEFIs occurs including the death of a child.

Which of the following statements address(es) failures in communication that could increase the risk of these adverse events “exploding” into a national crisis and putting the immunization programme at risk?

Several answers possible.

- A. No one took responsibility for managing the event locally - the correct actions were not taken, or not taken quickly enough.
- B. Local communication about the event was poor, adding to the uncertainty and insecurity about what actually went wrong and whether it was being addressed. The parents of the dead child were not counselled, neither was empathy shown to them.
- C. The event was inaccurately reported in the media before you could deal with it.
- D. Rumours started circulating on social media sites.
- E. Someone involved in the original event was not truthful when interviewed about it and the lie was later exposed, adding to the perception that there was a conspiracy to hide the problem and that the health authorities could not be trusted.

Impact of rumours and crises

The history of immunization is not only characterized by its unique success at achieving huge reductions in mortality (deaths) and morbidity (illness and disability) from vaccine-preventable infections and the global eradication of smallpox. It is also notable for the emergence of vaccine sceptics who firmly believe that vaccines are harmful and lobby against them. This – often very vocal – opposition has been a persistent challenge to immunization programmes since they first began over two centuries ago.⁹⁰

Example 1: Whole-cell pertussis “scare”

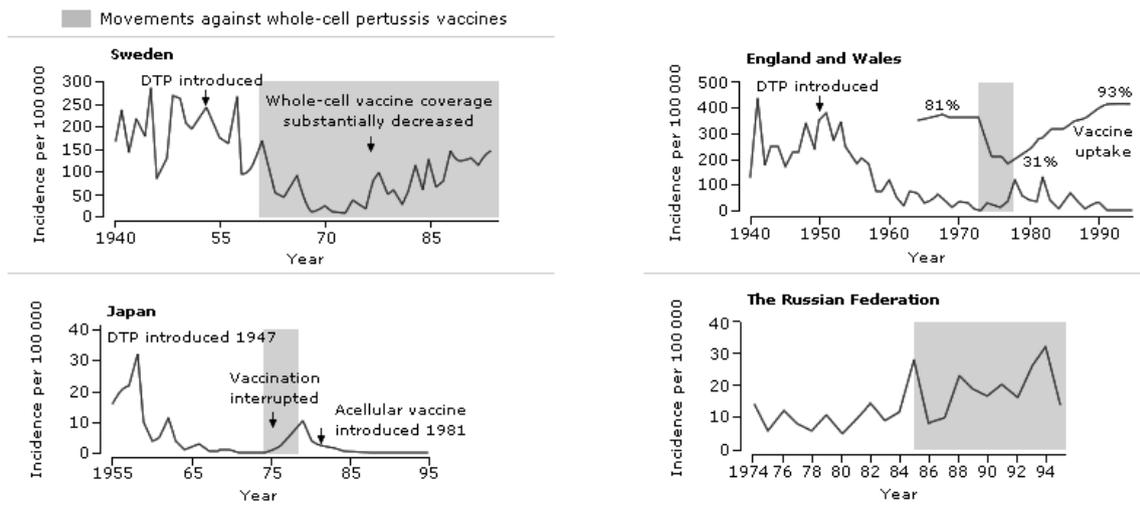
Many recent immunization programmes have suffered setbacks from immunization scares. Children have been needlessly put into danger by frightened parents that refused immunization for their children after “scare stories” about particular vaccines.

The graphs illustrate the impact of rumours about the pertussis whole-cell vaccine from about 1960 onwards in four different locations. Note how affected the vaccine coverage entails a rise in the incidence of pertussis.

These examples also show how negative beliefs about a particular vaccine can spread around the world and reduce public confidence in its safety.

* The answer to all questions can be found at the end of this manual (page 202).

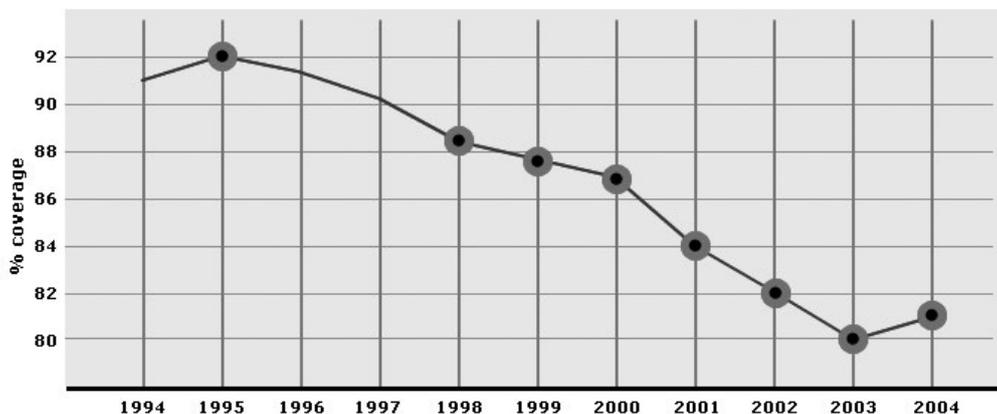
Incidence of pertussis in countries affected by active anti-vaccine movements.



Example 2: MMR and autism controversy in the UK

In 2008, 14 years after the local transmission of measles was halted in the UK, the Health Protection Agency for England and Wales declared it had once again become endemic, i.e. continuously circulating in the population. This was seen as a result of almost a decade of low MMR vaccination coverage across the UK.

Burgess, Burgess and Leask⁵⁴ (2006) analysed how a report of a hypothesised link between measles-mumps-rubella vaccination and autism in 1998 became a major public health issue in the United Kingdom, leaving most experts surprised by its overwhelming influence on public opinion about MMR vaccination. Effectively communicating with parents of autistic children and members of the general public who believed that the truth about the vaccine was being concealed would have been critical to avoid the reduction of vaccination coverage.



- 1995:** Uptake of MMR vaccine peaks at 92% of eligible infants.
- 1998:** Research studies claiming an association between MMR and autism are published in 1998 by a group led by Andrew Wakefield
- 1999:** Wakefields claims prompt huge coverage in the media and a crisis of confidence in the vaccine, which leads to a rapid decline in its uptake.
- 2000:** Confidence in the vaccine continues to decline. Outbreaks of measles occur in the UK and in some other countries as the MMR coverage rate declines.
- 2001:** Tony Blair, the Prime Minister at the time, is placed under extreme pressure to say whether his young son Leo has been given the MMR vaccine. Blair’s refusal to answer the question adds to public concerns.
- 2002:** Vaccine uptake continues to decline. Further outbreaks of measles occur.
- 2003:** Vaccine uptake continues to decline.
- 2004:** Evidence from large-scale studies begins to prove that there is no casual association between autism and MMR, and Wakefield’s research is eventually exposed as without foundation. Vaccine confidence starts to grow again.

Health-damaging outcomes of negative rumours are not confined to high-income countries. There are many other cases from all over the world. For example, in 2009, the death of a 7-year-old child in Taiwan, following his vaccination against the H1N1 strain of influenza virus, led to rumours that the vaccine was responsible. These rumours were followed by a 30% drop in the number of children receiving it.



Question 5*

Which of the following statements would you think to be the main reason for less tolerance towards vaccines, making them more likely to be the subject of negative rumours and “scare stories” than is the case for medical drugs?

- A. Vaccines are more expensive than many drugs which creates less tolerance in the public's perception.
- B. Public tolerance towards adverse reactions is lower compared to side-effects of drugs as vaccines are given to healthy people.
- C. Parents consenting to vaccinating their child, perceive a harm possibly linked to a vaccine as more grave because it could have been avoided.
- D. The public awareness towards vaccine preventable diseases in industrialized countries is high, leading to a resentment towards vaccines.

Responding to rumours and crises

Preparatory work



Key point

Expect crises! They will happen. Be prepared.

When planning your communication to effectively deal with rumours and crises, consider the following three questions:

- Who are your “allies” in dealing with a crisis in public confidence in vaccine safety?
- What are the main elements of your communication plan to deal with rumours and crises effectively?
- Why could your crisis communication plan fail?

Particularly knowing the persons available to support you during a crisis is important. Think of who is best positioned to support you in developing and implementing your crisis communication plan. Professionals working in your post-marketing surveillance system may be well positioned to resolve a crisis swiftly by providing facts and information and supporting the communication. Also think about possible alliances outside your usual contacts, who could add their expertise or support; for example, an organization that might fund aspects of your communication strategy such as printing leaflets, or a scientific journalist who might write an evidence-based article counteracting unfounded information arising from a rumour.

DEFINE THE NATURE OF THE CRISIS

- Is the crisis linked to immunization or not?
- How soon will facts be available?
- What is the damage potential?

DEFINE THE NATURE OF THE RUMOUR

- Where does it come from?
- Is it based on facts?
- Who is likely to be affected by it?
- How is it spread and by whom?

* The answer to all questions can be found at the end of this manual (page 202).

Before you begin work on your crisis communication plan, also make sure that you have clear information and understanding of the crisis or rumour.

Developing a crisis communication plan

Communication in the context of a vaccine-related crisis follows the same steps as any other planning process, but because of the urgency of the situation, compressed time scales apply and you must be able to implement the plan quickly. Inclusive planning and action are critical – all stakeholders should be involved as soon as possible. Remember that communication is not an isolated exercise, but part of a broader action plan for handling the crisis.

Key point

Do not hesitate in taking essential actions if some stakeholders cannot be contacted immediately or do not respond quickly.

CHECKLIST OF POSSIBLE INTERVENTIONS

Mass media

- Are they open to your message?
- What are risks of further distortion?

Advocacy

- Target key opinion leaders?

Advertising

- Will this increase credibility?

Community mobilization

- Do you have time and resources?
- Support the health community: seek collaboration and maintain contact with them.

There are four basic elements of a communication plan.



Decide on your overarching objectives

What are the overarching objectives of your communication strategy? It may be, for example:

- Within 1 year, to reverse the 10% drop in immunization coverage caused by adverse rumours about the vaccine,
- To demonstrate increased public confidence in the vaccine and the immunization programme within 6 months, through surveys of knowledge, attitudes and beliefs.

Define your target audiences

- The people most affected by the rumour or crisis,
- The most influential people to communicate your vaccine safety messages to,
- Internal to the immunization programme or the organizations that govern its operation: e.g. health workers, government ministers, national or international vaccine safety committees,
- External to the immunization programme: e.g. patients/clients, the public, community organizations, pressure groups or the media.

