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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SEND US FEEDBACK

Please let us know how you liked the course.
Send us an email with your suggestions to: vaccsafety@who.int.

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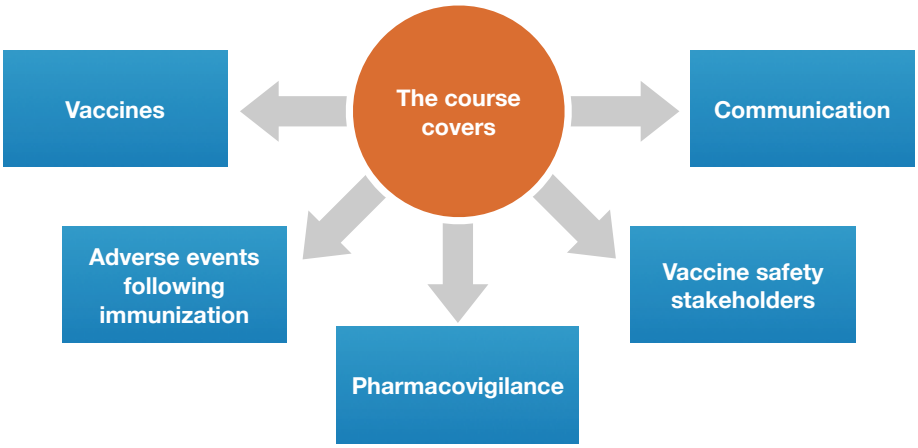
INTRODUCTION

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 pharmacovigilance system works in your country.

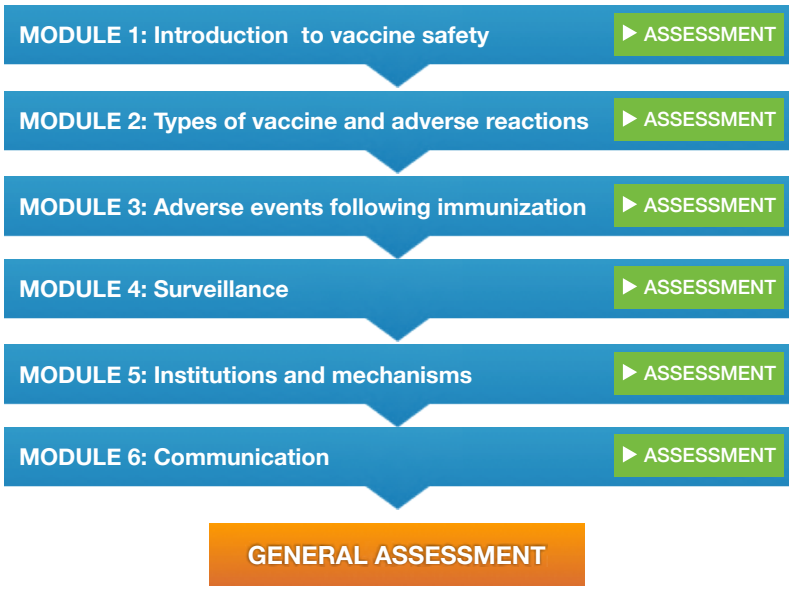
GETTING STARTING

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: https://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 certificate 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 immunisation 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 the quality, effectiveness and safety of vaccine initiatives.

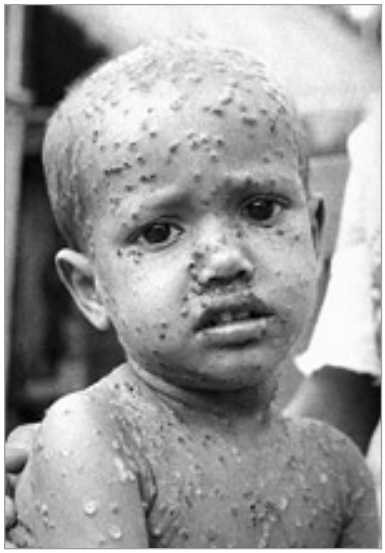
Module outcomes

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 2 to 3 million deaths every year. An additional 1.5 million deaths could be avoided, however, if global vaccination coverage improves.[2]



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

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 2017, vaccination reduced global deaths from measles by 80% worldwide (preventing an estimated 21.1 million deaths).[3]
- **Vaccines save lives and costs:** every dollar spent on childhood immunizations yields US$44 in economic benefits. These include savings on medical costs and productivity loss.[4]

Key point

Immunization reaches more people than any other health or social service and is a vital component of primary health care. It benefits individuals, communities, countries and the world. It is an investment in the future, as it saves lives and protects the heatlh of populations, improves countries' productivity and resilience and enables a safer, healthier, more prosperous world.[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.

You can read more about the state of the world's vaccines and immunization on this WHO page:

Immunization Analysis and Insights

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.

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 26 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 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.

* The answer to all questions can be found at the end of this manual (page 210)

Since then, new vaccines have become available. Some of them, such as hepatitis B, rotavirus, *Haemophilus influenzae* type b (Hib) and pneumococcal vaccines, Human Papillomavirus vaccine, are recommended by the WHO for global use. Others, such as yellow fever vaccine, Typhoid conjugate vaccine, Ebola 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

1800 — 1899	1900 — 1949	1950 — 1979	1980 — 1999	2000 — 2020
1798 Smallpox	1923 Diphtheria	1955 Polio (IPV)	1981 Hepatitis B	2000 Pneumococcal conjugate
1885 Cholera	1923 Tuberculosis	1962 Polio (OPV)	1986 Meningitis B	2006 Human papilloma virus
1885 Rabies	1924 Tetanus	1963 Measles	1989 Hepatitis A	2007 Avian influenza
1891 Anthrax	1926 Pertussis	1967 Mumps	1995 Varicella zoster	2012 Seasonal influenza
1896 Typhoid	1927 Tetanus	1969 Meningitis A	1998 Rotavirus	2019 Ebola
1897 Plague	1935 Yellow fever	1970 Rubella	1999 Meningitis C (conjugate)	
	1943 Typhus	1972 *Haemophilus influenzae*		
		1976 Viral influenza		
		1976 Pneumococcal polysaccharide		
		1977 Meningitis C (polysaccharide)		

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 2000, the Global Alliance for Vaccines and Immunization (GAVI) was created to bringing together public and private sectors with the shared goal of creating equal access to new and underused vaccines for children living in the world's poorest countries.

The Global Vaccine Action Plan (GVAP) — endorsed by the 194 Member States of the World Health Assembly in May 2012 — was a framework to prevent millions of deaths by 2020 through more equitable access to existing vaccines for people in all communities. GVAP was the product of the Decade of Vaccine Collaboration, an unprecedented effort that brought together development, health and immunization experts and stakeholders.

In May 2017, the new resolution on strengthening immunization was endorsed by the ministries of health from 194 countries. The resolution urges countries to strengthen the governance and leadership of national immunization programmes, and improve monitoring and surveillance systems to ensure up-to-date data guides policy and programmatic decisions to optimize performance and impact. It also calls on countries to expand immunization services beyond infancy, mobilize domestic financing, and strengthen international cooperation to achieve GVAP goals.

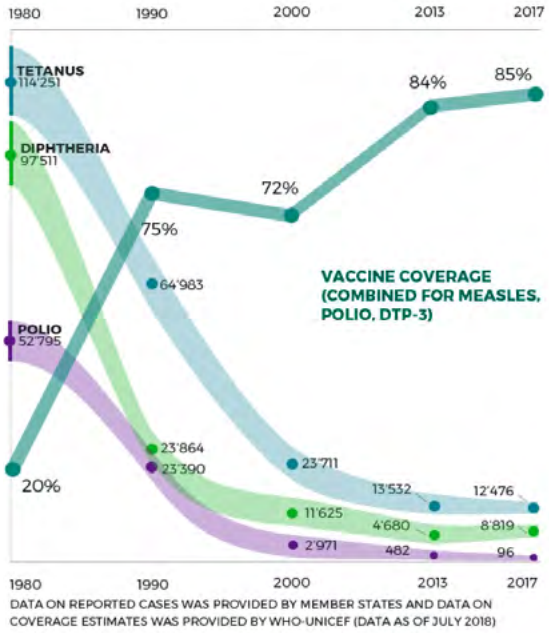
In 2020, WHO is leading the creation of the Immunization Agenda 2020 (IA2020), to address the challenges related to vaccines over the next decade. The IA 2030 strategy — to extend the benefits of vaccines to everyone, everywhere — is underpinned by four core principles: it puts people in the center, it is led by countries, it is implemented through broad partnerships, and it is driven by data.

Strengthening immunization

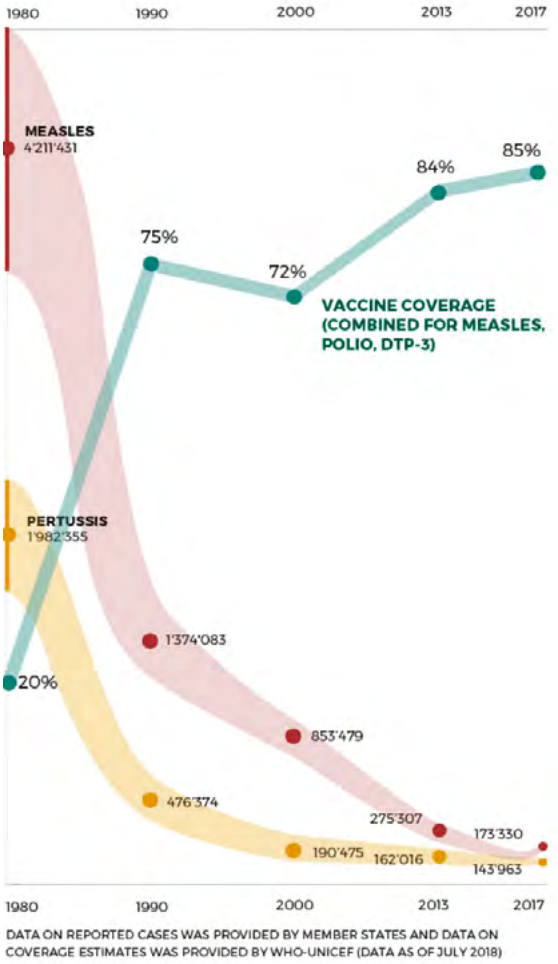
1974	**WHO launches EPI** **Goals:** ▸ Every child (< 1 year) receives protection against six childhood diseases: – tuberculosis – pertussis – polio – tetanus – diphtheria – measles ▸ Tetanus toxoid vaccinations protect women and their newborns
1990	**Vaccination protects >80% of world's children from six main EPI diseases** ▸ New vaccines are continually being added to the EPI programmes in many countries
2000	**Global Alliance for Vaccines and Immunization (GAVI)** ▸ Extends reach of EPI ▸ Helps poorest countries introduce new vaccines in national programmes
2011	**WHO launches GVAP** **Goal:** ▸ Deliver universal access to immunization
2017	**194 countries endorse the new resolution on strengthening immunization:** ▸ Reinforce national immunization pogrammes ▸ Expand immunization beyond infancy ▸ Mobilize domestic financing
2018	▸ **116 million children completed vaccination** ▸ **19.4 million children are not fully vaccinated with DTP3**

In 2018, about 86% of infants worldwide (116.3 million) received 3 doses of diphtheria-tetanus-pertussis (DTP3) vaccine, protecting them against infectious diseases that can cause serious illness and disability or be fatal, leaving 19.4 million children vulnerable to vaccine preventable diseases. By 2018, 129 countries had reached at least 90% coverage of DTP3 vaccine. While immunization is probably the most successful public health intervention, reaching 86% of infants is not enough. The upward trend in coverage has increased by only 5% in the past decade and has plateaued.[3]

Global annual reported incidence of tetanus, diphtheria and polio and immunization coverage between 1980 — 2017[5]



Global annual reported incidence of measles and pertussis and immunization coverage between 1980 — 2017[5]



EXPECTATIONS TOWARDS SAFETY OF VACCINES

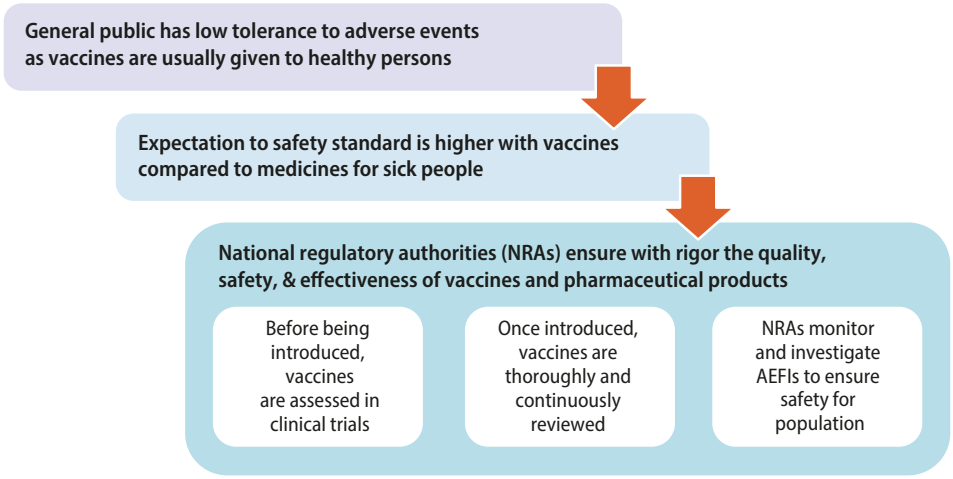
Key point

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 immunisation. 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



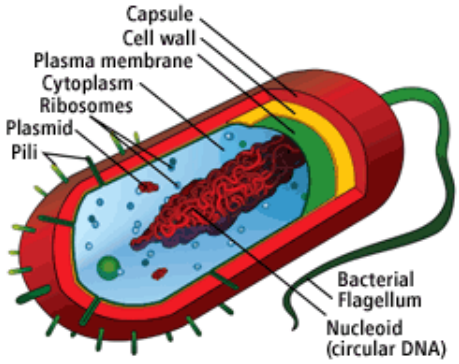
National regulatory authorities (NRAs) are responsible to ensure the quality, safety, and effectiveness of vaccines and other pharmaceutical products. Before their introduction into an immunization programme, vaccines undergo several steps of evaluation to assess their safety and efficacy in clinical trials. Once introduced, vaccines undergo very thorough and continuous reviews of their manufacturing process and NRAs and national immunization programme continue to monitor their safety. Adverse events following immunization are carefully investigated, their cause determined, and feedback provided 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.

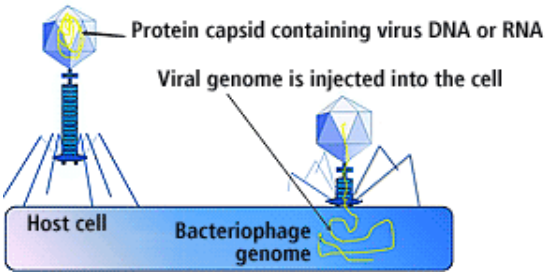
Bacterium (example). Source: wikipedia.org



- **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.

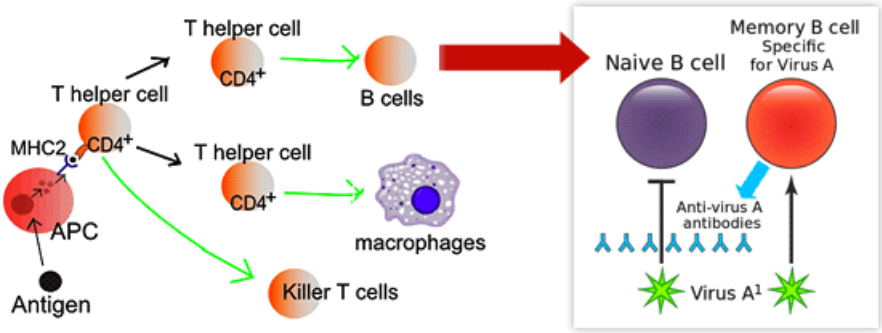
The immune system responds to bacteria and viruses in a very complex way: it recognizes unique molecules (antigens) from bacteria and viruses and produces antibodies (a type of protein) and special white blood cells called lymphocytes that mark the antigens for destruction.

Virus infecting cell. Source: wikipedia.org



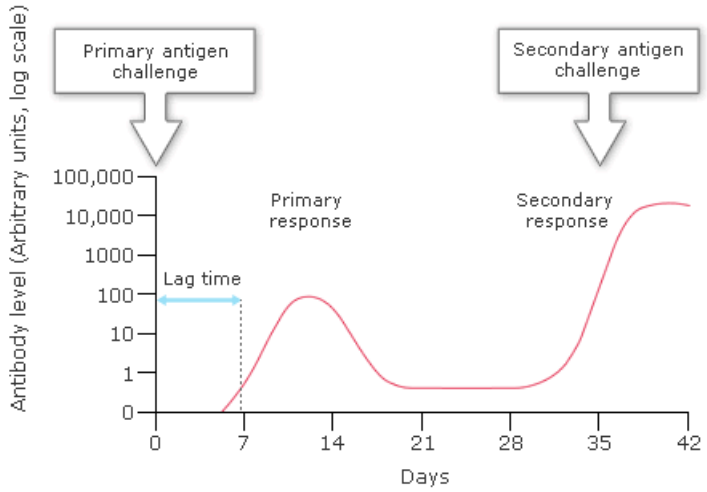
During the primary immune response to the first encounter with a specific pathogen, some lymphocytes called memory cells develop with the ability to confer long-lasting immunity to that pathogen, often for life. These memory cells recognize antigens on the pathogens they have encountered before, triggering 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.

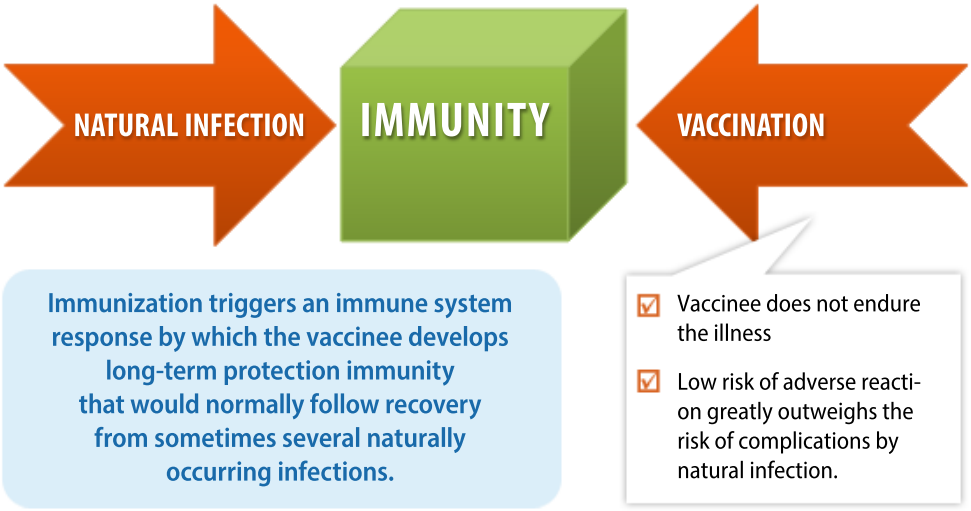
HOW VACCINES WORK

> **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:

- ❒ tuberculosis
- ❒ pertussis
- ❒ polio
- ❒ tetanus
- ❒ diphtheria
- ❒ 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, infections or cervical cancer caused by human papillomavirus, 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 and the associated vaccines

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

* 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

Live attenuated (LAV)

- Tuberculosis (BCG)
- Oral polio vaccine (OPV)
- Measles
- Rotavirus
- Yellow fever
- Varicella-Zoster virus (VZV)
- Seasonal influenza (nasal spray)

Inactivated (killed antigen)

- Whole-cell pertussis (wP)
- Inactivated polio virus (IPV)
- Hepatitis A
- Seasonal Influenza (injectable)

Subunit (purified antigen)

- Acellular pertussis (aP)
- Haemophilus influenzae type b (Hib)
- Pneumococcal (PCV-7, PCV-10, PCV-13)
- Hepatitis B (HepB)
- Human papillomavirus (HPV)

Toxoid (inactivated toxins)

- Tetanus toxoid (TT)
- Diphteria toxoid

Viral vector vaccine

- Zaire Ebola virus (rVSV-ZEBOV)

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 and definition

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 can be related to the vaccine itself (product or quality defect-related reactions), to the vaccination process (error or stress related reactions) or can occur independently from vaccination (coincidental).

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, aseptic meningitis following mump vaccine.

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. Quality defect is defined as any deviation of the vaccine product as manufactured from its set quality specifications.

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. Inappropriate usage is defined as the usage other than what is authorized and recommended in a given jurisdiction based on scientific evidence or expert recommendation.

Example: transmission of infection by contaminated multidose vial.

Immunization anxiety-related reaction

An AEFI arising from anxiety about the immunization. The term "immunization anxiety-related reaction" is used to describe a range of symptoms and signs that may arise from anxiety about immunization and include vasovagal-mediated reactions, hyperventilation-mediated reactions and stress-related psychiatric reactions or disorders. The term "anxiety" does not, however, adequately cover the presentation of all these AEFI and anxiety may not manifest during such events. Thus, a new term is proposed that better describes this cause-specific AEFI, which is "immunization stress-related response (ISRR)".

Example: syncope or hyperventilation.

Coincidental event

An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety, but where a temporal association with immunization exists.

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.

* AEFI is used in accordance with "Definition and Application of Terms for Vaccine Pharmacovilance", a report of CIOMS/WHO, working group on Vaccine Pharmacovigilance: https://cioms.ch/wp-content/uploads/2017/01/report_working_group_on_vaccine_LR.pdf.

Key point

The difference between an adverse 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

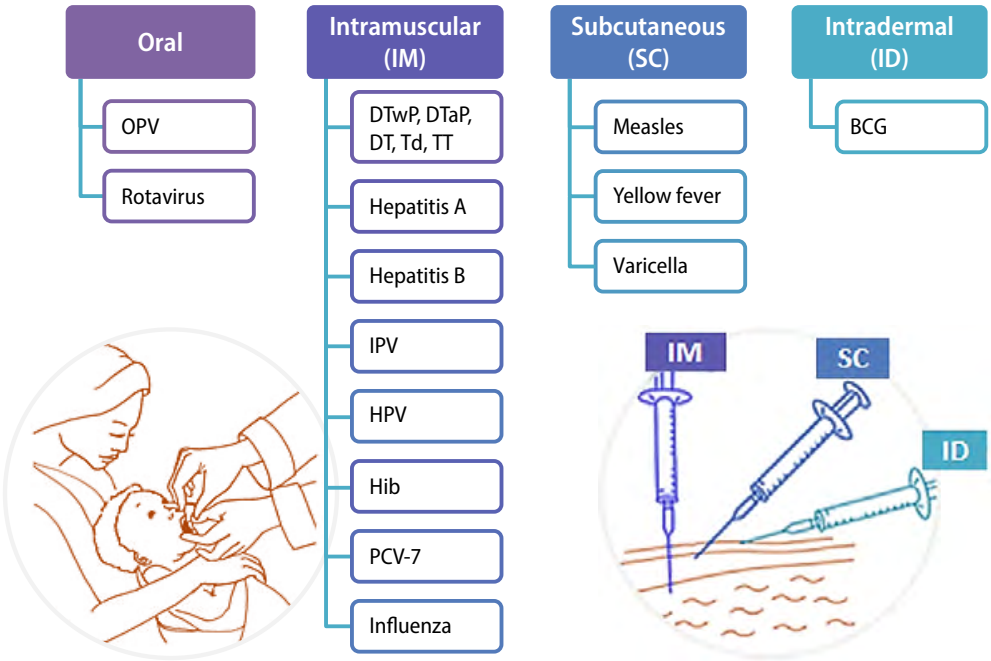
Vaccines contain different components to make them effective. However, each component in a vaccine adds a potential risk of an adverse reaction. Regulatory authorities must ensure that all vaccine components, singly and in combination, do not compromise vaccine safety.

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.

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 reactions 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.

Frequency and severity of adverse vaccine reactions

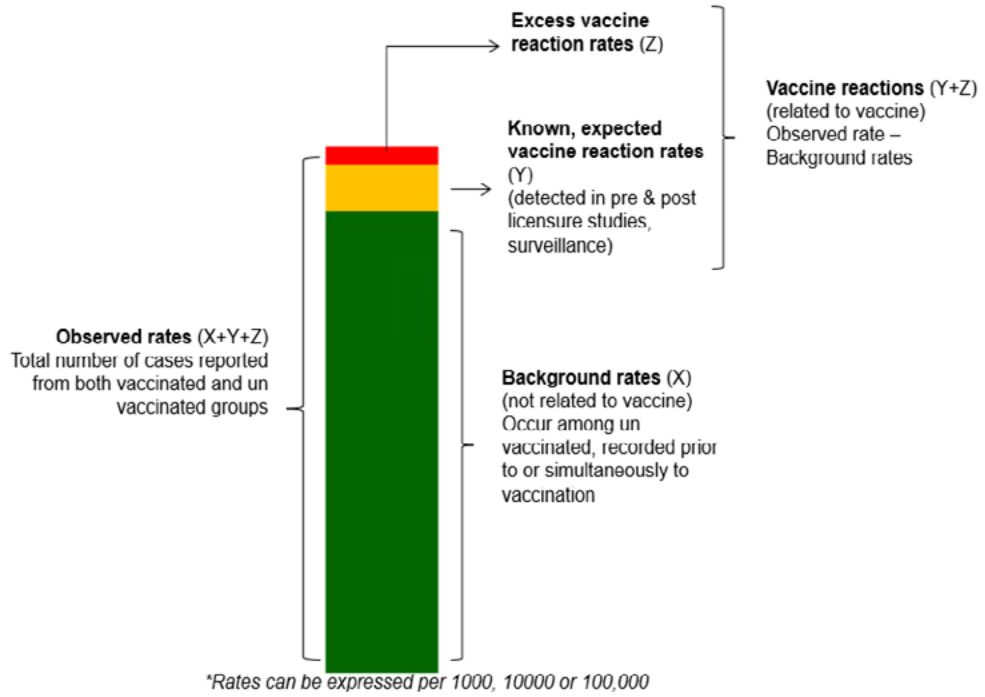
Frequency	Occurrence among persons vaccinated in percent	Severity of reactions
Very common	≥ 10%	**Common and usually minor reactions:** • Are part of the immune response to vaccine, • Reactions settle on their own, • Examples include: – Fever, – Malaise.
Common (frequent)	≥ 1% and < 10%	
Uncommon (infrequent)	≥ 0.1% and < 1%	**Rare, usually more severe reactions:** 1. Usually require clinical management, 2. Examples include: – 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 vaccine pharmacovigilance 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

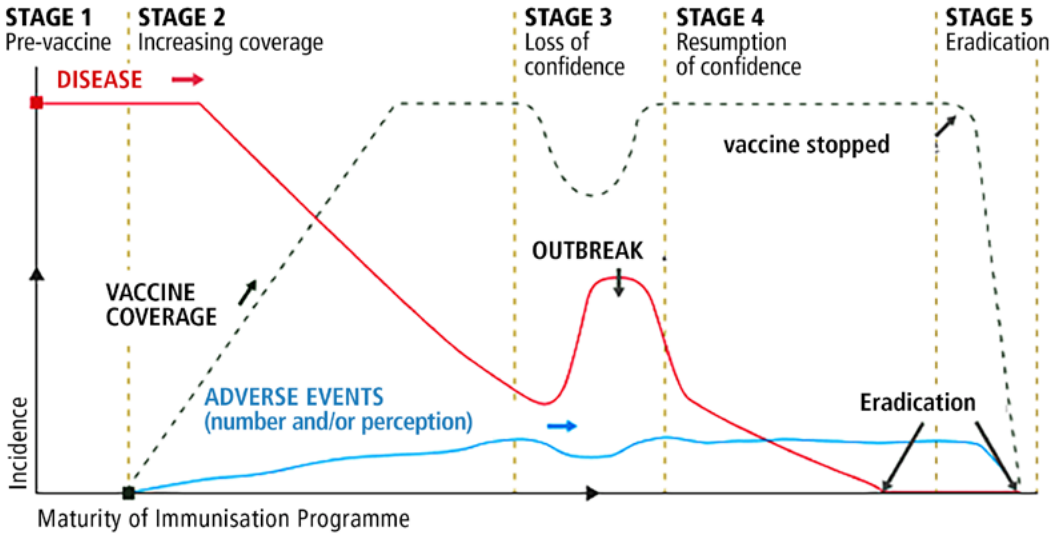


Diagram adapted from Chen RT et al. The Vaccine Adverse Event Reporting SystemVaccine Adverse Event Reporting System (VAERS). Vaccine, 1994: 12(6):542–550.

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**).

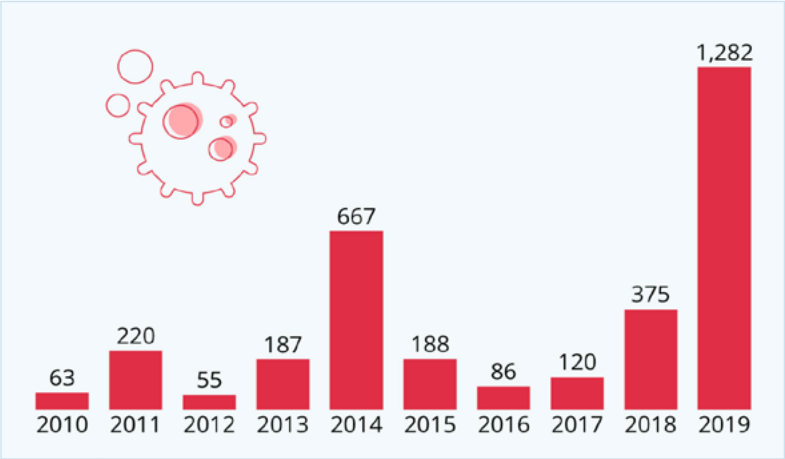
The resurgence of disease or the availability of an alternative vaccine results in renewed public acceptance of vaccination against the disease. Vaccination levels increase and the disease is reduced to earlier low levels (**STAGE 4**).

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.

Resurgence of measles outbreak following a decrease in immunization coverage

In the recent years, vaccination rates among children in the US have fluctuated considerably and vary from one state to another. Between 2009 and 2018, states such as Georgia or Arkansas have seen their vaccination rates drop by over 6%. The states of Colorado, Kansas and Idaho now have vaccination rates below 90% when it comes to MMR vaccines. Anti vaccination sentiment due to religious or philosophical concerns is one of the main reasons behind the decline. As a result, in 2019, USA was in the midst of its largest measles outbreak since the diseases was declared eliminated in 2000. 73 percent of 1300 cases registered in 2019 were linked to outbreaks in New York where different communities, among them Orthodox Jews, are often unvaccinated. In 2014, measles numbers spiked as well, after an Amish missionary who visited the Philippines caused nearly half of the registered cases in a mostly unvaccinated Amish community in Ohio.

Number of measles cases reported in the US (2010–2019)



Source: CDC Measles Statistics and surveillance.

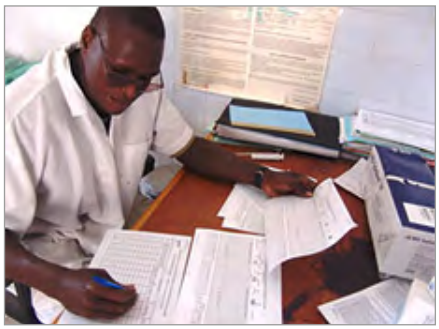
Key point

The more effective the vaccination for a particular disease 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 antitoxin 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 measures — legal, administrative and technical — that governments take to ensure the vaccines' safety, efficacy and quality. They can vary from country to country, both in scope and implementation, but generally include at least the following functions:

- licensing the manufacture, import, export, distribution, promotion and advertising of vaccines;
- assessing the safety, efficacy and quality of vaccines, and issuing marketing authorization;
- inspecting, and conducting surveillance of, manufacturers, importers, wholesalers and dispensers of vaccines;
- controlling and monitoring the quality of vaccines existing on the market;
- controlling the promotion and advertising of vaccines;
- monitoring adverse reactions related to the vaccines in use;
- providing independent information on vaccines to the professionals and the public.