Choose your key messages

- What do you want the audience to hear and retain?

Select the channels of communication

- Choose methods that will reach the largest possible number in your target audience and have highest impact – based on the funding and other resources you have available,
- Be creative about the “how” – effective communication channels may be neglected by opting for the obvious routes,
- Do not underestimate “people power”, for example, by using social media to counteract misleading rumours.

**Question 6***

“Patients die after being given measles vaccine in Bukkala.” Imagine that a crisis was triggered by a report in a mainstream newspaper. A paper has alleged that several children died due to a measles vaccine in a local immunization clinic. You have been asked to formulate a statement on the situation.

Which of the following suggested actions is/are correct (several statements possible)?

- A. Provide a simple explanation of the situation.
- B. State if there is no evidence that the death was caused by the vaccine itself.
- C. Inform if there is an investigation ongoing.
- D. Provide information on the safety profile of the vaccine.
- E. Provide information on the risk posed by the disease that the vaccine prevents.
- F. If you do not have sufficient information to respond to a journalist’s request available, answer with “No comment”.

* The answer to all questions can be found at the end of this manual (page 202).

Communicating with the media

“The media” have already been mentioned, referring to a wide range of communication organizations, methods and technologies. In the final part of this module, the focus is on how someone like you can:

- Communicate your key messages about vaccine safety to the mass media – including the countering of negative rumours,
- Deal effectively with questions from journalists working for newspapers, television, radio and (increasingly) the authors of online blogs and internet news services,
- Design a press release or prepare for an interview by following some simple principles.

There are positive and negative aspects of media coverage.

Positive aspects of media coverage

Well-researched, responsible journalism is important. It can help:

- Communicate public health messages,
- Expose malpractice and negligence, and
- Highlight controversy and inconsistencies in policies and strategies affecting the public.

Negative aspects of media coverage

The news media have to make a profit, e.g. by selling newspapers or advertising space on television. If some journalists are only interested in features of your story that boost sales figures, the task of communicating is becoming more difficult.

Journalists decide on what the news agenda is and cover news that interest their target audience:

- Newsworthy stories are more likely to be dramatic, are targeted at affecting many people, and may focus on famous people or young children,
- Stories could be controversial (e.g. the MMR vaccine and autism), or involve conflict between individuals or organizations and often focus on scandal, corruption and fraud.

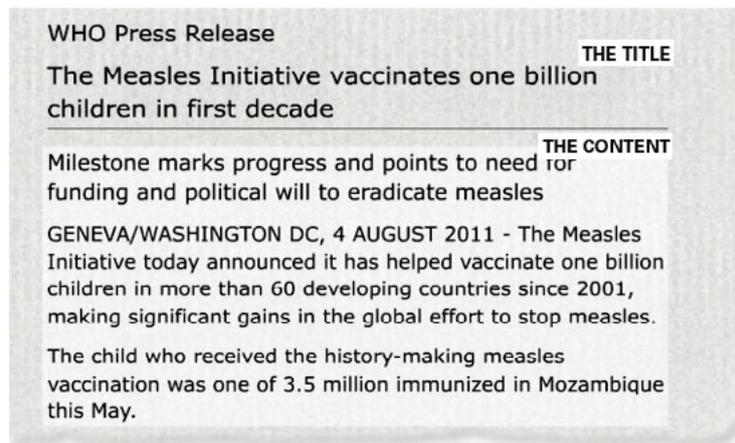
Adverse events following immunization are likely to be reported as they involve children and possibly prevalent negative rumours. They can result in sensationalist reporting, especially if the journalist did not fully understand the issue.

AEFI coverage can be extremely negative if you are not prepared to answer media questions and to get on top of the news before journalists do. Understanding the media, how they work and what they want and establishing good relations with specific media and journalists will help to ensure fair coverage.

CAN HELP YOUR WORK 	CAN HARM YOUR WORK 
<ul style="list-style-type: none"> ◆ Communicating public health messages keeping the public informed. ◆ Exposing malpractice and negligence. ◆ Helping improve inconsistencies in policies and strategies affecting the public. 	<ul style="list-style-type: none"> ◆ Inaccurate or unbalanced news coverage. ◆ Gearing conflicts by publishing dramatic stories. ◆ Publishing sensational stories (implying conspiracies, scandal, corruption and fraud).

Preparing a press release

Frequent press releases from the authorities concerned in investigating the death ensure that journalists are kept informed of the facts as they become known. This prevented adverse and ill-informed speculation from growing about the cause of the tragedy. In preparing an appropriate press release, you should consider two aspects: the title and the content. The title should be short and to the point – but it should also arouse interest, as in this example. The content of the press release should be clear and simple – short sentences are best.



-  Present all the relevant facts in a logical sequence, getting your main points in at the beginning – get help from your colleagues to design your press release.
-  Include a quote if you can get one from a well-known person or someone with a prestigious job title.
-  If the press release is in response to “bad news” (e.g. a cluster of AEFIs) – do not avoid the negative or controversial issues; if you do not deal with them, you will leave room for misinterpretation.
-  Two pages of text are the most you should write (less is better) – anything longer risks getting cut back by an editor who may change the intended message when your press release is shortened.
-  At the end, give your name, title, organization, telephone number(s) and email address if you have one for journalists to contact you for interview requests or more information.

Interactive exercise

Below are various parts of a press release which have been mixed up by your assistant. Bring the information units into the right sequential order by entering numbers 1–4 in the corresponding boxes beside the press release.

Try to describe the situation, outline which follow up action has been taken, provide additional background information and close with an action statement by the Ministry of Health.



Question 7*

AEFI death in Lukurna, Lisusistan: Initial findings

- | | | |
|----|---|--------------------------|
| A. | Following standard procedures, the Ministry of Health of Lisusistan appointed a high level team of experts to investigate promptly the child's cause of death. | <input type="checkbox"/> |
| | The investigation revealed no link between the death of the child and the vaccination. According to the experts, the probable cause of death was asphyxia. | |
| B. | So far, no other serious adverse event was reported. Our officials will continue to monitor ongoing immunization activities to ensure the safety of children in Lisusistan. | <input type="checkbox"/> |
| C. | Every day, an estimated 20 children die from non-vaccine related causes in Lisusistan. Consequently it can be expected that a some death cases can coincidentally occur in short temporal relationship following vaccination. | <input type="checkbox"/> |
| | | |
| D. | Pentavalent vaccination was introduced 2 months ago and about 50,000 doses have been administered by today.
Two days ago, the death of a three month old boy from Lukurna Health Centre has been reported. | <input type="checkbox"/> |
| | This child had received a dose of pentavalent vaccine 4 days ago together with 23 other children. Of these other children, none had an untoward reaction to the vaccine. | |

Preparing for an interview

Preparing for an interview is comparable to preparing a press release, but it is even more important that you find out who is conducting the interview and which organization they work for. The individual or their organization may have a particular point of view (e.g. a bias in favour of or against vaccination), or they may have a reputation for fairness in news reporting. Another consideration might be whether the interviewer has medical or scientific training that will influence the kind of questions you could be asked. Above all consider the emphasis you need to place on the key messages you want to get across.



During the interview, follow these simple rules.

- Maintain eye contact with the interviewer,
- Dress in a professional manner,
- Think before you speak and take time to frame your answers,
- Speak clearly and audibly in simple conversational language,
- Stick to the facts and avoid speculation or personal opinions,
- Make sure you get your key message into the dialogue – more than once if possible,

* The answer to all questions can be found at the end of this manual (page 202).

- Be enthusiastic and engaged in the conversation – try not to look nervous, even if you feel uncomfortable about being interviewed,
- Never say “No comment!”,
- Remember that there is no such thing as an “off the record” statement that you can be certain the interviewer will keep confidential.

Most of all – try to imagine how the interview will appear to members of your target audience. Will they be persuaded by your message?



Build professional relationships with journalists you trust to maintain high standards.



Contact trusted journalists quickly if a rumour start to circulate- before a crisis develops – so you can give them the facts.



Keep your messages simple and to the point.



Be willing to answer questions and be completely honest. Refer to someone who knows the answer if you don't.



Give contact information so the journalist can follow up on the story or check facts with you later.



Remain polite and professional at all times – never lose your temper, even if provoked.



Know your work and be prepared.

Remember that journalists are not interested in destroying your reputation or tricking you!

Summary

You have now completed the learning for this module. These are the main points that you have learned.

- Clear communication is needed to dispel rumours and misconceptions about vaccine safety.
- Prepare your key messages so that they address the issues in a clear, simple way and that reach your specific audience.
- Know who your audience is, and understand their concerns and their perception of risk.
- Choose the most appropriate means of communicating as this will affect your success.
- Develop a plan for communicating, especially in the event of a crisis.
- When communicating with the media, understand their perspective and how it can affect you.

**You have completed Module 6.
We suggest that you test your knowledge!**

ASSESSMENT 6

Question 1

Read each of the points listed below and choose the correct option from the list below to indicate whether the information is:

■ more likely to influence how health experts evaluate vaccine risks

or

■ more likely to influence how members of the public evaluate vaccine risks.

1. Simplified key messages about vaccine safety and the risk of adverse events.

2. Morbidity and mortality rates following immunization with specific vaccines.

3. Adverse personal experiences of vaccination in the past. _____
4. Rumours of adverse events following immunization. _____
5. Population data on the incidence of AEFIs relative to the incidence of disease-related harm. _
6. Research studies on vaccine safety in specialist journals. _____
7. Information that supports informed consent to vaccination. _____
8. Information in accessible language about the symptoms and complications of vaccine-preventable diseases. _____

a General public

b Health experts

Question 2

Is this statement true or false?

More parents in developing countries compared to industrialized countries may feel that exposing a child to even a small potential risk from vaccination is unnecessary because they assume that infectious diseases are 'a thing of the past'.

Select one:

True

False

Question 3

Which of the following general principles of communication should be kept in mind when informing a community group about the local vaccination programme?

Select one or more:

- A. The messages about vaccination should be kept positive at all times and any unhelpful questions should be discouraged.
- B. The age range in the audience should be considered, so that age-appropriate language, information and diagrams can be used.
- C. Decide what your key messages are, the most important information you want your audience to hear, and state the points simply.
- D. Avoid mentioning anything that might concern parents and stop them from giving consent for their children to be vaccinated.
- E. Reflect on the fears and concerns your audience may have about vaccination and ensure that you give them all the information they need in order to make informed choices.