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 25. 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

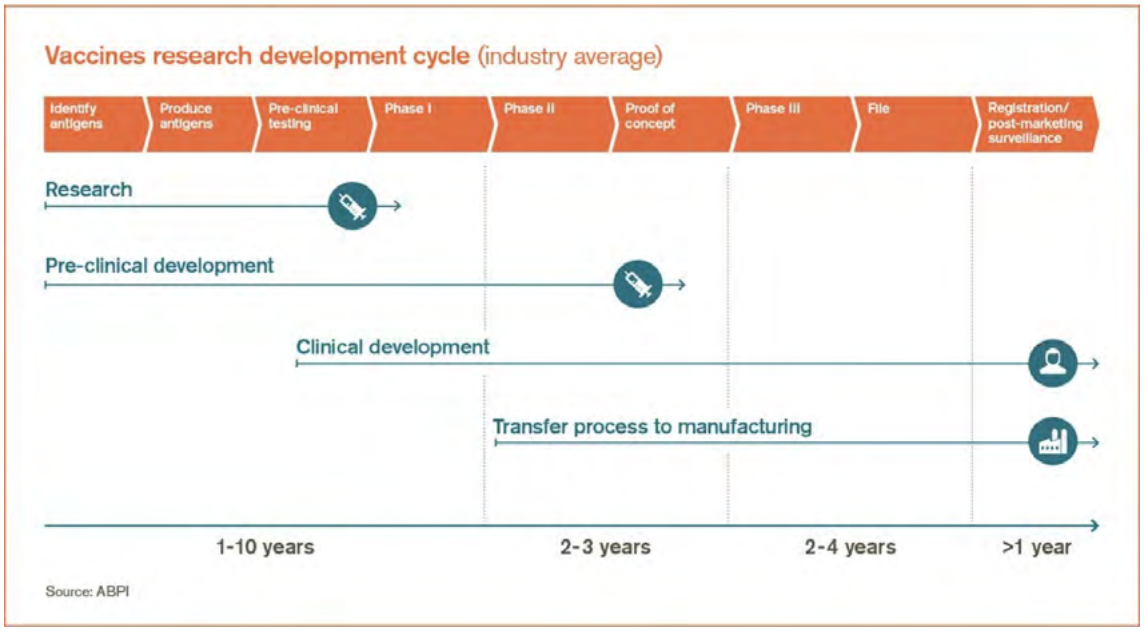
Pre-licensure studies often identify common and acute negative reactions that occur with a frequency greater than 1 in 10,000 vaccinations, depending on total sample size of the study.

The sensitivity of detection of uncommon or rare adverse events, or those with delayed onset, or occurring in particular populations (such as HIV positive people, malnourished individuals, etc) 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 hence the importance of effective vaccine pharmacovigilance system in all countries.

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 post-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;
- sometimes vaccines are used in campaigns or in special situations to specifically targeted populations and safety monitoring approaches can differ.

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, pharmacovigilance systems are used to monitor suspected adverse reactions related to all types of health medical products including vaccines.

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

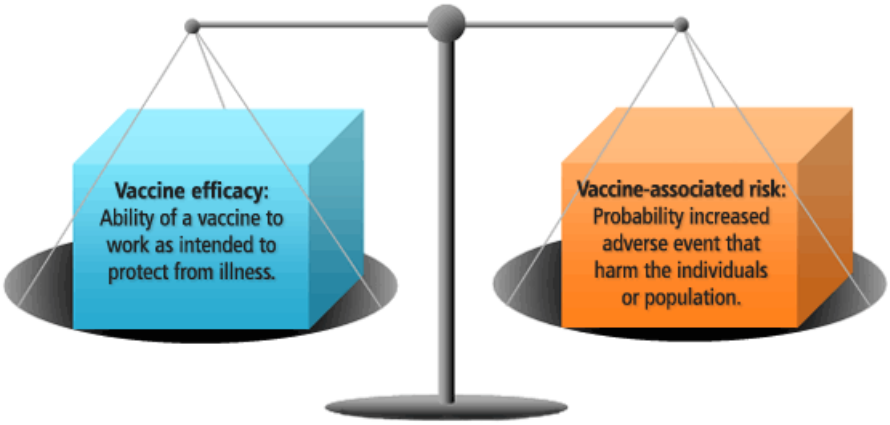
Passive surveillance systems	
Passive surveillance systems	■ Spontaneous reporting system is the corner stone of vaccine pharmacovigilance system because of its relative ease of implementation, its cost and ability to monitor all vaccines and capture all events. These reporting systems monitor events reported by health care providers and consumers and do not actively seek out and collect data or measure outcomes using study protocols.

Active surveillance systems	
Post-licensure clinical trials and phase IV surveillance studies	■ 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)	■ 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 enrolee 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	■ Tertiary clinical centers have been used to conduct research on immunization-associated health risks. ■ More recently, WHO piloted the establishment of a global network of hospital-based sentinel sites in LMICs across the WHO regions for vaccine safety signal verification and hypothesis testing the Global Vaccine Safety Multi Country collaboration project.[98] ■ 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 identified safety signals;
- the identified risk factors (specific population);

- the incidence, severity, morbidity and mortality resulting from adverse vaccine (product-related) 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 occuring 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/Immunization stress related response (ISSR)
  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/ Immunization stress related response (ISSR)
b Coincidental event
c Immunization error-related reaction
d Vaccine product-related reaction
e Vaccine quality defect-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
b secondary
c antibodies
d vaccine
e adjuvants
f immunity
g antigens
h memory cells

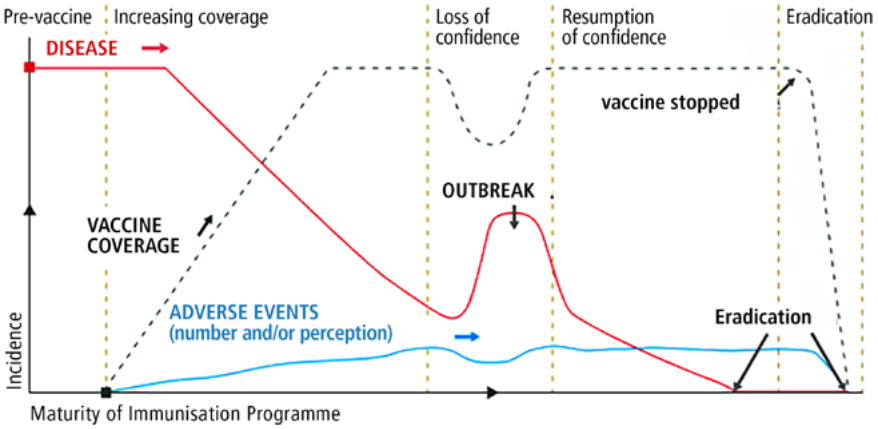
Question 4

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
b subunit (purified) antigen
c inactivated toxin
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/Immunization stress related response (ISSR).
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 be eradicated, vaccine use can be stopped, thereby removing the risk of any adverse event resulting from its use (**STAGE 5**).

MODULE 2

Types of vaccines 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 individuals?

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 VACCINES

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 vaccines

Live attenuated (LAV)

- Tuberculosis (BCG)
- Oral polio vaccine (OPV)
- Measles
- Rotavirus
- Yellow fever
- Varicella-Zoster virus (VZV)
- Seasonal influenza (nasal spray)

Inactivated (killed antigen)

- Whole-cell pertussis (wP)
- Inactivated polio virus (IPV)
- Hepatitis A
- Seasonal Influenza (injectable)

Subunit (purified antigen)

- Acellular pertussis (aP)
- Haemophilus influenzae type b (Hib)
- Pneumococcal (PCV-7, PCV-10, PCV-13)
- Hepatitis B (HepB)
- Human papillomavirus (HPV)

Toxoid (inactivated toxins)

- Tetanus toxoid (TT)
- Diphteria toxoid

Viral vector vaccine

- Zaire Ebola virus (rVSV-ZEBOV)

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
Varicella-zoster
Influenza (nasal spray)

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.

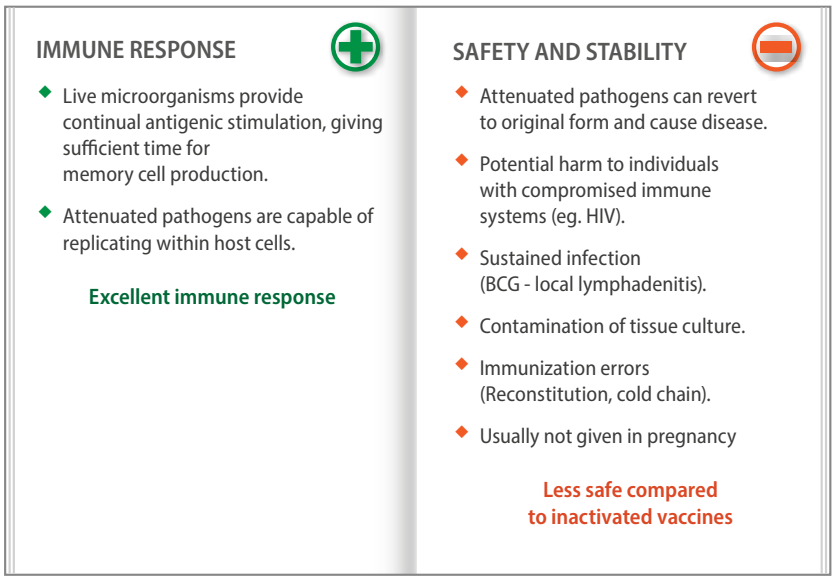
In the case of viruses or intracellular microorganisms where cell-mediated immunity is usually desired, attenuated pathogens are capable of replicating within host cells.

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).
- Theoretically, live attenuated virus vaccines given to pregnant women might be capable of crossing the placenta and infecting the foetus. As a result, most live attenuated vaccines are contraindicated or not recommended during pregnancy.[85]
- LAVs are contraindicated for patients following cancer treatment and for patients who have finished a cancer treatment for less than 6 months. Other types of vaccines are allowed during cancer treatment.[91]

- 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.



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).

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 1.56–4.29 per million doses	Almost exclusively occurs in inadvertently immunized persons with severely compromised cellular immunity.
		Osteitis and Osteomyelitis	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 2–4 per million doses	An essential component of the global polio eradication campaign despite adverse reactions.
	Measles[31]	Febrile seizures	uncommon at 3.4–8.7 per 10,000 doses	Adverse reactions, with the exception of allergic anaphylactic reactions, are less likely to occur after receipt of the second dose of measles vaccine.
		Transient thrombocytopenia	very rare at 2.5–3 per 100,000 doses	
		Anaphylaxis	very rare at 3.5–10 per million doses	Allergic reactions to vaccine components including neomycin and the stabilizers gelatine or sorbitol, may follow vaccination.
	Rotavirus[61]	Intussuception	1–2/100,000 infants	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 or anaphylactic reactions	0.8 per 100,000 doses	Sensitivity to egg, which is commonly used to stabilize the vaccine, may explain at least some of these cases.
		Vaccine- associated neurotropic disease (encephalitis)	0.25–0.8 per 100,000 doses	Infants seem more susceptible to vaccine-associated neurotropic disease than the YF-vaccinated population at large.
		Vaccine-associated viscerotropic disease	0.25 to 0.4 per 100,000	The elderly seem more susceptible to reaction (very rare at 4–5 per 10,000 doses) 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)
Typhoid

VIRUS
Inactivated polio virus (IPV)
Influenza (injectable)
Hepatitis A

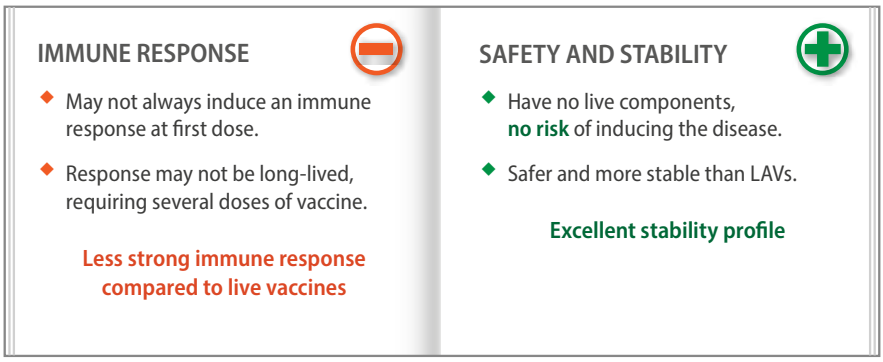
Immune response

- 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.



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, hyporesponsive 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]	None known	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.

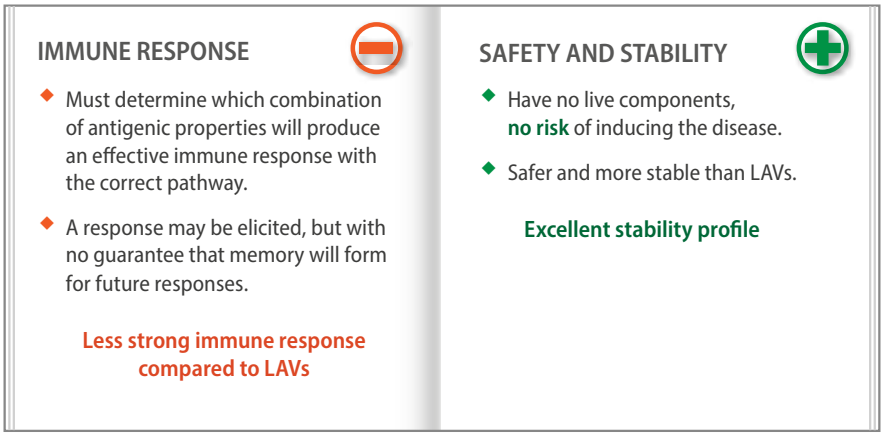
Protein-based

Polysaccharide

Conjugate

Safety and stability

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



Key point

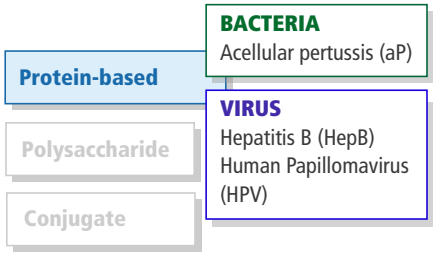
Rather than introducing a whole-cell vaccine (either inactivated or attenuated) to an immune system, a subunit vaccine contains a fragment of the pathogen and elicits an appropriate immune response.

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.
- **Human Papillomavirus (HPV)** vaccines consist of recombinant viral vaccine proteins containing highly purified virus-like particles (VLP) which are protein shells of the HPV virus. The VLP contain no viral DNA, thus they cannot infect cells, reproduce or cause disease.

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	Frequency	Comment
BACTERIA	Acellular pertussis (aP)[30]	Extensive limb swelling after booster doses	2–6 per 100 doses	Although these reactions may cause swelling which may involve the entire vaccinated limb, they resolve spontaneously and do not lead to any sequelae (Rennels, 2003).
		Seizures, persistent crying, HHE, and fever in excess of 40°C	Very rare	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]	Anaphylaxis	Very rare 1.1 per million doses	Reports of severe anaphylactic reactions are very rare.
	Human Papillomavirus (HPV)[101]	None known	None known	Report of severe adverse reaction for HPV remain very low.

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 individual's 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.

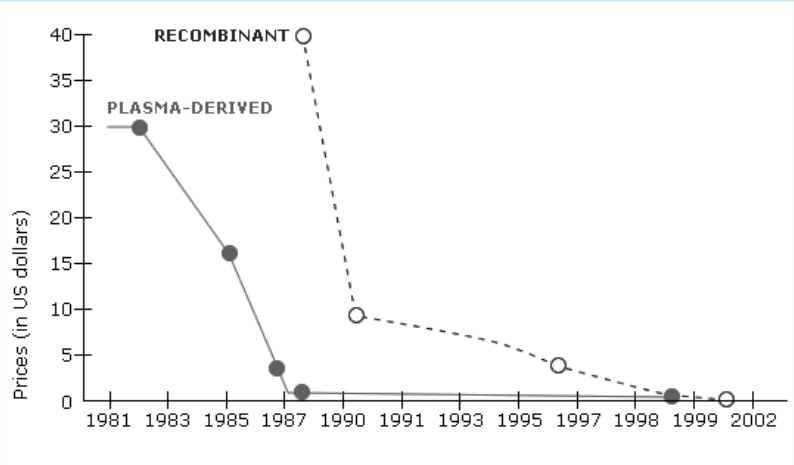
Because the price of wP is considerably less than aP, where resources are limited and the vaccine is well accepted by the local population, wP vaccine remains the vaccine of choice. In countries where a higher rate of adverse reactions after immunization with wP prevents high vaccination coverage, aP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

More about Hepatitis B vaccines

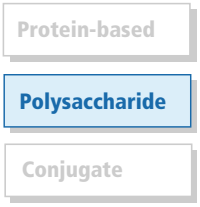
The first available hepatitis B vaccines were plasma-derived, produced by harvesting hepatitis B surface antigen (HBsAg) from the plasma of persons with chronic HBV infection. The particles are highly purified, and any residual infectious particles are inactivated by various combinations of urea, pepsin, 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



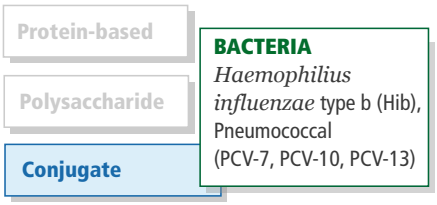
Some bacteria when infecting humans are often protected by a polysaccharide (sugar) capsule that helps the organism evade the human defense systems especially in infants and young children.

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.

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	*Haemophilus influenzae* type b conjugate (Hib)[65]	None known	Severe adverse events following administration of Hib vaccine are uncommon, making it one of the safest vaccines currently available.
	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.

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. Polysacharide vaccines provoke an immune response against the polysaccharide capsule.
- ❒ B. Conjugate vaccine binds the polysaccharide to a carrier protein.
- ❒ C. Polysacharide vaccines are targeted, but not very immunogenic. They induce only short-term immunity. Polysacharide 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

BACTERIA
Tetanus toxoid (TT)
Diphtheria toxoid

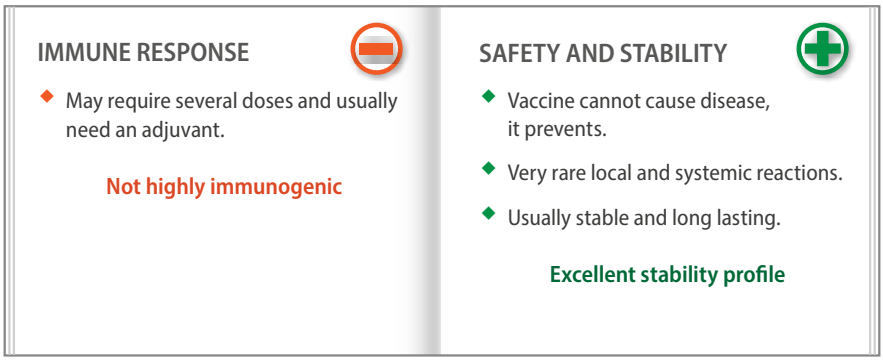
Toxoid vaccines are based on the toxin produced by certain bacteria (e.g. tetanus or diphtheria).

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]



Adverse reactions associated with toxoid vaccines

	Vaccine	Rare, more severe adverse reactions	Comment
BACTERIA	Tetanus toxoid (TT)[68]	Anaphylaxis (1.6 per million doses) and brachial neuritis (0.69 cases per 10 million) are extremely rare.	Local and systemic reactions increase with increasing number of doses.
	Diphtheria toxoid (DT and Td)[69]	Temperature in excess of 40.5 °C (0.3%), febrile seizures (8 per 100,000 doses) or hypotonic–hyporesponsive episodes (0–291 per 100,000 doses).	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.

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 aluminium-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).

- 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 that 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 reviews 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.

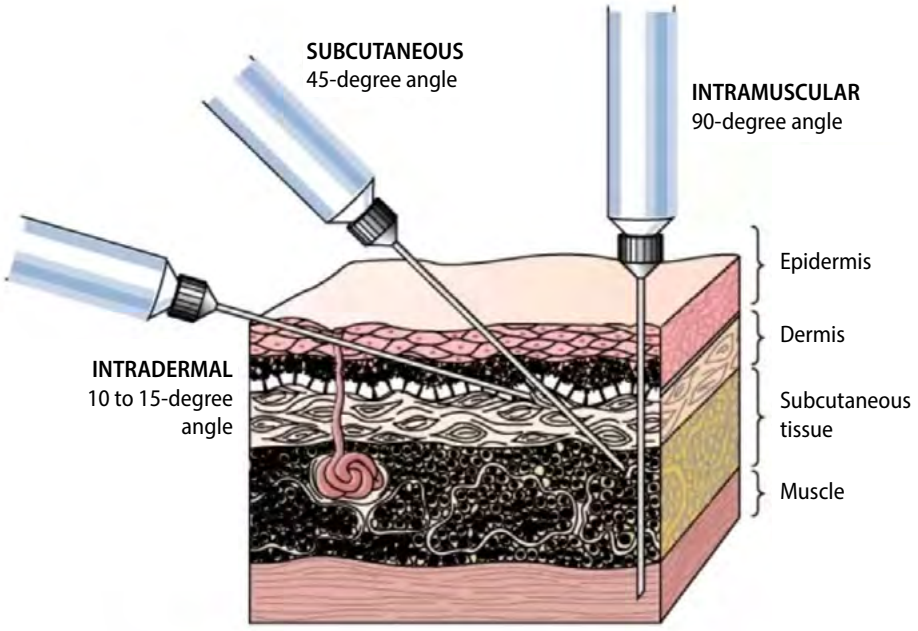
Question 5

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.

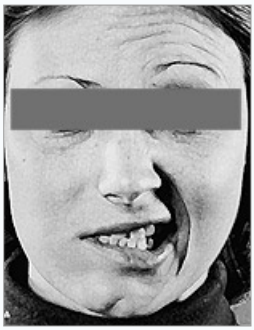
Intradermal (ID) injection administers the vaccine in the topmost layer of the skin. BCG is the only vaccine with this route of administration. Intradermal injection of BCG vaccine reduces the risk of neurovascular injury. Health workers say that BCG is the most difficult vaccine to administer due to 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.

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.



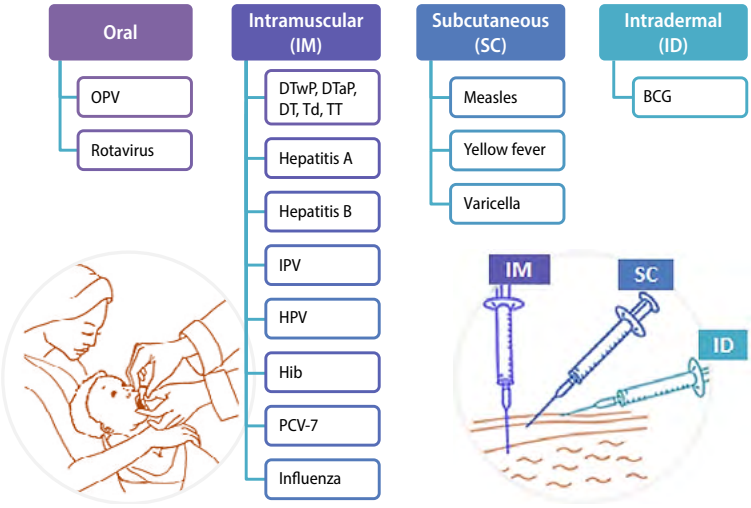
Bell's palsy (a one-sided paralysis of facial muscles) after intranasal immunization with the vaccine.

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.

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.

> **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.

Contraindications to vaccines

Childhood vaccine	Anaphylaxis after previous dose or severe allergy to vaccine component	Pregnancy	Severely immuno-compromised*	Comment
BCG[28]				Further information available at https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/bcg-vaccines in section "Safety of BCG vaccination in immunocompromised individuals"
DTwP[30]				

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

Childhood vaccine	Anaphylaxis after previous dose or severe allergy to vaccine component	Pregnancy	Severely immuno-compromised*	Comment
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.
HPV[102]				

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.us

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 overview of anaphylaxis as an adverse event following immunization (AEFI) and practical guidance on its identification, case management and response in primary care setting:

www https://www.who.int/publications/m/item/anaphylaxis-guidance

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 is a vital treatment, it stimulates the heart and reverses the spasm in the blood vessels and the lung passages, reduces oedema and urticaria, thus countering the anaphylaxis. But, if used inappropriately, this very potent agent can cause irregular heartbeat, heart failure, severe hypertension and tissue necrosis, 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 individuals 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 vaccination[72] — 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 life[73]. 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:

https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers/influenza

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 2020, 12 countries have yet to eliminate MNT.[74]

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 30,848 babies in 2017.[103]

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 38.

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)
b inducing the disease
c *Haemophilus influenzae* type b vaccine (Hib)
d common bacterial infections
e wild-type viruses
f acellular pertussis (aP) vaccines
g vaccine antigens
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 one of 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
b formaldehyde
c adjuvants
d preservatives
e stabilizers

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
b intranasal spray
c subcutaneous
d intradermal
e intramuscular

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 50).

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 53.

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 one of 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 **intradermal** 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 adverse 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 event?
- Was it related to the vaccine, or the way it was administered, or was it unrelated?
- Is the event serious?

This module will help you to answer these questions. You will learn the difference between adverse event and adverse reaction and 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. differenciate between event and reaction;
3. differentiate between serious and severe reactions, and between minor and severe 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 can be related to the vaccine itself (product or quality defect-related reactions), to the vaccination process (error or stress related reactions) or can occur independently from vaccination (coincidental).

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, aseptic meningitis following mump vaccine.

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. Quality defect is defined as any deviation of the vaccine product as manufactured from its set quality specifications.

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. Inappropriate usage is defined as the usage other than what is authorized and recommended in a given jurisdiction based on scientific evidence or expert recommendation.

Example: transmission of infection by contaminated multidose vial.

Immunization anxiety-related reaction

An AEFI arising from anxiety about the immunization. The term "immunization anxiety-related reaction" is used to describe a range of symptoms and signs that may arise from anxiety about immunization and include vasovagal-mediated reactions, hyperventilation-mediated reactions and stress-related psychiatric reactions or disorders. The term "anxiety" does not, however, adequately cover the presentation of all these AEFI and anxiety may not manifest during such events. Thus, a new term is proposed that better describes this cause-specific AEFI, which is "immunization stress-related response (ISRR).

Example: syncope or hyperventilation.

Coincidental event

An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety but where a temporal association with immunization exists.

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.

Serious event

Seriousness is based on patient/event outcome or action criteria and defines regulatory reporting obligations. 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, or
- is a congenital anomaly/birth defect.

The ICH E2A and E2D guidelines also state that other situations, such as other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes above, should also be considered serious after applying medical and scientific judgment. Those "other situations" are open to interpretation and could vary from jurisdiction to jurisdiction.[104]

Event severity

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.us

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.

Vaccine reactions

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

A vaccine reaction can be an individual's response to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly (*vaccine product-related reactions*). It can also be due to a defect in a vaccine (or its administration device) that occurred during the manufacturing process (*quality defect-related reactions*).

Vaccine reactions can be classified according to their severity into two groups:

Minor reactions	*Severe reactions*
■ 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).	■ 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

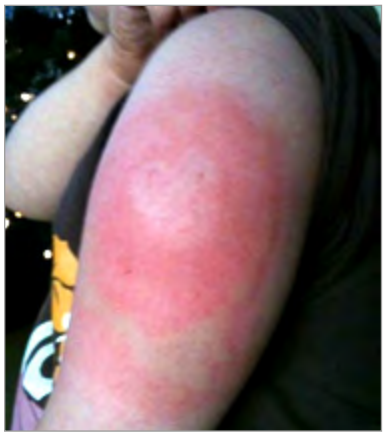
There is low public tolerance of vaccine adverse reactions. Vaccines are therefore only licensed when the frequency of severe reactions is very rare and when only minor, self-limiting reactions are reported.

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%

Vaccine	Local reactions	Systemic reactions	
	(pain, swelling, redness)	Fever > 38°C	Irritability, malaise and systemic symptoms
Tetanus/DT/aTd	~ 10%[d]	~ 10%	~ 25%
Treatment	• Cold cloth at injection site • Paracetamol[f]	• Give extra oral fluids • Wear cool clothing • Tepid sponge or bath • Paracetamol[f]	• 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: https://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, they should be reported within 24 hours to allow immediate action. Most severe vaccine reactions do not lead to long-term problems. Anaphylaxis, while potentially fatal, is treatable without leaving any long-term effects.

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.

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.

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

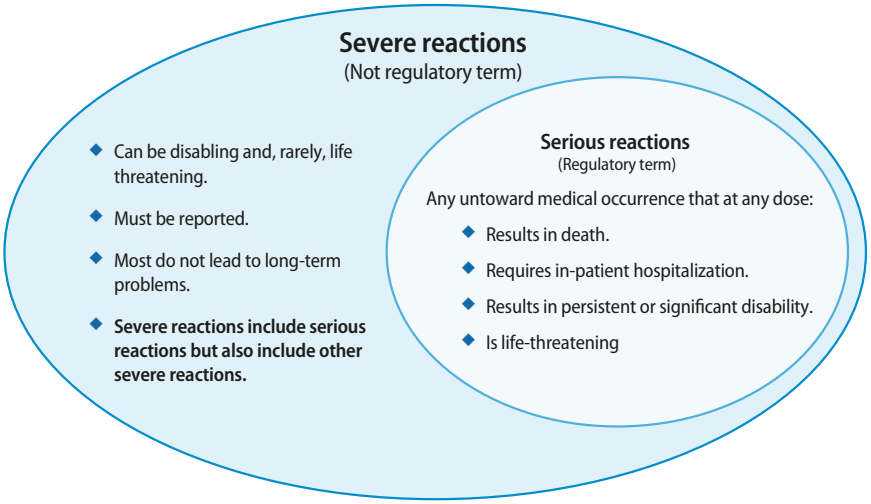
a. Reactions (except anaphylaxis) do not occur if already immune (90% of those receiving a second dose); children >6 years unlikely to have febrile seizures.

b. 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.

c. 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

'*Serious*' and '*severe*' are often used as interchangeable terms but they are not. *Severe* is used to describe the intensity of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance. Seriousness is based on patient/event outcome or action criteria and defines regulatory reporting obligations. 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, or is a congenital anomaly/birth defect, and any other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes above.[105]



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
Non-sterile injection • 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	• 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
Reconstitution error • Inadequate shaking of vaccine • Reconstitution with incorrect diluent • Drug substituted for vaccine or diluent • Reuse of reconstituted vaccine at subsequent session	• Local abcess • Vaccine ineffective* • Effect of drug, e.g., insulin, oxytocin, muscle relaxants • Toxic shock syndrome • Death
Injection at incorrect site • BCG given subcutaneously • DTP/DT/TT too superficial • Injection into buttocks	• Local reaction or abscess or other local reaction • Local reaction or abscess or other local reaction • Sciatic nerve damage
Vaccine transported/stored incorrectly • Freezing vaccine during transport • Failure to keep vaccine in cold chain, exposing to excessive heat or cold	• Increased local reaction from frozen vaccine • Ineffective vaccine*
Contraindication ignored • Vaccination staff ignoring or not becoming familiar with contraindications for a vaccine	• Avoidable severe reaction

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.

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

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 6[58] entitled "Holding an immunization session" includes the correct technique for giving each vaccine.