Question 4

Which of the following are helpful suggestion to get your message across with journalists?

Select one or more:

- A. Build professional relationships with journalists who you think you can trust to maintain high standards.
- B. Be proactive and contact journalists if a rumour about vaccine safety starts to circulate.
- C. Keep your messages simple and to the point.
- D. Journalists want to hear complex scientific information. Make sure to use academic jargon or complex arguments.
- E. Remain polite but authoritative – if you feel not confident to respond to a difficult question, respond with ‘No comment’.
- F. Give contact phone numbers and/or email addresses so the journalist can follow up on the story or check facts with you later.

Question 5

Below find the press statement of the interactive exercise in Module 6. Link the paragraph of the press statement to its corresponding main message from the list below.

AEFI death in Lukurna, Lisusistan: Initial findings.

1. Pentavalent vaccination was introduced 2 months ago and about 50,000 doses have been administered by today.

2. Two days ago, the death of a three month old boy from Lukurna Health Centre has been reported. This child had received a dose of pentavalent vaccine 4 days ago together with 23 other children. Of these other children, none had an untoward reaction to the vaccine.

3. Following standard procedures, the Ministry of Health of Lisusistan appointed a high level team of experts to investigate promptly the child's cause of death. The investigation revealed no link between the death of the child and the vaccination. According to the experts, the probable cause of death was asphyxia.

4. Every day, an estimated 20 children die from non-vaccine related causes in Lisusistan.

5. Consequently it can be expected that a some death cases can coincidentally occur in short temporal relationship following vaccination.

6. So far, no other serious adverse event was reported. Our officials will continue to monitor ongoing immunization activities to ensure the safety of children in Lisusistan.

- a Response undertaken to respond to this event
- b Future Follow-up actions
- c Supporting scientific facts
- d Information on the event
- e Information on possible cause
- f Introduction

You have completed Assessment 6.

Assessment solutions

Question 1

Correct answers are: 1–a, 2–b, 3–a, 4–a, 5–b, 6–b, 7–a, 8–a.

Perception of risk varies strongly depending on the audience.

Health experts do not view the risks associated with a medical procedure (such as vaccination) in the same way as members of the public. They understand risks in terms of numerical values and rates: for example, this table compares the risks of death due to three vaccine-preventable diseases and the risks of adverse events following immunization with the approved vaccines.

Parents, guardians and vaccinees, however, rather want to know whether they or their child could be the “one in a million” who develops encephalitis following immunization with measles vaccine.

Question 2

The correct answer is ‘False’.

The impressive decline in the rates and severity of childhood infections in *industrialized countries* has effectively faded memories of the threats to health and life posed by once-common diseases such as measles, polio, pertussis, diphtheria and tetanus. The benefits of vaccination are no longer being reinforced by direct experience of the diseases that vaccines prevent.

Question 3

Answers B, C and E are correct.

Answer A

Discouraging questions will prevent you from responding to concerns of the audience. Questions should be encouraged and negative attitudes and concerns should be openly discussed.

Answer D

Trust in vaccine safety can easily be eroded if you attempt to disguise or conceal the possible adverse effects that may follow immunization. Everyone, either the person receiving a vaccine or his/her parents, deserves to know the name of the vaccine, what the vaccine is protecting against, any what adverse event can be expected from it. They should also be informed on what to do if they or their child experience an adverse event. It is up to the health care provider to communicate information in understandable terms for each individual. Ideally, this would happen in written form ahead of the time of vaccination.

Question 4

Answer A, B, C and F are correct.

Answer D

Do not use academic jargon or complex arguments – this may lead to misunderstanding and frustration among your audience.

Answer E

Responding to journalists with 'No comment' may lead to acrimonies. Be willing to answer questions and be completely honest. If you are not sure of the facts, do not be evasive or speculate., but offer get back to journalists with this information shoertly after the interview.

Question 5

Correct answers:

1. Introduction,
2. Information on the event,
3. Response undertaken to respond to this event,
4. Supporting scientific facts,
5. Information on possible cause,
6. Future Follow-up actions.



You have completed Assessment 6.

A General Assessment is available online to test the knowledge you acquired in this course and to provide you with a certificate upon successful completion.

Visit the General Assessment at:

<http://assessments.vaccine-safety-training.org>

Glossary

A

Acellular pertussis (aP) vaccine

A preparation of subunit proteins from pertussis bacteria, used to immunize against pertussis.

Adjuvant

A pharmacological agent (e.g., aluminum salt, oil-in-water emulsions) that modifies the effect of other agents, such as a drug or vaccine, while having few if any direct effects when given by itself. Adjuvants are often included in vaccines to enhance the recipient's immune response to a supplied antigen, while keeping the injected foreign material to a minimum.

ADR surveillance

A surveillance system designed to collect adverse drug reactions following administration of a drug used for prophylaxis, diagnosis, or therapy of diseases, or for the alteration of a physiological process. This type of surveillance typically relies on health professionals associating an adverse reaction in an individual as a possible consequence of the drug and reporting it to the national pharmacovigilance centre, NRA or appropriate authority.

Adrenaline

A drug used to treat severe allergic reaction (anaphylaxis). Also a hormone produced by the adrenal gland.

Adverse drug reaction (ADR)

A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.

Adverse event (or adverse experience)

Any untoward medical occurrence that may appear during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment.

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.

Adverse event of special interest (AESI)

A relatively new AEFI classification that started with pandemic vaccine development. AESI refers to adverse events of significant scientific, medical, and public interest among pandemic vaccines.

AEFI surveillance (also known as vaccine safety surveillance)

A surveillance system designed to collect adverse events temporally associated with receipt of vaccines. This type of surveillance typically relies on health professionals associating an adverse event in an individual as a possible consequence of vaccination and reporting it to the NRA or appropriate authority.

Anaphylaxis

An acute, multi-system, allergic reaction (IgE mediated) to a substance, such as vaccination, drugs, and food. Symptoms of anaphylaxis may include breathing difficulties, loss of consciousness, and a drop in blood pressure. This condition can be fatal and requires immediate medical attention.

Antibiotic

A substance that kills or inhibits the growth of bacteria. Antibiotics (in trace amounts) are used during the manufacturing phase of some vaccines to prevent bacterial contamination of the tissue culture cells.

Antibody

A special protein produced by plasmocytes in response to antigens (foreign substances, e.g., bacteria or viruses). Antibodies bind with antigens on microorganisms as one of the initial steps of the body's protection against infection.

Antigen

A foreign substance in the body that triggers the production of antibodies.

Asthma

Chronic respiratory disease characterized by constriction of the bronchial tubes to the lungs, which causes sudden and recurring breathing problems, coughing, chest tightness and wheezing.

Asymptomatic carriage

An infection or colonization by a pathogen that does not cause symptomatic disease.

Atopy

A genetic predisposition toward the development of immediate hypersensitivity reactions against common environmental antigens (atopic allergy), most commonly manifested as allergic rhinitis but also as bronchial asthma, atopic dermatitis, or food allergy.

Attenuated vaccine – See Live attenuated vaccine.

Autism

A chronic neural development disorder usually diagnosed between 18 and 30 months of age. Symptoms include problems with social interaction and communication as well as repetitive interests and activities. At this time, the cause of autism is not known.

Auto-disable (AD) syringes

AD syringes are self-locking syringes that can be used only once. AD syringes are the preferred equipment for immunizations requiring injections.

Autoimmune disorders

A condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue. There are more than 80 different types of autoimmune disorders.

B

Bacillus Calmette-Guérin (or Bacille Calmette-Guérin, BCG) – See Tuberculosis vaccine.

Bacteria

Single-celled life-forms that can reproduce quickly on their own. Some bacteria cause disease.

Bacterial carriage

A bacterial infection or colonization that does not cause symptomatic disease.

Bacterial meningitis

Inflammation of the membranes that surround the brain and spinal cord; caused by a bacterial infection.

BCG osteitis

A rare reaction from BCG vaccination, causing inflammation of the bone.

Bell's palsy

Paralysis of one of the facial nerves (the nerves that supply muscles on the face), due to unknown cause. It is characterized by an asymmetric facial expression, due to the paralysis of one side. Several conditions can cause a facial paralysis, e.g., viral infections, brain tumor, stroke, and Lyme disease. However, if no specific cause can be identified, the condition is known as Bell's palsy.

Biologicals

A medical product prepared from biologic material of human, animal, or microbiologic origin (e.g., blood products, vaccines, insulin).

Biosynthetic technology

A method for producing a chemical compound using a living organism.

Booster injection

An additional vaccine dose needed to “boost” (increase) antibody levels after completion of the primary immunization, which may be a series of up to three doses.

Brachial neuritis (also known as brachial plexus neuropathy or neuralgic amyotrophy)

A neuropathy that presents as a deep, steady, often severe aching pain in the shoulder and upper arm and may include muscular weakness.

Bradycardia

Abnormally slow heartbeat.

Brighton Collaboration

An international voluntary collaboration to facilitate the development, evaluation, and dissemination of high quality information about the safety of human vaccines. For more information, see <http://http://www.brightoncollaboration.org>.

Buffers

Substances that minimize changes in the acidity of a solution when an acid or base is added to the solution. Buffers are used in the manufacturing process of some vaccines.

Burden of disease

The impact of a disease in a defined population, usually expressed in terms of mortality or morbidity rates, or some other measure such as years of healthy life lost or disability adjusted life years (DALYs).

C**Carrier protein**

A protein linked to a weak antigen to increase its immunogenicity when used as a vaccine.

Case control study

Study that compares a group of persons with an outcome of interest (e.g., a disease, health condition, unintended drug response) to a control group of people without it. The two groups are compared for differences in past exposures (e.g., drugs, vaccines) or other pre-existing conditions that might explain the difference in outcome.

Causality assessment (or causality association)

The systematic review of data about an AEFI case to determine the likelihood of a causal association between the event and the vaccine(s) received.

Cell-mediated immunity

An immune response not involving antibodies, in which specific blood cells, leukocytes, and lymphocytes attack and remove antigens.

Challenge, dechallenge and rechallenge

A testing protocol in which a medicine or drug is administered, withdrawn, then re-administered, while being monitored for adverse effects at each stage. It is one of the standard means of assessing adverse drug reactions but is usually not possible in vaccine trials or AEFI investigations.