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

Immunization anxiety-related reactions or Immunization Stress Related Response

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

The term "*immunization anxiety-related reaction*" is used to describe a range of symptoms and signs that may arise around immunization that are related to "*anxiety*" and not to the vaccine product, a defect in the quality of the vaccine or an error of the immunization programme. These reactions are described as AEFIs arising from anxiety about immunization and include vasovagal-mediated reactions, hyperventilation-mediated reactions and stress-related psychiatric reactions or disorders.[106]

ACUTE STRESS RESPONSE

An acute stress response is an internal physiological response to a threat in all mammals and is often referred to as a "fight or flight" response. It may manifest with variable severity of symptoms and may range from mild feelings of worry and "butterflies" in the stomach to sympathetic stimulation: increased heart rate, palpitations, difficulty in breathing or rapid breathing (hyperventilation).

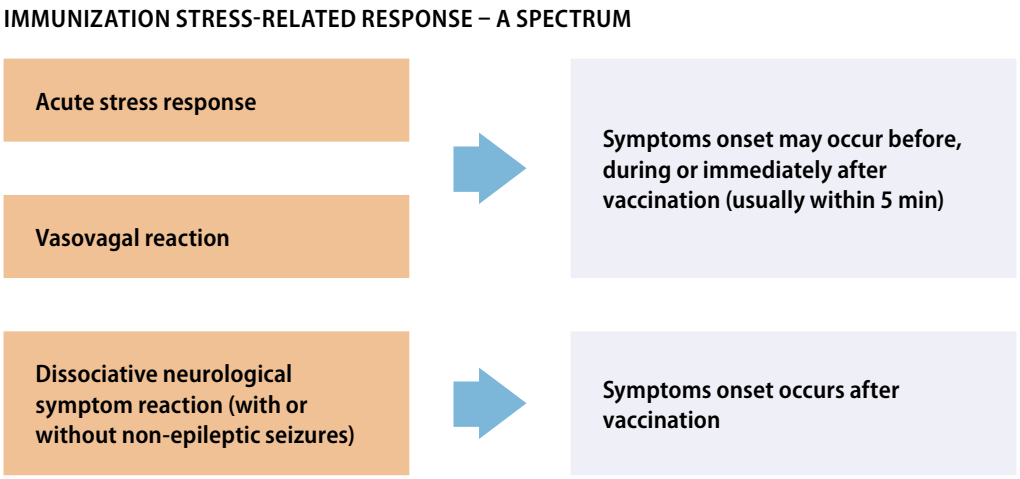
VASOVAGAL REACTION

A vasovagal reaction manifests as symptoms of mild dizziness or a brief loss of consciousness (syncope) because of insufficient blood flow to the brain after loss of blood pressure due to a decreased heart rate or vasodilatation of blood vessels. It may be associated with prodromal symptoms such as nausea, sweating or pallor. Some individuals who experience syncope may also have a syncopal seizure.

DISSOCIATIVE NEUROLOGICAL SYMPTOM REACTIONS

Dissociative neurological symptoms and signs can include weakness or paralysis, abnormal movements or limb posturing, gait irregularities, speech difficulties, and non-epileptic seizures with no apparent physiological basis. The symptoms and signs may take hours to days to develop after immunization. DNSRs appear to be more common in females; they are not usually diagnosed in infants. In children, DNSRs usually manifest as single symptoms.

Classification of stress responses and reactions



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.

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]

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.

*Expected coincidental deaths following DTP vaccination in selected countries (2018)**

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
			= (IMRxN/12)×nv×ppv	= (IMR×N/52)×nv×ppv	= (IMR×N/365)×nv×ppv
Australia	3	315,000	213	49	7
Cambodia	24	364,000	1,966	454	65
China	7	15,230,000	23,987	5,536	789
Japan	2	918,000	413	95	14
Laos	38	166,000	1,419	328	47
New Zealand	5	58,000	65	15	2
Philippines	22	1,668,000	8,257	1,905	271

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.

* https://childmortality.org

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 Informations sheets on observed rates of vaccine reactions:

https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/reaction-rates-information-sheets

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. 789
- ❒ C. 16,948
- ❒ B. 23
- ❒ D. 185

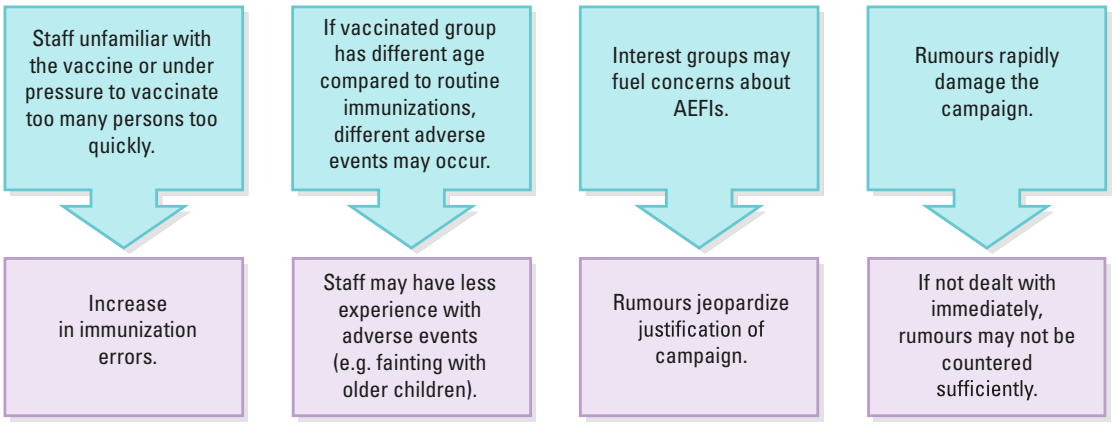
Key point

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.

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://apps.who.int/iris/bitstream/handle/10665/67726/WHO_V-B_02.10_eng.pdf

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.

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:

https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/reaction-rates-information-sheets

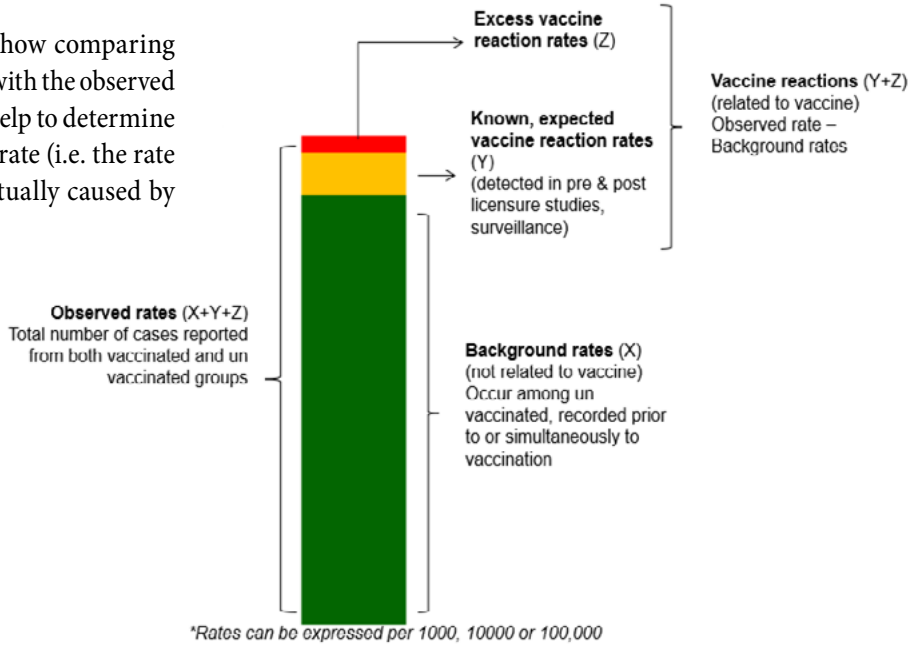
However, one of the main challenges in surveillance of AEFIs is to differentiate coincidental events from events that are caused by a raction to a vaccine or its components.

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 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).



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.
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 occuring 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 85.

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 90.

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 85.

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 97.

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 × 2/100,000 × 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 the science 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 detected, collected, analyzed and followed up. 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 pharmacovigilance 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)/Pharmacovigialnce center/Immunisation programme;
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, a specific lot or the immunisation procedure;
4. explain the value of AEFI investigation and its key steps.

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.

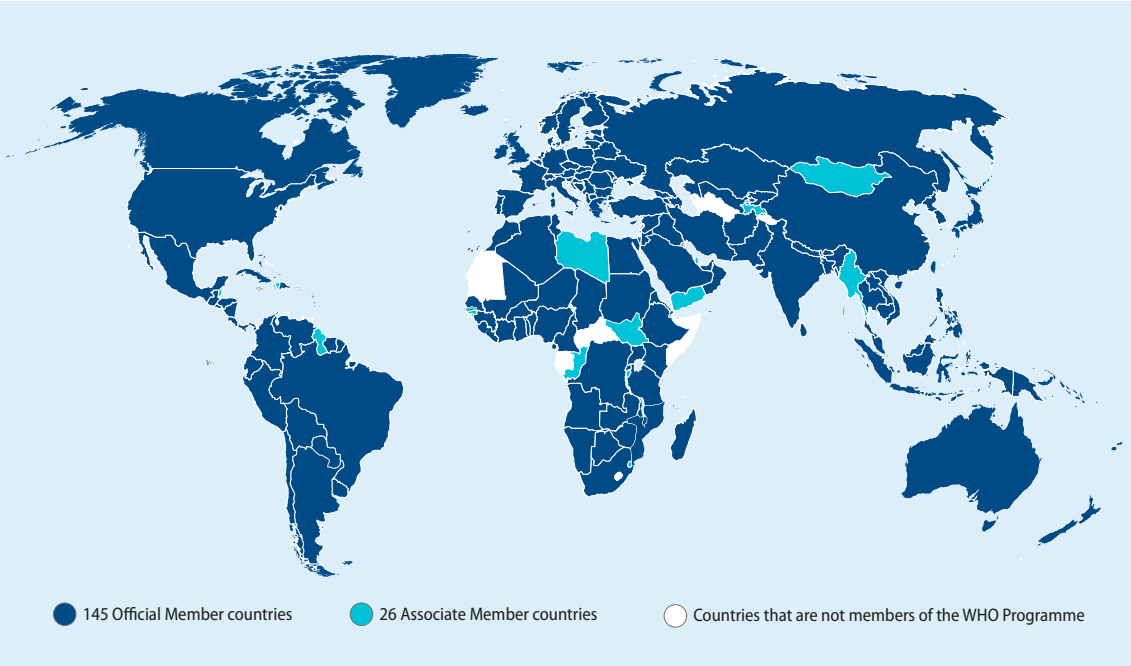
The specific aims of pharmacovigilance are to:[46]

- 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 (NPCs) 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) / Pharmacovigilance centers (NPCs) 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. NPCs 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) MONITORING

ADR monitoring 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 specific vaccinovigilance 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 the WHO Collaborating Centre for International Drug Monitoring, 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 145 as of May 2021.[42] The centres vary considerably in size, resources, support structure and scope of activities. Collecting and analyzing spontaneous reports of suspected ADRs and detecting signals 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 SPECIFIC PHARMACOVIGILANCE SYSTEM

Vaccines are considered drugs but require different "immunization safety" surveillance within a specific pharmacovigilance 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.

Several countries are developping an integrated vigilance system to deal with all adverse event including those related to genuine vaccine adverse reactions, as well as to prevent or manage fear caused by false or unproven signals from patients and health workers. This integrated approach helps, especially low and middle income countries to optimize ressources and competencies. Nevertheless, vaccines have their own specificities.

Some of the key differences between vaccines and drugs, which lead to the need for some adapted tools and method for vaccine pharmacovigilance, are listed in the table below.

VACCINES	OTHER DRUGS
Who gets them?	
Usually, healthy people including infants. Often most of the population, birth cohort, or group at high risk for disease or complications.	Usually, sick people.
Why?	
To prevent disease.	Usually to treat disease.
How do they get them?	
Vaccines are often administered through public health programmes. In some countries, vaccination may be a prerequisite for enrolment in school.	Often administered by a medical doctor or pharmacist.

VACCINES	OTHER DRUGS
When do they get them?	
Most childhood vaccines are administered at specific ages, or in relation to special circumstances such as outbreaks or travel. The age at the time of vaccination may coincide with the emergence of certain age-related diseases (e.g. neurodevelopmental disorders).	Normally at time of illness.
What about adverse events?	
Low acceptance of risk. Intensive investigation of severe AEFIs, even if rare, is necessary. 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.	Acceptance of adverse events often depends on the severity of illness being treated and the availability of alternative treatment options.
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?

VACCINE PHARMACOVIGILANCE

Definition

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

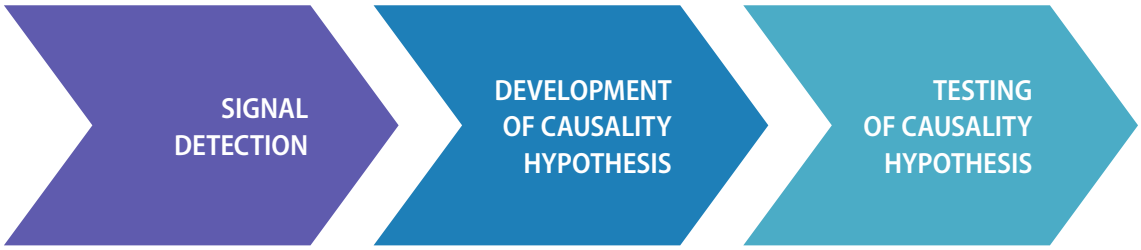
"*the science and activities relating to the*

- *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

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

Organisational

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 on 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.

Independent review is needed

There is a need for review of adverse events by a group of independant experts organised in a Committee for AEFI casuality assessment.

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

Functional

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.

Thorough and systematic procedures for AEFI investigation and causality assessment must be followed to come up with meaningful results.

INTERACTIONS BETWEEN AEFI AND ADR SURVEILLANCE SYSTEMS

The NRA 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 NRAs/NPC, monitoring the safety of vaccines requires the involvement of both the National Immunization Programme (NIP) and the NRA/NPC. Their good collaboration should be supported by clearly distinguishing their roles and responsibilities.

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

Because the NRA/NPC may have limited knowledge of the structure and management of the NIP, 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/NPC		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 NRA/NPC have failed to work with each other when developing national AEFI or ADR surveillance systems. This means they failed to: capture all relevant data in one central repository, avoid the duplication of efforts and optimise the capacity to analyse safety events regardless of the exposure. In addition, with separate systems, 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 NRA/NPC and NIP is usually a critical components of a strong AEFI surveillance system.

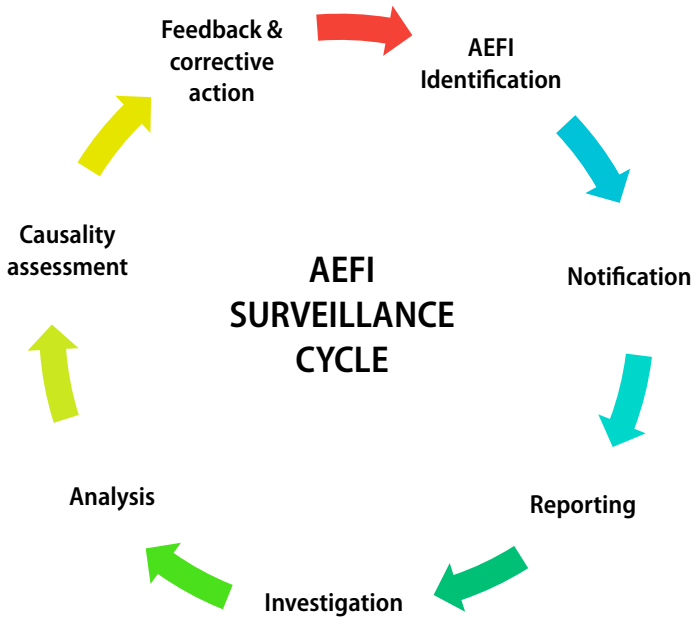
In some countries where the NRA/NPC is not in a position to execute the aforementioned tasks, the NIP may have taken over part of the activities of the NRA/NPC.