Cholera

An acute infectious disease of the small intestine, caused by the bacterium *Vibrio cholerae* and characterized by profuse watery diarrhea, vomiting, muscle cramps, severe dehydration, and depletion of electrolytes.

Chronic fatigue syndrome (CFS)

A debilitating and complex disorder characterized by profound fatigue of six months or longer duration that is not improved by bed rest and that may be worsened by physical or mental activity. Persons with CFS most often function at a substantially lower level of activity than they were capable of before the onset of illness. In addition to these key-defining characteristics, patients report various nonspecific symptoms, including weakness, muscle pain, impaired memory and/or mental concentration, insomnia, and post-exertional fatigue lasting more than 24 hours. In some cases, CFS can persist for years.

Clinical efficacy

The ability of a medical intervention (e.g., vaccine, drug, procedure) to produce the desired clinical effect (e.g., protection, cure, symptomatic relief).

Clinical trial

A systematic study of a medical intervention in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to the intervention. Clinical trials also study the absorption, distribution, metabolism, and excretion of the products with the objective of ascertaining their efficacy and safety. Clinical trials are generally classified into Phases I to IV. Phase IV trials are studies performed after the licensure and introduction of pharmaceutical products. They are carried out to expand the evidence base of the product characteristics for which the marketing authorization was granted.

Cluster

Two or more instances of an event related in time, place, population subgroup, or common exposure (e.g., vaccine). AEFI clusters are usually associated with a particular provider, health facility, and/or a vial of vaccine that has been inappropriately prepared or contaminated.

Coincidental event

An AEFI classification referring to an adverse event that occur after a vaccination has been given but are not caused by the vaccine or its administration.

Cold chain

A system used to transport vaccines at a constant temperature involving a chain of refrigerators and portable cool boxes. Most vaccines and diluents need to be transported and stored in a cold chain between 2°C to 8°C.

Combination or combined vaccine

A vaccine that consists of two or more antigens in the same preparation (e.g., MMR, DTP).

Confounding factor

A confounding factor is anything that is coincidentally associated with an event (for example, an AEFI), which may mislead the investigator into wrongly concluding that it is influencing the rate of an adverse vaccine reaction.

Congenital

A condition that is present at birth, though not necessarily hereditary.

Conjugated vaccine

A vaccine in which two compounds (usually a protein and polysaccharide) have been joined together to increase the vaccine's effectiveness.

Conjugation technology

A vaccine technology in which two compounds (usually a protein and polysaccharide) are joined together to increase the vaccine's effectiveness.

Contraindication

A condition that makes a particular treatment or procedure, such as vaccination with a particular vaccine, inadvisable. Contraindications can be permanent, such as known allergies to a vaccine component, or temporary, such as an acute febrile illness.

Controlled study

A study that compares a group with an exposure or outcome of interest with a group that does not have the exposure or outcome. When study subjects are randomly assigned to exposed or unexposed groups by the study researcher (e.g., are assigned to receive or not receive a vaccine or drug) and subsequent differences in outcomes measured, the study is called a randomized clinical trial. Studies in which exposure status is not controlled by researchers are called 'observational' and include cohort and case-control studies.

Convulsion – See Seizure.

Cost-effective

This refers to a type of economic analysis that allows comparison of different intervention options by estimating the cost per health outcome for each alternative intervention. It indicates which interventions provide the greatest impact for a given cost.

Cost-saving

The case in which the cost of an intervention (e.g., the cost of delivering a vaccine) is less than the cost of not intervening (e.g., the cost of disease in the absence of vaccination). In this example, the intervention saves money.

Crohn's disease

A chronic medical condition characterized by inflammation of the bowel. Symptoms include abdominal pain, diarrhea, fever, loss of appetite, and weight loss. The cause of Crohn's disease is not yet known, but genetic, dietary, and infectious factors may play a part.

D**Depot effect**

Some adjuvants used in injectable vaccine formulations act as a storage depot for the antigen, allowing its slow release and gradual absorption into the body; this depot effect maximizes the immune response to the vaccine.

Diabetes

A chronic health condition in which the body is unable to produce insulin and properly break down sugar (glucose) in the blood. Symptoms include hunger, thirst, excessive urination, dehydration, and weight loss. Treatment of diabetes requires daily insulin injections or other diabetes medication, proper nutrition, and regular exercise. Complications can include heart disease, stroke, neuropathy, poor circulation leading to loss of limb, vision problems, and death.

Diluent

A fluid provided in a vial or ampoule that is mixed with lyophilized vaccine powder before the vaccine can be injected. Diluents are not interchangeable. Vaccines have different diluents; mixing and administering the wrong diluent with a vaccine has led to serious adverse events including death.

Diphtheria

A disease caused by toxigenic strains of *Corynebacterium diphtheriae*. Often marked by the formation of a false membrane in the throat, diphtheria is a serious vaccine-preventable disease that can cause death in unvaccinated children.

Diphtheria toxoid vaccine

A vaccine containing diphtheria toxoid, used to immunize against diphtheria.

Disseminated BCG infection

Tuberculosis (BCG) vaccine-induced infection that is spread over a large area of the body, a tissue, or an organ. This can result in death (referred to as Fatal disseminated BCG infection).

Dose-response

The relationship between the dose of an active substance (e.g. a vaccine or drug) or radiation exposure, and the response in the body of exposed individuals.

Drug (or medicine)

Any substance in a pharmaceutical product that is used to modify or exploit physiological systems or pathological states for the benefit of the recipient. The term drug/medicinal product is used in a wider sense to include the whole formulated and registered product, including the presentation and packaging, and the accompanying information. Vaccines are drugs/medicines.

DT vaccine

A preparation of diphtheria and tetanus toxoids together in one vaccine, used to immunize children and adolescents against diphtheria and tetanus. The DT vaccine given to adults contains a reduced amount of diphtheria toxoid.

DTaP vaccine

A combination of diphtheria and tetanus toxoids with acellular pertussis vaccine together in one vaccine, used to immunize against diphtheria, tetanus, and pertussis.

DTP vaccine

A combined preparation of diphtheria and tetanus toxoids with pertussis vaccine together in one vaccine, used to immunize against diphtheria, tetanus, and pertussis (also sometimes referred to as DPT vaccine). When an acellular pertussis vaccine is used, the combination is usually abbreviated DTaP. When the whole cell pertussis vaccine is used, the combination is usually abbreviated DTwP.

DTwP vaccine

A combination of diphtheria and tetanus toxoids with whole cell pertussis vaccine together in one vaccine, used to immunize against diphtheria, tetanus, and pertussis.

E

Effectiveness – See Vaccine effectiveness.

Efficacy – See Vaccine efficacy.

Elimination

Reduction to zero (or a very low defined target rate) of new cases of an infectious disease in a defined geographical area as a result of deliberate efforts; continued measures to prevent re-establishment of transmission are required.

Emulsion

A mixture of two liquids that do not mix resulting in one of the liquids dispersed throughout the other in small droplets.

Encephalitis

Refers to an encephalopathy caused by an inflammatory response in the brain. This is usually manifested with systemic constitutional symptoms, particularly fever and pleocytosis of the cerebrospinal fluid. However, the terms encephalopathy and encephalitis have been used imprecisely and even interchangeably in the literature.

Encephalopathy

Refers to a variety of conditions affecting the brain resulting in alterations in the level of consciousness, ranging from stupor to coma. At times, febrile seizures, afebrile seizures, and epilepsy have been considered components of encephalopathy. However, the terms encephalopathy and encephalitis have been used imprecisely and even interchangeably in the literature.

Endotoxin

A toxin contained in the cell walls of some microorganisms, especially gram-negative bacteria, that is released when the bacterium dies and is broken down in the body. Fever, chills, shock, and a variety of other symptoms may result, depending on the particular organism and the condition of the infected person.

Epidemic

The occurrence of disease within a geographical area and/or population that is in excess of what is normally expected for a given period of time.

Epidemiology

The study of the distribution and determinants of health and disease in human populations.

Equine-derived

A substance extracted from horses, e.g. some antibodies used in passive immunization are extracted from the serum of horses exposed to the target antigen.

Eradication

The complete and permanent worldwide reduction to zero new cases of an infectious disease through deliberate efforts; no further control measures are required.

Evidence-based

Research based on systematic investigation of the outcomes of controlled interventions; the results have been verified by other researchers using the same methods.

Expanded Programme on Immunization (EPI)

An international programme launched by WHO in 1974 to increase immunization of the world's children. EPI originally targeted vaccines for six diseases: measles, diphtheria, pertussis, tetanus, tuberculosis and poliomyelitis. EPI and national immunization programme (NIP) are used interchangeably.

F**Fatal dissemination of BCG infection**

Tuberculosis (BCG) vaccine-induced infection that is spread over a large area of the body, a tissue, or an organ, and results in death.

Febrile

Relating to fever; feverish. A febrile seizure is a seizure or convulsion that occurs during a high fever. Common in children under five years of age, rarely resulting in long term injury.

Freund's adjuvant

A water-in-oil emulsion added to some vaccines to increase the immune response to the vaccine antigen.

G**Global Advisory Committee on Vaccine Safety (GACVS)**

Established in 1999, the GACVS advises the WHO on vaccine-related safety issues and enables WHO to respond promptly, efficiently, and with scientific rigor to issues of vaccine safety with potential global importance. The committee also assesses the implications of vaccine safety for practice worldwide and for WHO policies. For more information, see http://www.who.int/vaccine_safety/en/.

Good manufacturing practice (GMP)

Guidelines that outline the aspects of production that would affect the quality of a product. Many countries have legislated that pharmaceuticals, biologicals, and medical device companies must follow GMP procedures, and have created their own GMP guidelines that correspond with their legislation to assure the quality of those products. WHO also proposes GMP guidelines that are used by many countries.

Guillain-Barré Syndrome (GBS)

A rare neurological disease characterized by loss of reflexes and temporary paralysis. Symptoms include weakness, numbness, tingling, and sensitive disorders that spreads over the body. Muscle paralysis starts in the feet and legs and moves upwards to the arms and hands. Sometimes paralysis can result in the respiratory muscles causing breathing difficulties. Symptoms usually appear over the course of one day and may continue to progress for three or four days up to three or four weeks. Recovery begins within two to four weeks after the progression stops. While most patients recover, approximately 15 to 20% experience persistent symptoms. GBS is fatal in 5% of cases.