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 NPC, 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.

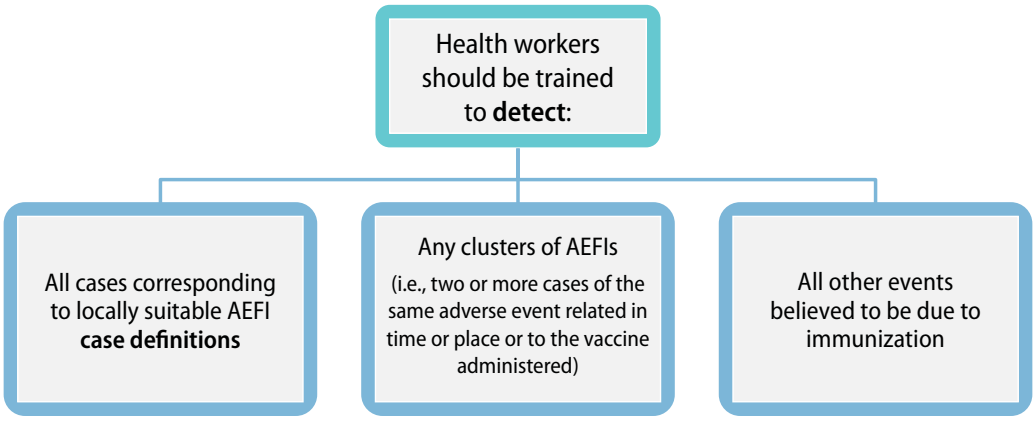
You will be introduced to the stakeholders involved in these processes, and their respective responsibilities.

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.

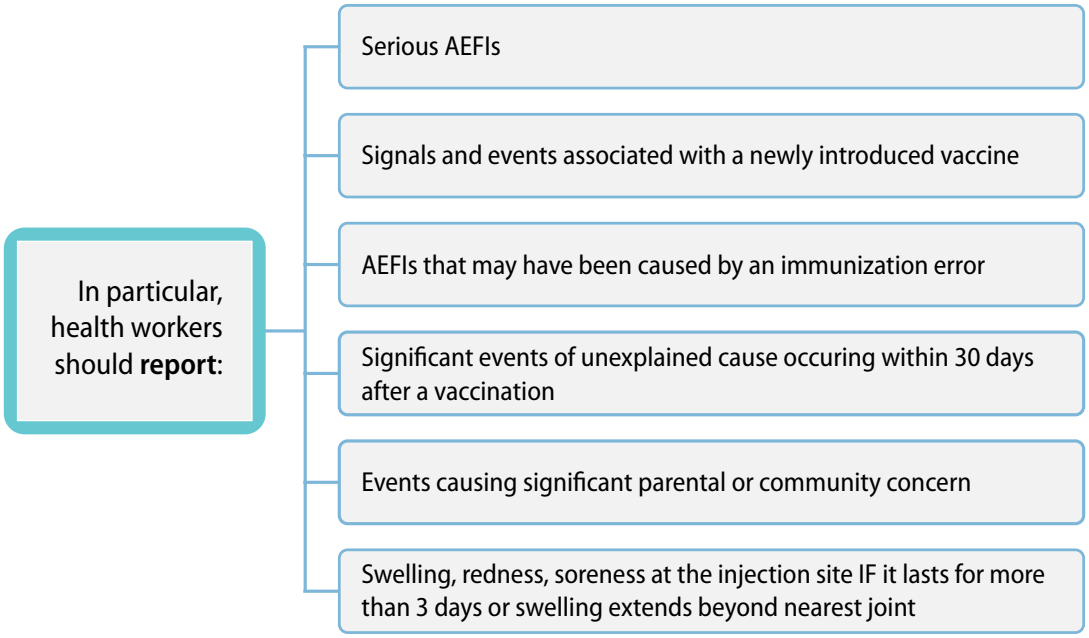
Health workers have the responsibility to detect AEFIs and report AEFIs when appropriate. They also have the responsibility to treat or refer patients for treatment. All immunization staff must be able to identify and report adverse events. Detection requires effective staff training and education to 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".

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-Mémoire on AEFI Investigation". Look at the Aide-Mémoire to find out more about key definitions, guidance to prepare for an investigation, as well as a checklist providing useful information for

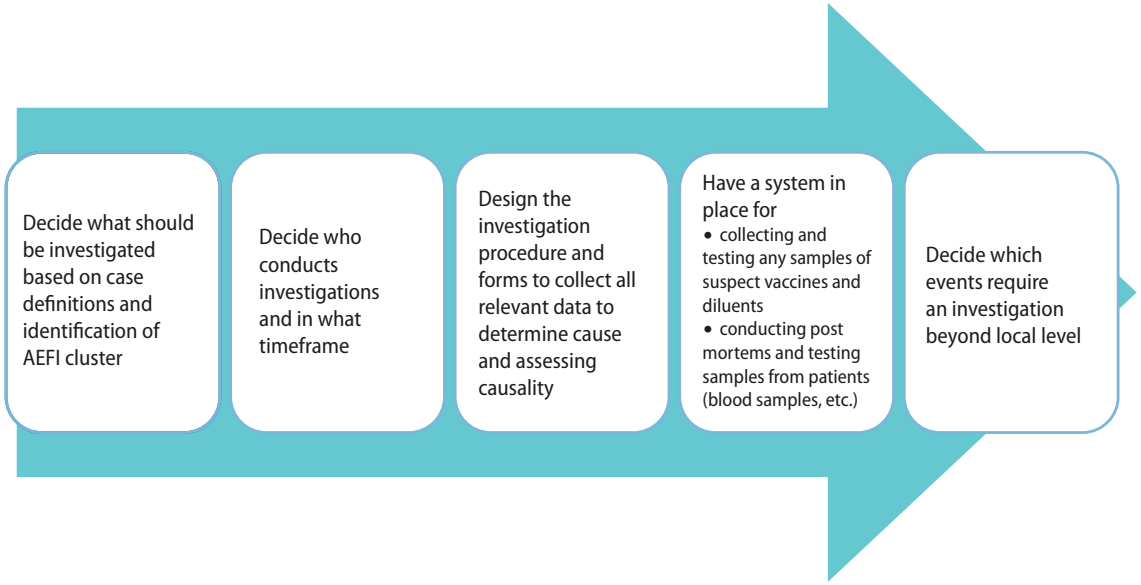
E-learning course on AEFI investigation to learn:
1) when to launch an investigation;
2) what information is required to successfully complete an investigation;
3) how to successfully manage inter-personal communication with relevant stakeholders.

https://vaccine-safety-training.org/investigation

The WHO Aide-Mémoire on AEFI Investigation proposes a systematic, standardized process to investigate reported serious adverse events following immunization (AEFI) and ascertain the underlying cause of the AEFI:

https://cdn.who.int/media/docs/default-source/global-vaccine-safety/new-aide-memoire-aefi.pdf

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 administrated. 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.

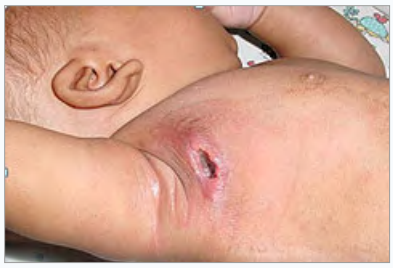


ILLUSTRATION 2

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.

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.

https://www.who.int/publications/i/item/causality-assessment-aefi-user-manual-2019

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.

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]

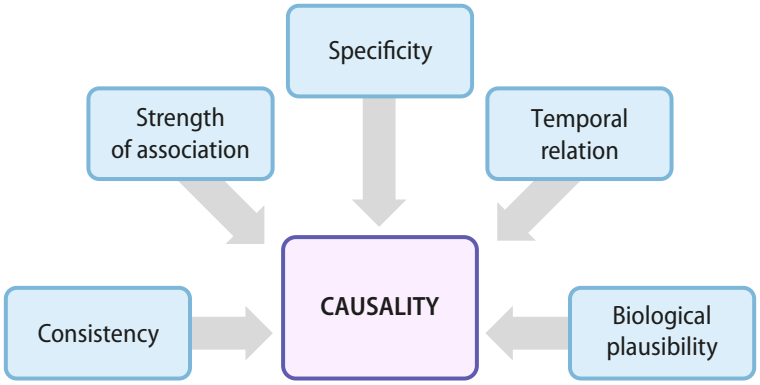
https://cdn.who.int/media/docs/default-source/global-vaccine-safety/new-aide-mem-causal-assmt.pdf

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.

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 38) 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.

BENEFIT EVALUATION	RISK EVALUATION
• 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.	• 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 identity 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 <u>not</u> 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 116.

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.

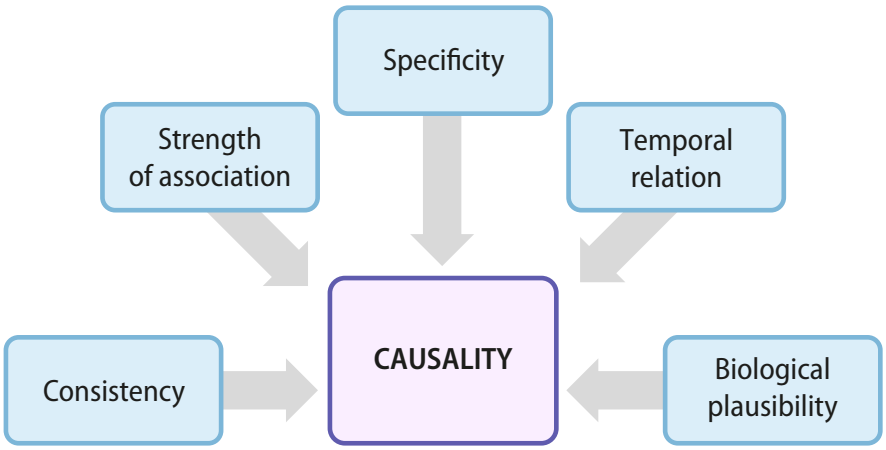
Answer E

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

Anwser 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), the national pharmacovigilance center (PVC) 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.

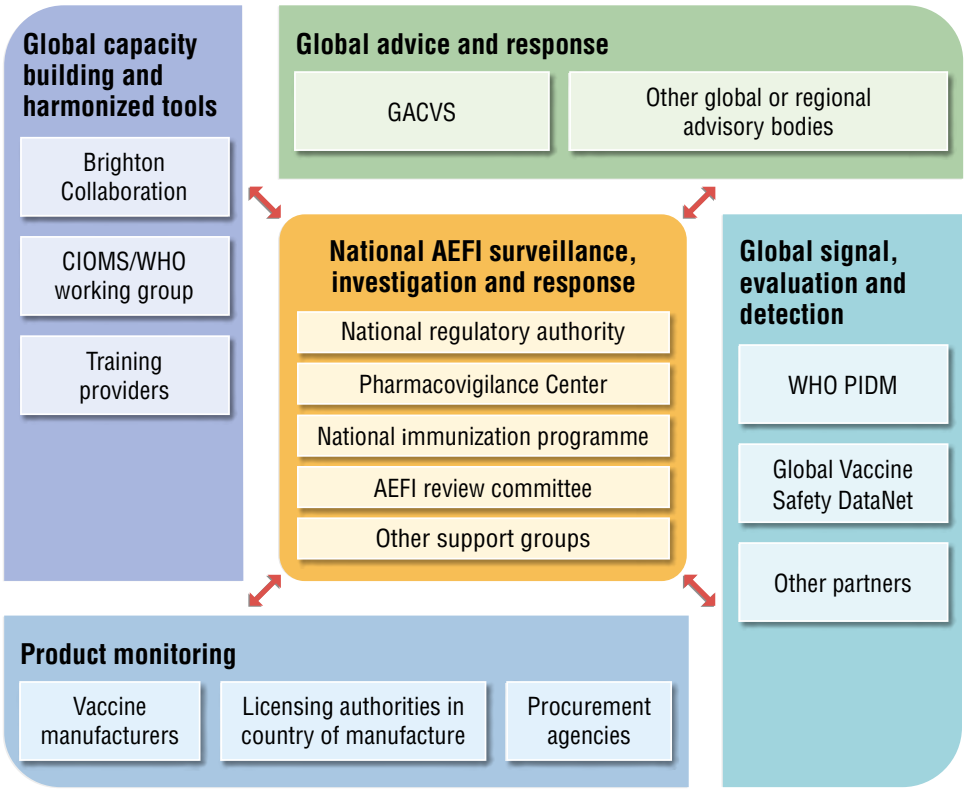
Module outcomes

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, Pharmacovigilance Center 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

National Regulatory Authority (NRA), Pharmacovigilance Center (PVC) and National Immunization Programmes (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 NIP, NRA and PVC. 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 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, PVC, 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 vaccine regulatory system including the National regulatory authority (NRA).

Note: The NIP is also involved, and indeed is a main player, in securing the safety of vaccines and their use. Roles and responsibilities of the NRA, the PVC and the NIP should therefore be clearly defined.

All countries should have a body(s) charged with regulatory oversight to ensure that all medial products, including vaccines, used within the country are safe, effective and of assured quality. The body legally mandated to regulate medical products is commonly known as the regulatory authority (RA) or national regulatory authority (NRA). These terms imply that a single organization is responsible for all regulatory functions. Nevertheless, medical products regulatory oversight may be undertaken by one or more institutions reporting to the same or different senior official. 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, accountability and other principles of Good Regulatory Practices (GRP).

After marketing authorization (also called registration) 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 NIP.

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.

Core functions specific to vaccines

The NRA is usually the main institution mandated to regulate medical products, including vaccines. It has the aim of ensuring the quality, efficacy and safety of the product as well as ensuring the relevance and accuracy of product information. A sustainable, well-functioning regulatory system will ensure an independent and competent oversight of medical products.

Strengthening NRAs

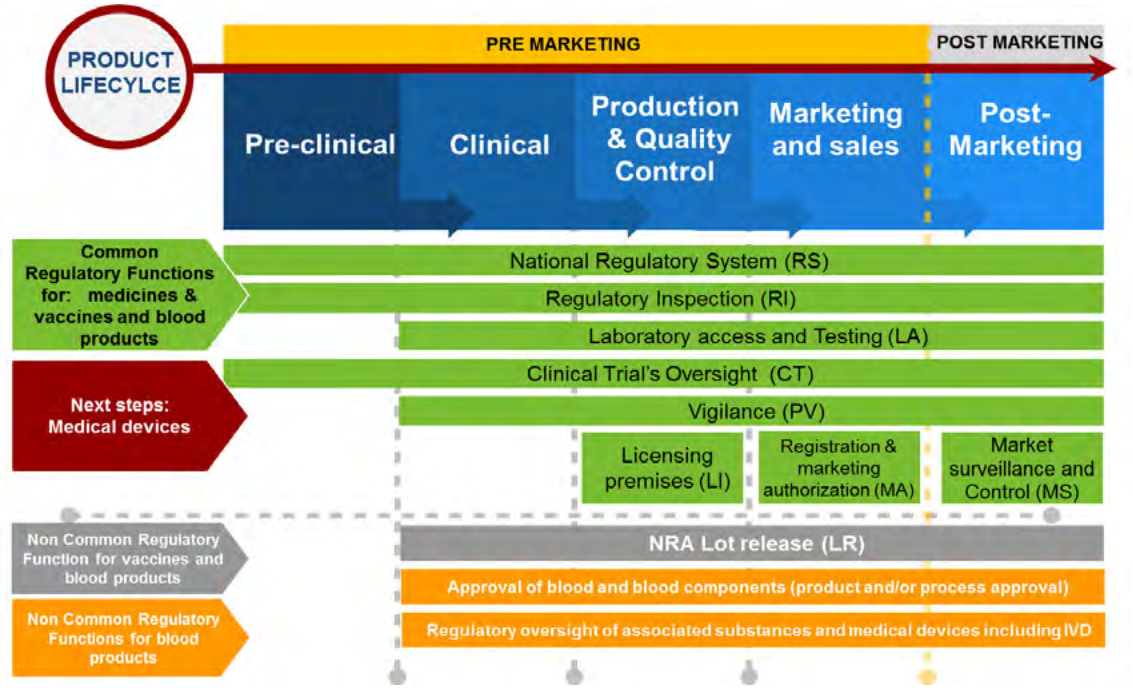
In 1997, WHO launched an initiative to strengthen and build the capacity of national regulatory systems. These include institutions such as NRAs, national control laboratories (NCL) and NIPs, and must operate in close collaboration with the vaccine manufacturers. The ultimate objective of this initiative was for all countries to have a stable, well-functioning and integrated regulatory system as called upon in several World Health Assembly resolutions (e.g., WHA Resolution 67.20). Towards this end, the WHO has over the last three decades established, implemented and refined a five-step model for strengthening regulatory systems:

1. development and maintenance of a benchmarking tool (the WHO Global Benchmarking Tool "GBT") and other means and instruments for evaluating national regulatory systems;
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 for building the capacity of NRAs, which may involve technical support, staff training, or networking to ensure proper performance of different regulatory functions;
5. continuous monitoring and documentation of programme outcomes and impact.