H**Haemophilus influenzae type b (Hib)**

Bacteria that can cause serious invasive illnesses, such as pneumonia and meningitis; most common in children and persons who are immune compromised (less able to fight off infections). Hib is one of six types of bacteria that are major causes of bacterial meningitis in unimmunized infants.

Haemophilus influenzae type b (Hib) vaccine

A subunit polysaccharide-conjugate vaccine used to immunize against invasive Hib disease.

Hepatitis B

A viral infection of the liver that is transmitted through contact with blood or other body fluids that are infected with the hepatitis B virus. Some infections, especially those acquired in infancy, can become chronic and result in cirrhosis and primary liver cancer in adulthood.

Hepatitis B vaccine (HepB)

A subunit protein-based recombinant vaccine used against hepatitis B infection.

Herd effect

The resistance of a group to invasion and spread of an infectious agent, based on the resistance to infection of a high proportion of individual members of the group. The resistance results from a small proportion of susceptible individuals in a population making it difficult for the infectious agent to sustain circulation.

Herd immunity

A population with a high proportion of individuals with immunity to a particular pathogen, as a consequence of immunization or infection and recovery, may confer protection from infection on the small proportion of its non-immune members because there are too few susceptible people in the 'herd' for the infection to circulate.

Herpes zoster

An inflammatory disease, also known as the shingles, caused by the same virus that causes chicken pox. Some people exposed to this virus during childhood develop partial immunity. After the primary infection as chicken pox the virus becomes dormant, reactivating years or decades later as herpes zoster. It is characterized by painful skin lesions that occur mainly on the trunk (back and stomach) of the body but which can also develop on the face and in the mouth.

HIV/AIDS

Acquired immune deficiency syndrome (AIDS) is a collection of symptoms and infections resulting from the specific damage to the immune system caused by the human immunodeficiency virus (HIV).

Holistic

All embracing, taking into account all aspects of a situation; in healthcare, holistic usually refers to a commitment to consider all aspects of the patient's situation, including social and psychological states as well as medical conditions.

Hypersensitivity

An excessive or abnormal sensitivity in a body tissue to an antigen or foreign substance.

Hypertension

High blood pressure.

Hypotension

Low blood pressure.

Hypothesized associations

Low blood pressure.

Hypotonic hyporesponsive episode (HHE)

A recognized serious reaction to immunization, especially pertussis-containing vaccine. It is defined as an acute loss in sensory awareness or loss of consciousness accompanied by pallor and muscle hypotonicity. No long-term sequelae have been identified in the small number of children who have had long term follow-up. HHE is not a contraindication for further doses of pertussis vaccine.

I**Immune response**

The body's defense against foreign objects or organisms, such as bacteria, viruses or transplanted organs or tissue.

Immune system

A complex system of organs and processes in the body responsible for fighting disease. Its primary function is to identify foreign substances in the body (including bacteria, viruses, fungi, parasites or transplanted organs and tissues) and develop a defense against them. This defense is known as the immune response.

Immunity

The body's response mechanism for fighting against bacteria, viruses and other foreign substances. If a cell or tissue (such as bacteria or a transplanted organ) is recognized as not belonging to the body, the immune system will act against the "invader." The immune system is the body's way to fight external invasions.

Immunization

The process by which a person or animal becomes protected against a disease through an enhancement of their immune response. This term is different from vaccination which is a form of immunization where the body learns to recognize a particular foreign object (active immunization). Passive immunization can be provided by administering external antibodies that will temporarily help strengthen the body's response without inducing memory against a specific foreign object.

Immunization anxiety-related reaction

An AEFI arising from anxiety about the immunization.

Immunization error

An AEFI classification that refers to events caused by errors in vaccine preparation, handling, or administration.

Immunization safety

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

Immunocompromised (also immunosuppression)

Unable to mount a normal immune response. This condition can be genetic, or caused by disease (like HIV infection or cancer) by certain drugs (such as those used in chemotherapy and organ transplantation). Individuals whose immune systems are severely compromised should not receive LAV vaccines.

Immunogenicity

The power of an antigen to induce an immune response.

Inactivated polio vaccine (IPV)

An inactivated (killed) polio vaccine, developed in 1955 by Dr. Jonas Salk. Unlike oral polio vaccine (OPV), a LAV vaccine, IPV must be injected to produce the desired immune response.

Inactivated vaccine (also known as killed vaccine)

A vaccine made from microorganisms (viruses, bacteria, other) that have been killed through physical or chemical processes. These killed organisms cannot cause disease.

Incidence

The number of new cases (e.g., of a disease, adverse event) occurring in a defined population during a given time interval, often one year.

Individual case safety report (ICSR)

A report received by a company or agency that describes an adverse event.

Inflammatory bowel disease

A general term for any disease characterized by inflammation of the bowel; examples include colitis and Crohn's disease. Symptoms include abdominal pain, diarrhea, fever, loss of appetite, and weight loss.

Influenza

A highly contagious viral infection characterized by sudden onset of fever, aches and pains, and inflammation of mucous membranes.

Informed consent

An ethical requirement that an individual who gives consent for an invasive medical procedure (e.g. a vaccination) is fully informed of all relevant risks and benefits of the procedure before making the decision to consent.

Inoculation

The practice of intentionally exposing someone to matter from smallpox pustules in order to initiate a mild, protective response to the disease.

Insulin

A hormone secreted by the islets of Langerhans and functioning in the regulation of the metabolism of carbohydrates and fats, especially the conversion of glucose to glycogen, which lowers the blood glucose level. It is also available as a pharmaceutical for the treatment of diabetes.

Intramuscular (IM) injection

Administration of vaccine into the muscle mass. Vaccines containing adjuvants should be injected IM to reduce the depot effect and formation of granulomas.

Intranasal influenza

A live attenuated influenza vaccine, administered through the nose. Advantages of this vaccine include easier and more acceptable administration than injection and possibly the stimulation of a broader immune response in some age groups.

Intussusception

A potentially life threatening obstruction of the bowel. When the first rotavirus vaccine was licensed in 1999, it was withdrawn from the market following evidence linking it to a small increase in the risk of intussusception.

J**Japanese encephalitis (JE)**

A mosquito-borne viral infection, the leading cause of viral encephalitis in Asia.

Japanese encephalitis (JE) vaccine

Two vaccines against JE are currently available internationally: the inactivated, mouse-brain derived JE vaccine and the live attenuated SA-14-14-2 JE vaccine.

K**Key message**

A key message gives the most important information that you want the public to know, for example in relation to a health education campaign on the benefits of vaccination.

Killed vaccine – See Inactivated vaccine.

L**Large linked databases (LLDBs)**

Administrative databases of relatively large size that were created separately from each other and linked to enable the sharing of data across platforms. Such linked databases have become popular in vaccine safety surveillance where specific disease's occurrence can be linked to a person's vaccination history.

Leukemia

Any of a group of neoplastic diseases of the blood-forming organs, resulting in an abnormal increase in the production of leukocytes, often accompanied by anemia and enlargement of the lymph nodes, spleen, and liver.

Licensure

The granting of a license to conduct a regulated procedure, for example, to conduct a trial of a new vaccine or to approve a vaccine for routine delivery to the public in a vaccination programme.

Live attenuated vaccine (LAV)

A vaccine prepared from living micro-organisms (viruses, bacteria currently available) that have been weakened under laboratory conditions. LAV vaccines will replicate in a vaccinated individual and produce an immune response but usually cause mild or no disease.

Local (or localized)

Restricted or limited to a specific body part or region.

Lot (or lot-release)

Vaccines are produced in “lots” or batches. Prior to releasing a “lot” of vaccine for public use, the NRA provides a vital check on the manufacturer’s performance. As a minimum, lot release should be based on review of the summary lot protocols, which contain details of that particular lot. In addition, selected laboratory testing can be carried out. Lot release should be included in the regulations that cover biological products.

Lymphadenitis

Lymphadenitis is the inflammation and/or enlargement of one or more lymph nodes. Most cases indicate an immune response in the node to local infection or antigen stimulation, for example in a vaccine. Generalised lymphadenitis is a widespread inflammation of the lymph nodes due to systemic (circulating) infection.

Lyophilized

Freeze-dried; e.g. measles and BCG vaccines are transported as lyophilized powders which must be reconstituted with specific liquid diluents before use as injectable vaccines. Lyophilised vaccines must be discarded within 6 hours of reconstitution, or at the end of a vaccination session, whichever comes first.

M**Macrophagic myofasciitis**

A disease causing muscle pain, joint pain, muscle weakness, fatigue, fever, and muscle tenderness. It is characterized by microscopic muscular infiltration with macrophages. Specific causes are unknown, but the disease has been associated with the persistence of aluminum hydroxide used in some vaccines. The diagnosis can only be confirmed through a muscle biopsy.

Malaria

An infectious disease caused by a parasite (plasmodium) that is transmitted from human to human by the bite of infected female Anopheles mosquitoes. Malaria is a leading cause of morbidity and mortality in sub-Saharan Africa.

Measles

A contagious viral disease marked by fever, the eruption of red circular spots on the skin that can be deadly to young and weakened individuals.

Measles vaccine

A preparation of live attenuated measles virus used to immunize against measles.

Meningococcal disease

Bacterial diseases caused by the meningococcus (*Neisseria meningitidis*). Meningococcal diseases include clinical forms of the disease, in particular meningitis, sepsis and pneumonia.

Microorganisms

Tiny organisms (including bacteria and viruses) that can only be seen with a microscope.

Minor (or mild) vaccine reaction

Vaccine reactions that usually occur within a few hours of injection, resolve after a short period of time, and pose little danger.

MMR vaccine

A preparation of live attenuated measles, mumps, and rubella viruses together in one vaccine, used to immunize against measles, mumps, and rubella.

Monovalent vaccine

A monovalent vaccine is designed to immunize against a single antigen or single microorganism whereas polyvalent vaccines aim to immunize against several strains of the same microorganism, or against several microorganisms.

MR vaccine

A preparation of live attenuated measles and rubella viruses together in one vaccine, used to immunize against measles and rubella.

Multiple Sclerosis (MS)

A disease of the central nervous system characterized by the destruction of the myelin sheath surrounding neurons, resulting in the formation of “plaques.” The cause of MS is unknown, although it appears to require a genetic susceptibility combined with an environmental ‘trigger’, possibly a viral infection. While extensively investigated, there is no epidemiologic evidence to support a link between vaccination and onset or recurrence of MS.

Mumps

An acute contagious viral illness marked by swelling, especially of the parotid glands.

N**National immunization programme (NIP)**

The organizational component of government Ministries of Health charged with preventing disease, disability, and death from vaccine-preventable diseases in children and adults. NIP is used interchangeably with the Expanded Programme on Immunization (EPI) that originally focused on preventing vaccine-preventable diseases in children.

National immunization technical advisory groups (NITAGs)

Advisory groups whose general objective is to guide national governments and policy-makers to develop and implement evidence-based, locally relevant immunization policies and strategies that reflect national priorities.

National pharmacovigilance centre

A governmentally recognized centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyze, and give advice on all information related to drug safety.

National regulatory authority (NRA)

The regulatory body that approves procedures to ensure that medicines, including vaccines, are of adequate safety and potency. The vaccine manufacturer is responsible for demonstrating that the vaccine batch produced meets the requirements, based on the test specifications given by the NRA. The NRA is also responsible both for the official vaccine lot release process, based on the data and information provided by the manufacturer and, eventually, for confirmatory testing.

Necrosis

The death of living cells or tissues.

Neisseria meningitidis (aka meningococcus)

A bacterium that causes meningitis, as well as infections elsewhere in the body.

Neomycin

A broad-spectrum antibiotic that is used in the manufacture of some vaccines.

Neonatal tetanus

Tetanus that occurs in a newborn infant.

Neuritis

Inflammation of the nerves.

Neurodevelopmental disorders

A disorder of neural development, an impairment of the growth and development of the brain or central nervous system.

Neuropathy

A general term for any dysfunction in the nervous system. Symptoms include pain, muscle weakness, numbness, loss of coordination, and paralysis. This condition may result in permanent disability.

O**Oedema**

The presence of an excessive amount of fluid in or around cells, tissues, or serous cavities of the body.

Options analysis

A system for ranking multiple options in order to decide the best course of action in the prevailing circumstances.

Oral polio vaccine (OPV)

A preparation of live attenuated polio virus, used to immunize against polio and developed by Dr. Albert Sabin in 1961. OPV is administered orally (by mouth).

Otitis media

An inflammation of the middle ear usually caused by a virus or a bacteria. This condition usually occurs in conjunction with an upper respiratory infection. Symptoms include earache, high fever, nausea, vomiting, and diarrhea. In addition, hearing loss, facial paralysis, and meningitis may result.

Oxytocin

A hormone secreted by the posterior pituitary gland that stimulates contractions of the uterus and ejection of milk. As a pharmaceutical it is used in childbirth and lactation to cause muscles to contract in the uterus (womb) and mammary glands in the breast.

P**Pan-American Health Organization (PAHO) Revolving Fund for Vaccine Procurement**

A mechanism developed by PAHO in 1979 for the purchase of vaccines, syringes/needles, and cold chain equipment for countries in Latin America and the Caribbean. Through a system of bulk purchasing, the Fund has secured for the past 30 years a supply of high quality vaccines for national immunization programs at affordable prices, and it has also allowed for the orderly planning of immunization activities.

Pandemic

An epidemic occurring over a very large area and affecting a large number of people.

Paracetamol (also known as acetaminophen)

A widely used over-the-counter analgesic (pain reliever) and antipyretic (fever reducer).

Passive reporting – See Passive surveillance.

Passive surveillance (also known as spontaneous reporting)

A surveillance system designed to collect adverse events that follow vaccination. This type of surveillance typically relies on health professionals noticing and reporting adverse events in individuals after vaccination to the NRA or appropriate authority.

Pathogen

Any disease-causing substance. Most commonly used for organisms (e.g., bacteria, viruses) and their biological products (e.g. toxins).

Pertussis (also known as whooping cough)

An infectious bacterial disease caused by *Bordetella pertussis* that produces violent, spasmodic coughing; also called whooping cough.

Pertussis vaccine

Two types of pertussis vaccines are currently available: the inactivated whole-cell vaccine (wP) and subunit protein-based vaccine (aP).

Pharmacovigilance

The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem.

Placebo controlled

A randomized clinical trial may include controls in which some of the subjects receive a product which has no active ingredients, referred to as a placebo, e.g. a sugar pill or an injection of normal saline. None of the people in the clinical trial nor the clinical team administering the intervention know who was given the placebo, or the test product, or the best performing existing product. A placebo controlled trial enables researchers to evaluate whether the simple act of being given a pill or an injection has a beneficial effect.

Plague

A serious, potentially life-threatening infectious disease that is usually transmitted to humans by the bites of rodent fleas. It was one of the scourges of early human history.

Pneumococcal conjugate vaccine (PCV-7, PCV-10, PCV-13)

Three subunit polysaccharide-conjugate vaccines exist against pneumococcus. PCV-7 vaccine protects against seven serotypes and PCV-10 protects against ten serotypes of *Streptococcus pneumoniae*, and PCV-13 protects against 13 serotypes of *Streptococcus pneumoniae* most commonly isolated from young children.

Pneumococcal disease

Bacterial diseases caused by *Streptococcus pneumoniae*. Pneumococcal diseases include meningitis, sepsis, and pneumonia, all of which cause significant illness and death.

Poliomyelitis (also known as polio)

An acute infectious viral disease characterized by fever, paralysis, and atrophy of skeletal muscles. The Global Polio Eradication Initiative was launched in 1988 with the goal of eradicating polio from the earth through routine and mass polio vaccination programs.

Polysaccharide vaccine

A vaccine that is composed of long chains of sugar molecules that resemble the surface of certain types of bacteria. Polysaccharide vaccines are available for pneumococcal disease, meningococcal disease, and Hib.

Post-licensure surveillance (also known as post-marketing surveillance)

Pharmacovigilance conducted after a product has been licensed and introduced for use in a population.

Potency

A measure of strength or immunogenicity in vaccines.

Prequalified vaccine

A vaccine that has been approved as acceptable, in principle, for purchase by United Nations agencies, such as WHO, after full assessment of all procedures involved in its production. The purpose of the assessment is to verify that prequalified vaccines: (a) meet the specifications of the relevant UN agency; and (b) are produced and overseen in accordance with the principles and specifications recommended by WHO, for good manufacturing practice (GMP), and for good clinical practice (GCP). This is to ensure that vaccines used in national immunization services in different countries are safe and effective for the target population at the recommended schedules and that they meet particular operational specifications for packaging and presentation.

Preservatives

Compounds that are added to multi-dose vaccine vials to prevent bacterial and fungal growth. The most commonly used product is called thiomersal, a mercury-containing compound.

Priming

The process of artificial induction of immunity, in order to protect against infectious disease. Priming the immune system involves sensitizing or stimulating an immune response with an antigen that can produce immunity to a disease-causing organism or toxin (poison). Vaccinations involve the administration of one or more of these antigens, which can be administered in several forms.

Programme for International Drug Monitoring (PIDM)

This programme, established in 1968, consists of a network of national pharmacovigilance centres, WHO Headquarters in Geneva, and the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre, in Uppsala, Sweden. For more information, see <http://www.who-umc.org/DynPage.aspx?id=98080>.

R**Rabies**

A potentially fatal viral infection spread through the bite of certain warm-blooded animals. It attacks the central nervous system and, if left untreated, is highly fatal in animals.

Randomized clinical trials

A systematic study of medical interventions in human subjects (including patients and other volunteers) in which study subjects are randomly assigned to treatment and control groups. Used to discover or verify the effects of and/or identify any adverse reactions to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the objective of ascertaining their efficacy and safety. Studies in which neither the investigator nor the study subjects know to which group, treatment or control, they have been assigned until the conclusion of the study are referred to as 'double-blind randomized clinical trials' and are considered the gold standard for drug and vaccine efficacy research.

Reactogenicity

Being able to produce adverse reactions.

Reassortant vaccine

A live attenuated vaccine in which attenuation is achieved by using virus strains in which some gene sequences have been rearranged (reassorted); for example, RotaTeq vaccine contains five reassortant rotavirus strains.

Recombinant DNA

A vaccine technology that uses genetic material from a disease-causing organism into a live vector, often a yeast cell, in order to replicate a protein antigens of the disease-causing organism. The proteins are then purified and used as vaccine.

Reconstituted vaccine

The mixing of a powdered (usually lyophilized) form of a vaccine with a fluid called a diluent prior to injection.

Retrovirus

An RNA virus (a virus composed not of DNA but of RNA). Retroviruses have an enzyme called reverse transcriptase that gives them the unique property of transcribing RNA (their RNA) into DNA. The retroviral DNA can then integrate into the chromosomal DNA of the host cell to be expressed there. HIV is a retrovirus.

Risk

The probability that an individual will experience a certain event during a defined period of time.

Risk-benefit analysis

Evaluation and assessment of the relative risks and benefits of an intervention, e.g. the potential benefit of protection from measles and its complications due to vaccination, relative to the potential risk of adverse reactions to the vaccine.

Rotavirus

A group of viruses that cause diarrhea (rotaviral gastroenteritis) in children.

Rotavirus vaccine

A preparation of live attenuated rotavirus used to immunize against infant rotaviral gastroenteritis.

Rubella (German measles)

A viral infection that is usually milder than measles but can cause serious damage or death to a fetus when a pregnant woman is infected.

Rubella vaccine

A preparation of live attenuated rubella virus used to immunize against rubella.

S**Safety profile**

A summary of the evidence on the safety of a medical product, such as a vaccine or drug, under ideal conditions of use, including the incidence of any adverse reactions relative to the number of doses given.

Sciatic nerve

The largest nerve in the human body providing both motor and sensory control for much of the lower limbs. Vaccination of infants and children in the buttock is not recommended because of concern about potential injury to the sciatic nerve, which is well documented after injection into the buttock.

Second opportunity

WHO recommends that all children receive two doses of measles vaccine, either through routine services or mass vaccination campaigns. Often when the second dose is delivered through campaigns, it is considered the second opportunity for measles vaccination.

Seizure

Uncontrolled electrical activity in the brain, resulting in convulsion, physical signs, thought disturbances, or a combination of symptoms.

Sensitivity

In the context of public health surveillance, the proportion of all incident cases of a health condition detected by a surveillance system.

Sepsis (also known as “blood stream infection”)

The presence of bacteria (bacteremia) or other infectious organisms or their toxins in the blood (septicemia) or in other tissue of the body.

Serious adverse event

A regulatory term defined as any untoward medical occurrence that at any dose: results in death; requires inpatient hospitalisation or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or, is life-threatening. For more information, see <http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm>.