As of July 2020, among the 194 WHO Member States, only 53 countries (27%) have what are considered to be mature medical products including vaccines regulatory systems, whilst the remaining 141 countries have suboptimal regulatory systems. Although not all countries were benchmarked against the WHO global benchmarking tool (GBT), the maturity level status of remaining countries have been estimated based on previous assessments done by WHO using other tools, or being a Stringent Regulatory Authority (SRA). Vaccine-producing countries are prioritized for regulatory system benchmarking activities since these are the ones having vaccine manufacturers and thus contribute to world's vaccine supply. In 1997, 20 (38%) of the 52 vaccine-producing countries had a reliable, functioning NRA. By July 2020, the numbers had risen to 38 (88%) of the 43 vaccine-producing countries.

NRA functions relating to vaccines

WHO defines a national regulatory system (RS) in terms of the enabling legal system and infrastructure, common regulatory functions and non-common regulatory functions (see figure below) that apply across medical products life cycle starting from the research and development (R&D) through to pre-clinical; clinical; production and quality control; commercialization and sale; and other post marketing activities.



Seven common functions apply to the regulation of all medical products: registration and marketing authorization (MA), vigilance (VL), market surveillance and control (MC), licensing establishments (LI), regulatory inspection (RI), laboratory testing (LT), and clinical trials oversight (CT).

In addition, a number of non-common functions apply to certain medical products. Non-common functions include NRA lot release (LR) for vaccines, plasma derived medicinal products (PDMD) and blood related in-vitro diagnostics.

As far as vaccine regulatory system in concerned, in addition to the national regulatory system (RS), there are eight (8) core regulatory functions (as explained in the below table), which between them cover the whole product life cycle of medical products.

NRA functions relating to vaccines [2]

FUNCTION 1 **Registration and marketing authorization**	Marketing authorizations (also known as product licensing or registration) are the procedures for approval of a medical product for marketing after it has been evaluated for safety, efficacy and quality of the product, and the appropriateness of the product information.
FUNCTION 2 **Vigilance**	Vigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medical product-related problems.
FUNCTION 3 **Market surveillance and control**	An NRA's market surveillance and control function activities are primarily concerned with control of import activities; prevention, detection and response to substandard and falsified (SF) medical products; quality monitoring throughout the supply chain; and control of promotional, marketing and advertising activities.
FUNCTION 4 **Licensing Establishments**	The NRA is responsible for ensuring that all establishments throughout the medical products supply chain are licensed to undertake the respective activities (e.g., manufacturing, distribution, wholesale, retail if applicable).
FUNCTION 5 **Regulatory inspections**	Regulatory inspections ensure that operations are carried out in accordance with approved standards, norms, and guidelines and are in compliance with the national medical products legislation and regulations. These, in turn, should be consistent with WHO recommendations and other internationally recognized guidelines.
FUNCTION 6 **Laboratory Testing**	The laboratory testing regulatory function is intended to ensure that the NRA is able to assess the quality of medical products by performing quality tests when needed.
FUNCTION 7 **Clinical trials oversight**	Clinical trials oversight is aimed at protecting the safety and rights of humans participating in clinical trials, ensuring that trials are adequately designed to meet scientifically sound objectives, and preventing any potential fraud and falsification of data.
FUNCTION 8 **National regulatory authority lot release**	Lot release (also called official authority batch release) is a non-common regulatory function that does not apply to all medical products. Rather, it applies only to some specific products (e.g., vaccines), verifying consistency of the safety and quality of different batches of vaccine coming off the production line.

The above mentioned functions may be undertaken by one or more institutions reporting to the same or different senior official. When distributed across institutions, the degree to which they communicate and have clearly defined mandates defined in law, determines in large part how well the designated regulatory bodies perform as an integrated system.

Regulatory functions depending on the source of 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 aforementioned WHO model is designed to be used across the spectrum of regulatory settings and levels of sophistication. Adaptation to the specific country context may be sought when needed through adjustment of the WHO model. For example:

- countries which do not domestically produce medical products including vaccines are not required to conduct regulatory inspections of manufacturers to ensure their compliance with the concepts and principles of good manufacturing practices (GMP). Nevertheless, regulatory inspection of good storage and distribution practices still applies for those same countries;
- countries self-procuring their vaccines or UN supplied countries are not recommended to establish and implement NRA lot release, provided that NRA lot release is undertaken by NRA of the vaccine producing country;
- UN supplied countries are not recommended to perform laboratory testing for WHO pre-qualified vaccines.

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 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 (i.e., they encounter what is called inherent variability), NRAs should conduct tests before a vaccine lot is released for public use. NRAs often delegate testing to a national control laboratory (NCL). 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. In terms of figures, by July 2020, from 153 vaccine products prequalified by WHO, 75 are manufactured in low- or middle-income countries. The number of doses of WHO prequalified vaccines produced in low- or middle-income countries , however, prevails the number of doses produced by high-income countries by far.

Testing of every batch is not usually done for other drug products, particularly medicines. The lot release system is perhaps the greatest difference between the NRA vaccine functions and NRA functions for other medicines. NRA lot release may apply to other medical products (e.g., blood products) according to the NRA lot release policy.

Once the NRA releases a vaccine lot, the NIP takes responsibility for its proper storage and handling until it can be safely administered 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. Nevertheless, the overall vaccine supply chain, including the part taken over by the NIP, should be inspected by the NRA and corrective and preventive actions may be needed in case of detected shortcomings (non-compliance with the Good Storage and Distribution Practices "GSDP").

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, which is subject to GSDP inspections by NRA.

Regulatory oversight of vaccine safety

NRAs are responsible for ensuring that every medical product, 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.

While common side effects are likely to be detected during pre-approval clinical trials (phases I, II and III), 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.

Vigilance of vaccine products, is often conducted by several players of the vaccine regulatory system including the NRA, the PVCs and the NIP. It is worth to mention that PVCs may or may not be an integral part of the NRA. In order for the aforementioned entities to have a significant role in the surveillance of adverse drug reactions after licensing, including for vaccines, several enablers are essentially required:

- legal provisions, regulations and guidelines required to define regulatory framework of vaccine vigilance;
- arrangements for effective organization and good governance;
- established vigilance strategies/policies including crisis management plans;
- the availability of the essential resources including human and financial resources; as well as infrastructure and equipment required to perform regulatory activities;
- the regulatory processes and procedures are well established and consistently implemented following the proper quality and risk management approaches;
- mechanism in place to monitor regulatory performance and output; and
- mechanism for promotion of transparency, accountability and communication including the essential quality management systems (IMS).

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.

Example AEFI reporting form:

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

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 from your own country may be different. This demonstrates the importance of clearly defined roles and close coordination between organizations responsible for pharmacovigilance and NRAs.

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 (NPC) functioning as the 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 NPCs. Continuous and appropriate educational activities improves knowledge, and stimulates and encourages health workers to report AEFIs.

NATIONAL IMMUNIZATION PROGRAMMES

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 operates 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 NIP to protect the population against vaccine-preventable diseases.

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 AEFI happens, it is the health staff administering vaccines that often detect, record and report safety events. They assess and treat the adverse event, reporting it, and may be called to contribute to an AEFI investigation. The NIP 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 NIP 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 NIP should also work in collaboration with NPCs 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 NIP, 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 91.

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 NIP 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, single-use, auto-disable syringes for all vaccine administration;
- 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 NPCs;
- 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.

An AEFI Review Committee should be composed of members that are independent of the NIP and the NRA. 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.

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.

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

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.

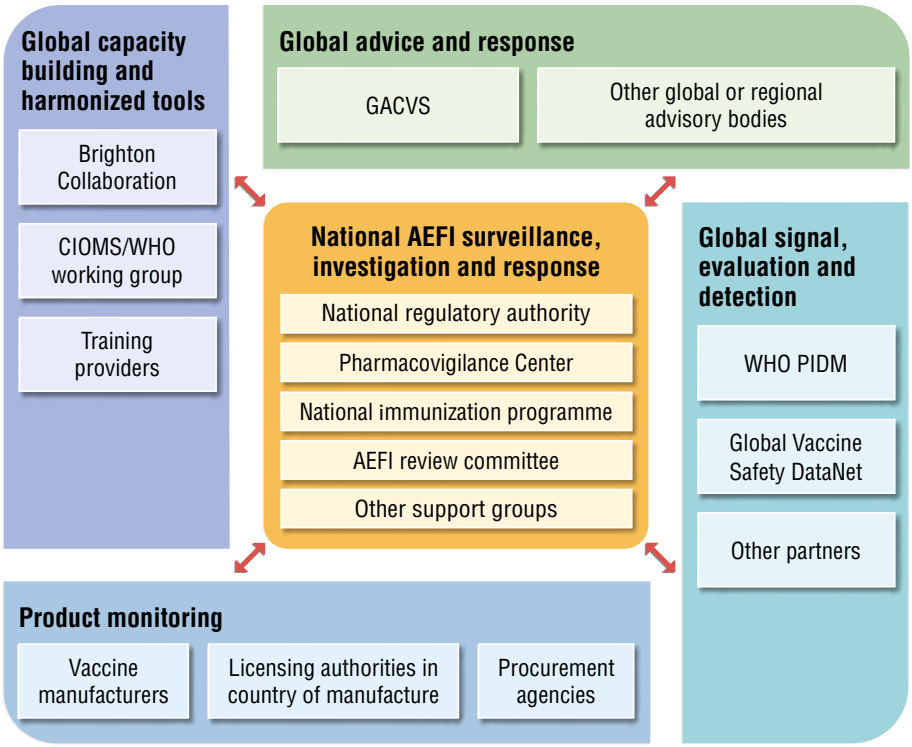
INTERNATIONAL LEVEL

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 systems[39]

GACVS

The Global Advisory Committee on Vaccine safety (GACVS), established in 1999, 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)

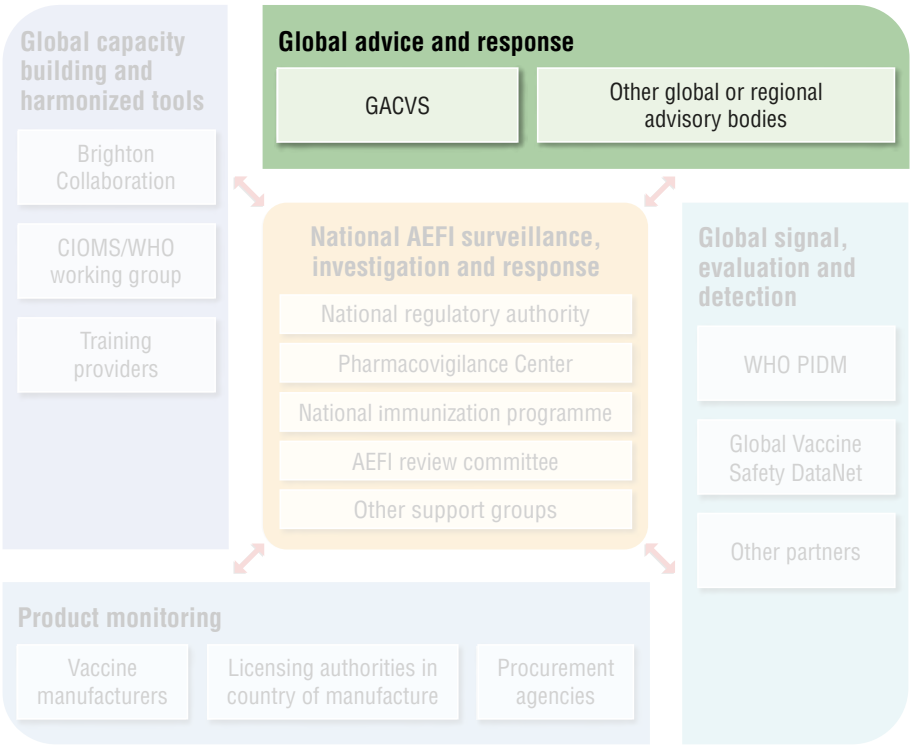
The WHO Programme for International Drug Monitoring (PIDM), established in 1968, consists of a network of NPCs, WHO headquarters in Geneva, and the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, Sweden.

Other support groups

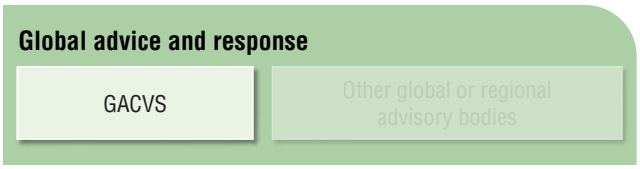
Depending on the countries, other groups such as academic institutions or technical agencies (e.g. national immunization technical advice groups, NITAGs) provide significant support to drug safety activities.

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, 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 (https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/committee-reports).

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 15 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.

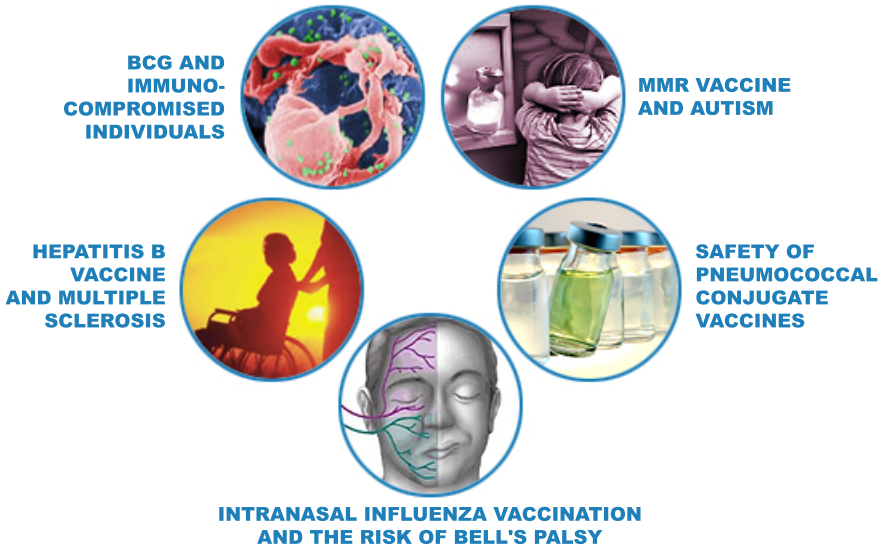
Based on evidence available, and considering the significant risk of BCG disease, GACVS advised that routine BCG vaccination shall no longer be recommended for infants known to be HIV-infected with or without symptoms of HIV infection.

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.

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

Interactive excercise

Seek advice on the vaccine-specific concerns addressed by GACVS by visiting the GACVS topic list: https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics.



Question 1

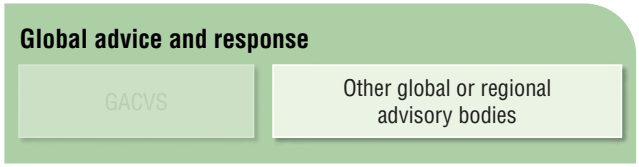
Based on the information provided in the *GACVS example*, define, which of the following statements is correct:

- ❒ 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.