Severe vaccine reaction

This is not a regulatory term. It refers to vaccine reactions that usually do not result in long-term problems, but can be disabling and, rarely, life threatening. Severe reactions include serious reactions but also include other severe reactions.

Side effect

Any unintended effect of a pharmaceutical product (including vaccines) occurring at a dose normally used in man.

Signal

Reported information on a possible causal relationship between an adverse event and a drug, the relationship being previously unknown or incompletely documented. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

Simple message

A simple message is ‘jargon free’ and easy for the general public to understand – it ‘translates’ complex concepts and information into readily accessible ideas and examples.

Smallpox

An acute, highly infectious, often fatal disease caused by a variola virus and characterized by high fever and aches with subsequent widespread eruption of pimples that blister, produce pus, and form pockmarks. Declared eradicated by the World Health Assembly in 1980.

Sorbitol

An alcohol used in the manufacture of some vaccines.

Specificity

In the context of surveillance, the measure of the degree to which cases detected through a surveillance system actually have the disease.

Spontaneous reporting – See Passive surveillance.

Stabilizers

Compounds that are used to help vaccine maintain its effectiveness during storage. Vaccine stability is essential, particularly where the cold chain is unreliable. Factors affecting stability are temperature and pH.

Standard case definition

A common, formal definition for the health-related event under surveillance. The case definition of a health-related event can include clinical manifestations (i.e., symptoms), laboratory results, epidemiologic information (e.g., person, place, and time), and/or specified behaviors, as well as levels of certainty (e.g., confirmed/definite, probable/presumptive, or possible/suspected). The use of a standard case definition increases the specificity of reporting and improves the comparability of the health-related event reported from different sources of data, including geographic areas.

Strain

A specific genetic grouping of an organism. Many organisms, such as viral influenza, pneumococcus and meningococcus, have multiple strains that cause disease.

Stridor

A whistling sound generated when breathing (usually heard on inspiration) that indicates obstruction of the trachea or larynx.

Subcutaneous (SC) injection

Administration of vaccine into the subcutaneous layer above the muscle and below the skin.

Subunit conjugate vaccine

A vaccine in which two compounds (usually a protein and polysaccharide) are joined together to increase the vaccine's effectiveness.

Subunit polysaccharide vaccine

A vaccine that uses portions of bacteria that are composed of long chains of sugar. Polysaccharide vaccines are available for pneumococcal disease, meningococcal disease and Hib.

Subunit protein-based vaccine

A vaccine made from fragments of viruses or bacteria that involve a protein to increase the vaccine's effectiveness.

Subunit vaccine

A vaccine made from components of viruses or bacteria instead of the whole organism.

Sudden Infant Death Syndrome (SIDS) (also known as “crib” or “cot” death)

The sudden and unexpected death of a healthy infant under one year of age. A diagnosis of SIDS is made when an autopsy cannot determine another cause of death. The cause of SIDS is unknown.

Suppurative lymphadenitis

This is a common adverse reaction to tuberculosis (BCG) vaccine and involves the inflammation of the lymph nodes associated with skin ulceration.

Surfactant

A chemical agent capable of reducing the surface tension of a liquid in which it is dissolved.

Surveillance

The systematic collection, analysis, interpretation, and dissemination of health data on an ongoing basis, to gain knowledge of the pattern of disease occurrence and potential in a community, in order to control and prevent disease in the community.

Surveillance system

The systematic collection, analysis, interpretation, and dissemination of health data on an ongoing basis, to gain knowledge of the pattern of disease occurrence and potential in a community, in order to control and prevent disease in the community.

Synthetic vaccine

A vaccine consisting mainly of synthetic peptides or carbohydrates as antigens. They are often considered to be safer than vaccines from bacterial cultures.

Systemic

Relating to a system, or affecting the entire body or an entire organism (e.g., fever).

T**Tachycardia**

A heart rate that exceeds the normal range for a resting heart.

Td vaccine

A preparation of tetanus and diphtheria toxoids together in one vaccine used to immunize adults against diphtheria and tetanus. This vaccine contains a reduced amount of diphtheria toxoid used in the DT preparation for children. When given to women of childbearing age, vaccines that contain tetanus toxoid (TT or Td) not only protect women against tetanus, but also prevent neonatal tetanus in their newborn infants.

Temporal association

Two or more events that occur around the same time. The preceding event may or may not be causally related to the later one.

Tetanus

A disease caused primarily by toxigenic *C. tetani*. The rare but often fatal disease affects the central nervous system by causing painful muscular contractions.

Tetanus toxoid (TT) vaccine

A preparation of tetanus toxoid used to immunize against tetanus. When given to women of childbearing age, vaccines that contain tetanus toxoid (TT or Td) not only protect women against tetanus, but also prevent neonatal tetanus in their newborn infants.

Thiomersal

Thiomersal is a mercury-containing preservative that has been used in some vaccines and other products since the 1930's. While there is no evidence that the low concentrations of thiomersal in vaccines have caused any harm other than minor reactions like redness or swelling at the injection site, in July 1999 the US Public Health Service, the American Academy of Pediatrics, and vaccine manufacturers agreed that thiomersal should be reduced or eliminated from vaccines as a precautionary measure. Today, all routinely recommended childhood vaccines manufactured for the US market contain either no thiomersal or only trace amounts.

Thrombocytopenia

A severe decrease in the number of blood platelets, the cells involved in clotting. Thrombocytopenia may stem from failure of platelet production, splenic sequestration of platelets, increased platelet destruction, increased platelet utilization, or dilution of platelets.

Thrombocytopenic purpura

Severe thrombocytopenia characterized by mucosal bleeding and bleeding into the skin in the form of multiple petechiae (small purplish spot), most often evident on the lower legs, and scattered small bruises at sites of minor trauma. In children, idiopathic thrombocytopenic purpura is usually self-limited and follows a viral infection.

Time to onset

The period of time between an intervention (in this case, a vaccination) and the onset of an adverse reaction to the vaccine.

Toxic shock syndrome

A rare serious adverse event resulting from improper vaccine preparation and injection practices. It is a life-threatening illness that is caused by toxins (poisons) that circulate in the bloodstream. Bacteria that have infected some part of the body release these toxins. People with toxic shock syndrome develop high fever, rash, low blood pressure, and failure of multiple organ systems in the body.

Toxoid

Inactivated or killed toxin (poison) used in vaccine production.

Toxoid vaccine

A vaccine made from a toxin (poison) that has been made harmless but that elicits an immune response against the toxin.

Tuberculosis (TB)

A disease caused by the bacterium *Mycobacterium tuberculosis*. The bacteria usually attack the lungs. But, TB bacteria can attack any part of the body such as the kidney, spine, and brain. If not treated properly, TB disease can be fatal.

Tuberculosis vaccine (Bacillus Calmette-Guérin, BCG vaccine)

A vaccine against tuberculosis that is prepared from a strain of the live attenuated bovine tuberculosis bacillus. Tuberculosis vaccine is used in many countries with a high prevalence of tuberculosis to prevent childhood tuberculous meningitis and miliary disease. It is administered intradermally and often leaves a scar.

Typhoid (typhoid fever)

A serious disease caused by a bacteria called *Salmonella Typhi*. Typhoid causes a high fever, weakness, stomach pains, headache, loss of appetite, and sometimes a rash. If it is not treated, it can kill up to 30% of people who get it. There are different vaccines to prevent typhoid: inactivated vaccines that require injection, and live attenuated vaccines that are taken orally (by mouth).

U**Uppsala Monitoring Centre (UMC)**

An independent centre which receives adverse drug reactions from national pharmacovigilance centres in WHO member countries and generates signals of possible side-effects. For more information, see <http://www.who-umc.org>.

Urticaria (also known as hives)

The eruption of red marks on the skin that are usually accompanied by itching. This condition can be caused by an allergy (e.g., food, vaccine, drugs), stress, infection, or physical agents (e.g., heat, cold).

V**Vaccination**

Inoculation with a vaccine for the purpose of inducing immunity.

Vaccine

A material containing live attenuated or inactivated (killed) microorganisms, or constituents of microorganisms, capable of eliciting protection against infection.

Vaccine Adverse Event Reporting System (VAERS)

A passive surveillance system in the US intended to collect reports of reactions to vaccines. Under the aegis of the US Centers for Disease Control and Prevention and the US Food and Drug Administration.

Vaccine effectiveness

The probability that a vaccine, when used in the field under routine vaccination circumstances, confers immunity in a population. Expressed as a percent.

Vaccine efficacy

The potential of a vaccine to protect from a disease in controlled clinical trials. Expressed as a percent.

Vaccine pharmacovigilance

The science and activities relating to the detection, assessment, understanding and communication of adverse events following immunization and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization

Vaccine reaction (also referred to as adverse vaccine reaction or adverse reaction)

A classification of AEFI referring to events caused or precipitated by the vaccine when given correctly, caused by the inherent properties of the vaccine.

Vaccine safety

The process of ensuring and monitoring the safety of vaccines through their life cycle.

Vaccine safety surveillance – See AEFI surveillance.

Vaccine-associated neurotropic disease

A very rare disease of the nervous system that follows vaccination against yellow fever.

Vaccine-associated paralytic poliomyelitis (VAPP)

A very rare risk of paralytic polio resulting from oral poliomyelitis vaccine (OPV). Associated with approximately one in every 2.5 million doses of OPV. VAPP is not a risk with IPV.

Vaccine-associated risk

The probability of an adverse or unwanted outcome occurring, and the severity of the resultant harm to the health of vaccinated individuals in a defined population, following immunization with a vaccine under ideal conditions of use.

Vaccine-associated viscerotropic disease

A disease that presents with fever, liver damage and blood disorders that very rarely results from vaccination against yellow fever.

Vaccine-derived poliovirus (VDPV)

Where polio vaccine coverage rates decline but OPV use continues, person-to-person spread of vaccine polioviruses can lead to increased virulence that resemble the wild virus.

Vaccine-preventable diseases

Diseases for which vaccines exist that can confer partial or complete protection.

Vaccinee

The individual receiving a vaccine.

Valent

The number of types of a microorganism that are covered in a vaccine product (e.g. seasonal influenza vaccines that typically cover three virus types are called tri-valent).

Validity

The degree to which an estimate reflects the true value of what it purports to measure.

Varicella (also known as chickenpox)

An acute contagious disease characterized by papular and vesicular lesions.

Vasculitis

Refers to a heterogeneous group of disorders that are characterized by inflammatory destruction of blood vessels that cause a visible rash.

Vasovagal syncope

A neurovascular reaction that leads to fainting.

Virus

An ultramicroscopic infectious agent that consists of genetic material surrounded by a protein coat. A virus can replicate themselves only within cells of living hosts.

W**Whole cell pertussis (wP) vaccine**

A preparation of inactivated whole cell pertussis bacterium, used to immunize against pertussis.

Wild poliovirus

A strain of poliovirus that occurs naturally, as opposed to vaccine-related strains.

World Health Organization (WHO)

A United Nations specialized agency established to coordinate international health activities and to help governments improve health services.

Y**Yellow fever**

An infectious viral tropical disease transmitted by mosquitoes and characterized by high fever, jaundice, and gastrointestinal bleeding.

Yellow fever vaccine

A preparation of live attenuated yellow fever virus, used to immunize against yellow fever. A single dose provides protection against the disease for at least ten years and often for 30 years or more.

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Questions solutions

Module 1

Question 1

Answer A and D are correct.

Eradication refers to the complete and permanent worldwide reduction to zero new cases of the disease through deliberate efforts.

 If a disease has been eradicated, no further control measures are required.

Elimination refers to the reduction to zero (or a very low defined target rate) of new cases in a *defined geographical area*.

 Elimination requires continued measures to prevent re-establishment of disease transmission.

Question 2

All the answers are correct.

 The initial EPI goals were to vaccinate every child against **tuberculosis, polio, diphtheria, pertussis, tetanus** and **measles** by the time they were one year of age, and to give **tetanus toxoid vaccinations** to women to protect them and their newborns against tetanus.

Question 3

Answers A and D are correct.

 An AEFI is any adverse event observed following immunization. Some may be due to the vaccine, some due to error in the administration of the vaccine, and some are the result of unrelated coincidence.

 An adverse vaccine reaction is a subset of AEFI. It refers to a vaccine-related event caused or precipitated by a vaccine when given correctly. Note that the rate of adverse vaccine reactions is very much lower than the rate of health-damaging complications resulting from the disease in unvaccinated individuals.

Question 4

All answers are correct.

All of the listed components can contribute to the risk of an adverse reaction.

Question 5

Answer D is wrong.

An event that occurs in 2 out of a thousand persons is regarded as uncommon (infrequent). Please compare the frequency and the Percentage of persons vaccinated in the table above.

Module 2

Question 1

Answers A and D are correct.

Answer B: Allergic anaphylactic reactions are more likely to occur after receipt of the second dose of measles vaccine.

Answer C: Pertussis (wP) is an inactivated vaccine. Live vaccines include:

- Tuberculosis (BCG),
- Oral Polio Vaccine,
- Measle,
- Rotavirus,
- Yellow Fever.

Question 2

Answer C is incorrect.

 **Inactivated vaccines** can be considered safer than live vaccines, which, however, comes with a reduced effectiveness of the vaccine. Inactivated vaccines should not be seen as ineffective – the immunization schedule foresees repeated doses to ensure adequate immune responses in patients.

 **Live vaccines** on the other hand should not be seen as unsafe – their production is usually done with meticulous quality checks ensuring their safety. It is rather important to have well trained health staff screening patients for counter indications to the vaccines.

Question 3

Answer D is incorrect.

 Measles vaccine is a live vaccine, not a conjugate vaccine.

Question 4

This pentavalent vaccine combines five ('penta') antigens in one formulation: diphtheria toxoid, tetanus toxoid, whole-cell pertussis, hepatitis B and *Haemophilus influenzae* type b.

Question 5

Answer B is incorrect.

 Aluminium salts primarily slow the escape of the antigen from the site of injection. As the exposure between the antigen and the immune system, they increase the effectiveness of the vaccine.

Module 3

Question 1

This statement is true.

 Events that are life-threatening or result in the death of a patient are defined as “serious”.

Question 2

Answer C is correct.

 Incorrect storage can lead to reconstitution errors: The drug may be given to the client in mistake for a vaccine or may be used instead of the correct diluent to reconstitute a freeze-dried powder vaccine.

Question 3

Answer A is correct.

 The number of expected infant deaths occurring the day after DTP immunization would total 2,421.

Question 4

Answer B is correct.

 The vaccine attributable rate is 0.2:1,000 or 2 additional cases of convulsions in infants in every 10,000 vaccinations, compared with the background rate.

Module 4

Question 1

 Parents may be anxious about immunization because they are voluntarily exposing their healthy children to the risk of an adverse reaction. Any benefit from the vaccination is not immediate and can only be imagined in terms of protection from future disease.

Question 2

 Pharmacovigilance authorities concluded that the original clinical trial contained too few vaccinees to detect the real incidence of such a rare adverse event. As a consequence, subsequent rotavirus vaccines were subject to clinical trials containing at least 60,000 infants. This example illustrates why signal detection, hypothesis generation and testing are vital in post-licensure pharmacovigilance of vaccines.

Question 3

Answers B and C are correct.

 **Answer A:** According to the Brighton Case definition, fever higher than 40.5 degrees Celsius is “extreme”.

 **Answer D:** To be due to DTP vaccination, encephalopathy symptoms should occur within 48 hours of vaccination.

Question 4

The case was isolated and clinical & laboratory investigations were carried out. A brain biopsy was collected immediately after the child's death and sent for culture, microscopy and electronic microscopy. It was determined that herpes virus was responsible for the clinical picture. This example shows, that it is critical to take additional information into account.

Apart from the additional information that was made available, one has to be aware, that the nature of the problem is also a potential factor:

- Disease level and incidence – is this a common vaccine-preventable condition (e.g. measles) or relatively rare (e.g. diphtheria)?
- Is this a crisis situation – for example, a life-threatening vaccine reaction or a threat to the continuation or success of the immunization programme?
- Is the risk caused by an immunization error that can be identified and corrected, or is it an unavoidable and inherent risk?
- Why has concern been raised about the risk and by whom?

Module 5

Question 1

Answer C is correct.

For infants known to be HIV infected, **the risks linked to the vaccination outweigh its benefits** with or without signs and symptoms.

 They should not be immunized.

For infants with unknown HIV status who have signs and symptoms of infection and are born to infected mothers **the risks usually outweighs benefits**.

 They should not be immunized. If infection status can be established early (virology), BCG may be administered once HIV infection ruled out.

For infants born to women of unknown HIV status **the benefits outweigh the risks**.

 These infants should be immunized.

For infants whose HIV status is unknown and who demonstrate no signs or reported symptoms suggestive of HIV infection but who are born to known HIV-infected women **benefits usually outweigh the risks**.

 These infants should be immunized after consideration of local factors (details in guideline⁷⁹).

Question 2

Answers A and D are correct.

 Pooling and analysing data from several countries provides additional statistical power for identifying rare adverse events, such as intussusception following rotavirus vaccination. It could reduce the time taken to investigate and establish a causal association between the AEFI and the vaccine and take appropriate action.

Module 6

Question 1

The AEFIs are due to an immunization error as the investigation revealed that unsterile needles had been used.

To avert this practice, WHO recommends the use of sterile, disposable auto-disable (AD) syringes with attached needles for all vaccine injections; AD syringes cannot be used a second time because the plunger “locks” when it has been pushed forward to deliver the vaccine and it cannot be pulled back.

Note how the key messages are listed to support the main message of the statement:

- Information specifying the event,
- Possible cause of the AEFI,
- Scientific evidence on the disease,
- Scientific evidence on the vaccine,
- Response undertaken to respond to the event.

Question 2

All of the statements above are correct.

Relevant tools include discussions on social media channels, e.g. Facebook, Twitter; blogs (diaries, opinion pieces and commentaries on news and events written by members of the general public as well as journalists and all kinds of experts); or Wikipedia, the online encyclopaedia, with content freely created by its worldwide contributors.

All these forms of communication can be harnessed to deliver correct health messages on vaccine safety and to counteract misleading or health-damaging information that is causing concern locally or nationally.

Question 3

A, C and D are correct.

The best means of communicating with a nervous young mother may be a one-to-one interview in a room where you will not be disturbed and the conversation is private. Take time to listen to her concerns and reassure her that they are understandable. Use simplified messages in language that she can understand and do not overload her with too much technical detail. Leaflets that provide additional information to read later may serve well to reinforce your messages.

Communication with teachers at a large school can take place in a group meeting, so that your message can influence many of them at the same time. The room should be large enough to seat everyone comfortably, so they can all see you. Make, however, sure that the group is small enough that they can be heard by everyone if they ask questions. Use display materials (e.g. posters, video, slides) and provide hand-outs to read later to reinforce your messages.

Question 4

All of the statements above are correct.

Question 5

Statements B and C are correct.

A vaccine reaction or immunization error means that a previously healthy person was subjected to some form of harm as a result of the immunization. By contrast, medical drugs are given to people who are already sick, to make them better. This difference results in a much lower public tolerance to adverse reactions of vaccines than there is to the side-effects of drugs.

Most vaccine recipients are babies and young children who were vaccinated with their parents' consent; any harm that occurs following an immunization is seen as "avoidable" by parents because the vaccine could have been refused. There is much less tolerance for instances of avoidable harm than there is for adverse events that could not be avoided.

Due to a decline of childhood infections in industrialized countries the threats to health and life posed by once-common vaccine preventable diseases (measles, polio, pertussis, diphtheria and tetanus) is *low*. The benefits of vaccination are no longer being reinforced by directly experiencing the diseases that vaccines prevent.

Question 6

Statements A, B, C, D, and E are correct.

Your key message should be a simple explanation of the situation: If there is no evidence that the death was caused by the vaccine itself, state this. If there is an investigation ongoing, say this.

As with any new vaccine, health authorities closely monitor adverse events following the vaccination, so that any safety issues are quickly identified and followed up. State how many people have been vaccinated with this vaccine, how many serious adverse events have been reported, and how many of those have proven to be related to the vaccine itself, to put this particular event into perspective. For example, state how many people die or are seriously ill each year as a result of influenza.

If you do not have information to respond to a journalist's request, offer the journalists to share the information with them later, or refer them to the specialist who has this information available. After the interview, provide the offered information to the journalist in a timely manner.

Question 7

Sequence: D: 1, A: 2, C: 3, B: 4.

(other sequences are possible).