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:

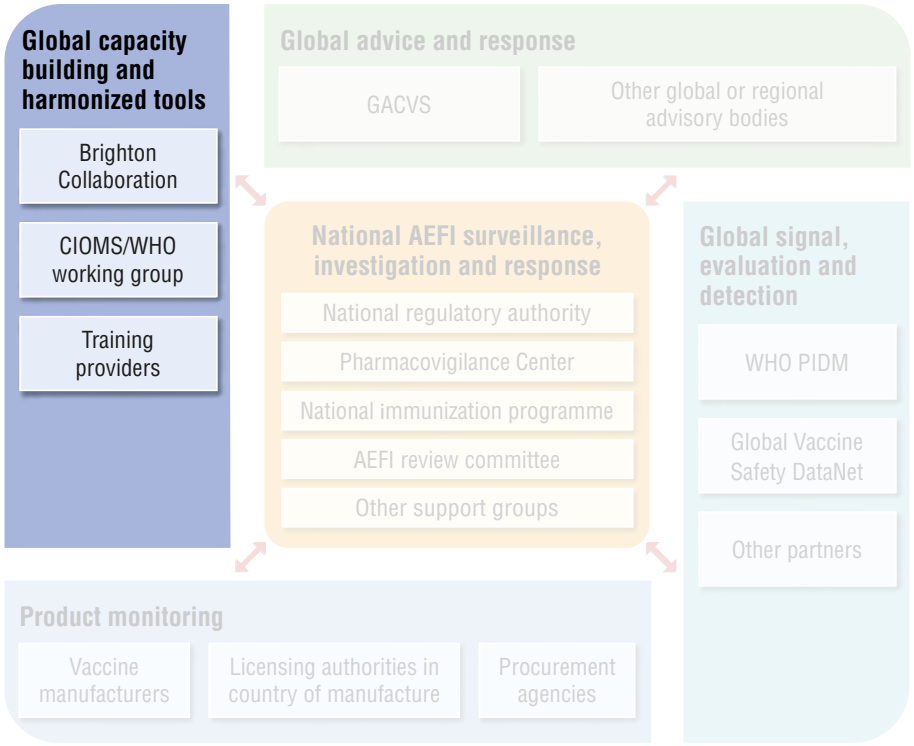
- criteria with respect to the **credibility** of the website: these criteria aim at ensuring transparency regarding basic elements such as ownership of the website, financial sponsorship of the website and others. These elements can help website visitors make an informed decision regarding whether this is a trustworthy resource that they wish to consult, to learn about issues related to vaccine safety;
- criteria with respect to the **quality and the quantity of the vaccine safety content** of the website. These criteria ensure that the website content is accurate, current and reliable. They include: the source of information (including any potential conflicts of interest the authors may have related to the content), how site content is selected and reviewed and by whom, whether all reasonable sides of issues are presented in a fair way, and others. Transparency regarding these critical factors contributes to the credibility of the website and helps to inspire confidence among website visitors;
- criteria with respect to **accessibility**. They seek to ensure that the website is accessible as possible and cover a broad range of issues such as the existence of standard operating procedures (including access levels, content management and login credentials), mobile-friendly web design to enable users to access the content independent of the device used and others;
- criteria with respect to **design** ensure that the website is user-friendly. These include the website design, colors, photos, fonts and graphics, as well as the website structure, including availability of tools that aid in navigation such as site maps and internal search engines and others.

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;
- corporate websites and websites that are not reviewed regularly, e.g. no activity for more than two (2) years despite availability of new information, are not eligible to join the VSN.

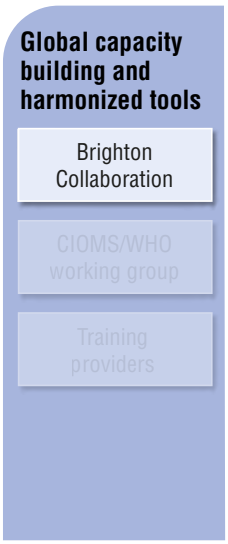
As of June 2021, 97 websites from 42 countries from the 6 WHO regions, providing vaccine safety information in 36 languages, successfully met the GACVS criteria and are listed on the WHO website. Listed sites are re-evaluated for their adherence to the good information practices criteria every one or two years, depending on the type of institution they belong to. Evaluation dates are included within each site description.[45]

GLOBAL CAPACITY BUILDING AND HARMONIZED TOOLS



Brighton Collaboration — setting standards in vaccine safety

The Brighton Collaboration[85] 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, as well as to educate about the benefit of vaccines, and monitor their global use;
- 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

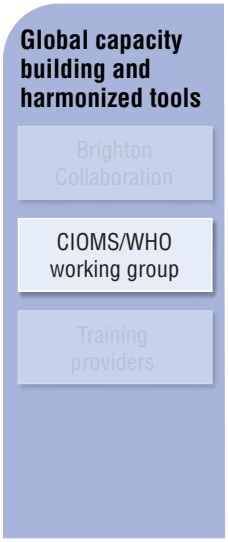
In Module 4, chapter "*AEFI surveillance: Detection and reporting*" (page 123) you have learnt about the use of standard case definitions and guidelines. Without globally accepted standard case definitions for assessing AEFIs, it is difficult, if not impossible, to compare safety data across trials with 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.

CIOMS/WHO Report on Vaccine Pharmacovigilance:

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

Vaccine safety communication guideline:

https://cioms.ch/publications/product/cioms-guide-vaccine-safety-communication/

Guide to Active Vaccine Safety Surveillance:

https://cioms.ch/publications/product/cioms-guide-to-active-vaccine-safety-surveillance/

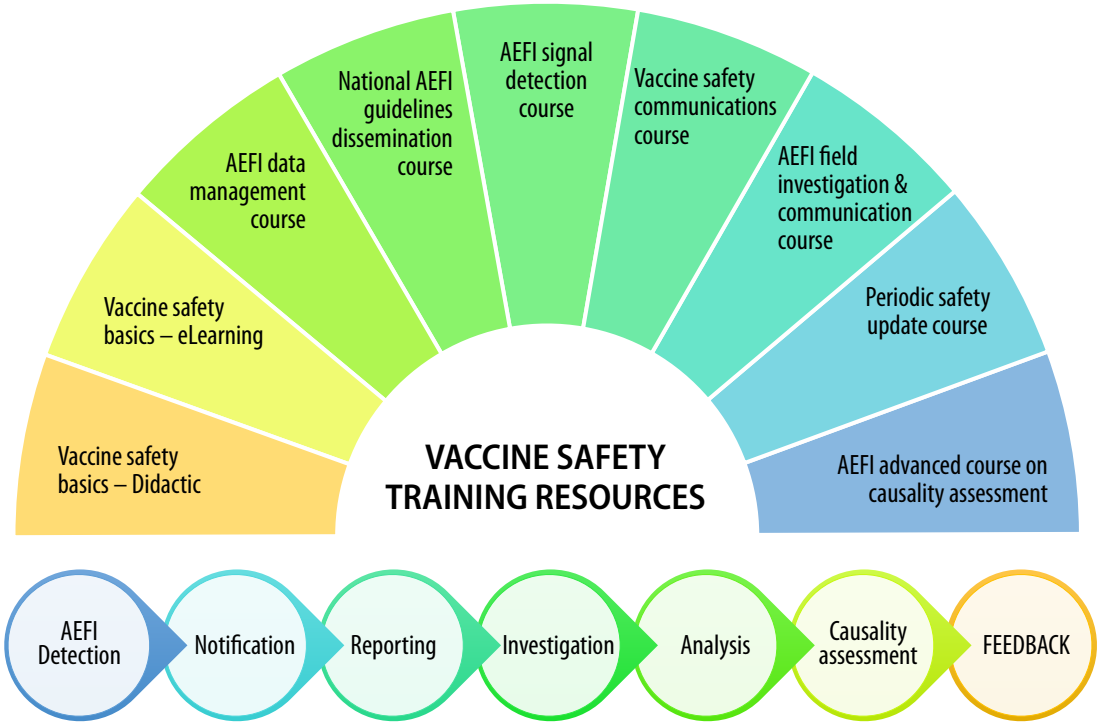
Additional activities that the CIOMS/WHO Working Group on Vaccine Pharmacovigilance has engaged in, although not formally incorporated in its terms of reference, have included providing consultations and expert inputs to other vaccine pharmacovigilance initiatives, such as the Global Vaccine Safety Blueprint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

Vaccine safety training opportunities

WHO's Vaccine Safety training resources provide capacity strengthening both in form of workshops and online courses, offering learning opportunities to national public health officials, immunization programme managers, vaccination staff.

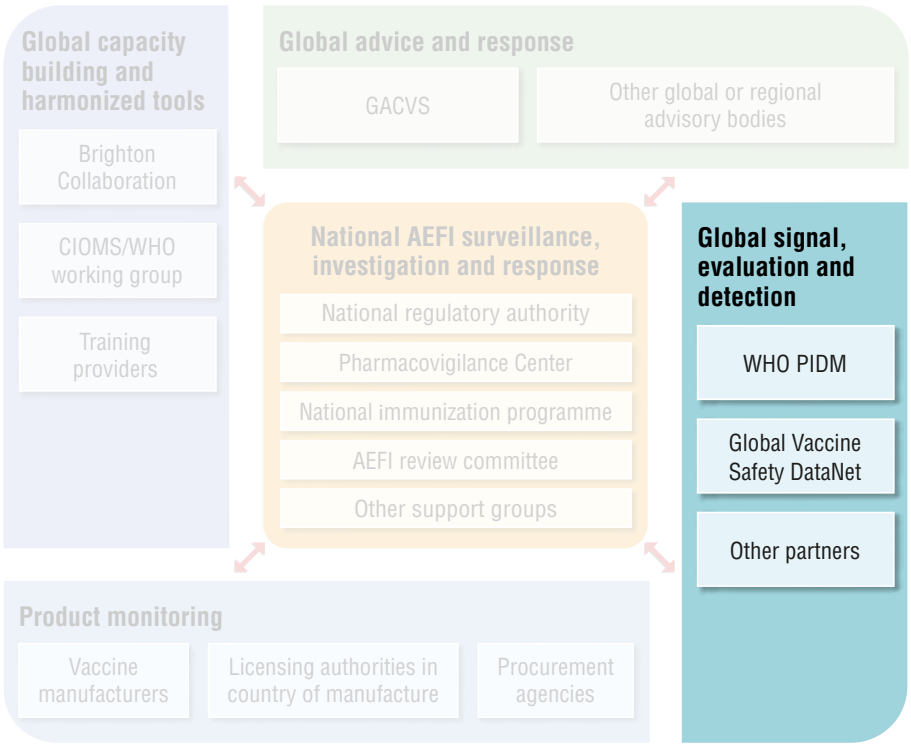
Among the resources available are:

- 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.



Go to https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info to access more information on the available vaccine safety training opportunities.

GLOBAL SIGNAL EVALUATION AND DETECTION

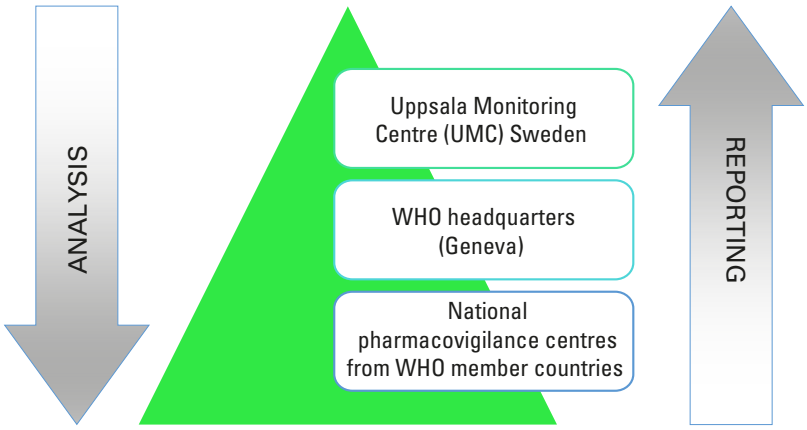


WHO Programme for International Drug Monitoring

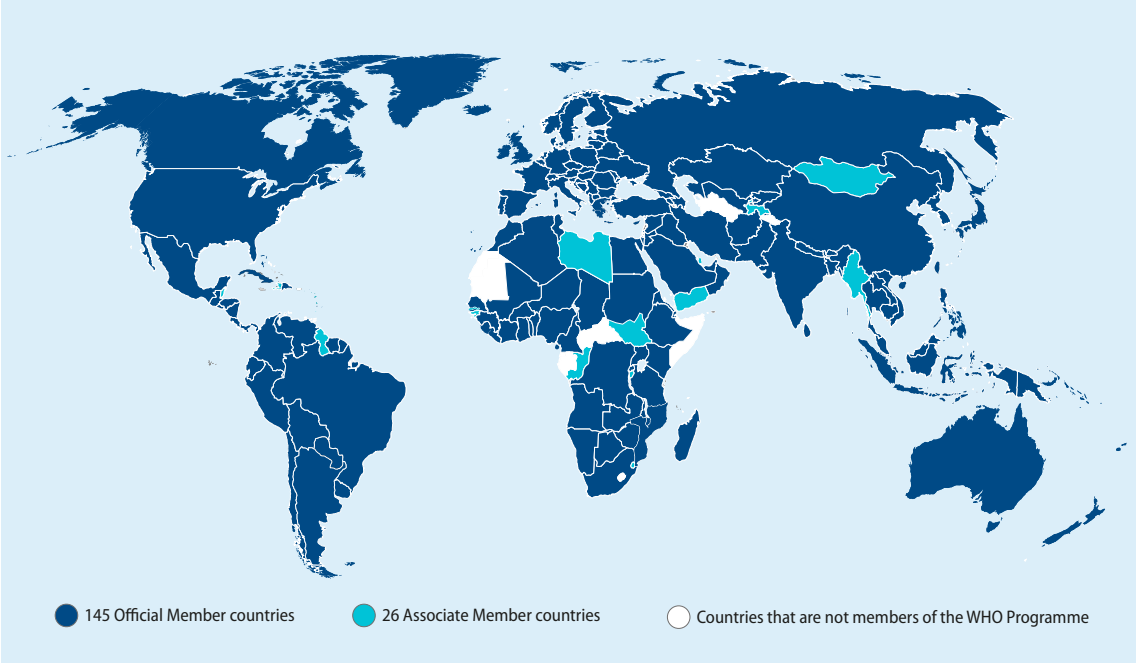
Established in 1968, The WHO Programme for International Drug Monitoring (PIDM)[82] provides a forum for WHO Member States to collaborate in the monitoring of drug safety, and notably, the identification and analysis of new adverse reaction signals from data submitted to the WHO global individual case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

The programme consists of a three-part network:[42]

- NPCs 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.



As of June 2021, 145 countries had joined the programme, and more than 26 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;
- 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.

Global Vaccine Safety DataNet meeting:

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

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.

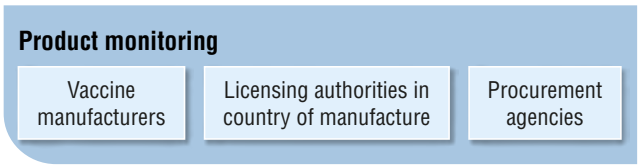
Question 2

Think back to the *example of the introduction of rotavirus vaccines* (page 34) 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.

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;
- Pan-American Health Organization (PAHO) Revolving Fund for Vaccine Procurement;
- WHO.

In addition, WHO provides courses in strengthening vaccine procurement skills, which can be accessed at the Global Learning Opportunities for Vaccine Quality[88] website.

Licensing authorities in countries of manufacture

All vaccines supplied by international procurement agencies, and used within a national immunization programme must meet WHO prequalification requirements for quality and safety. To assure the quality and safety of vaccines, a vaccine manufacturing country must have a competent and functioning independent 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 NRA 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 have to be made.

GLOBAL VACCINE SAFETY INITIATIVE

Hundreds of millions of doses of vaccines are used every year in developing countries. However, assessments of NRAs 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 Strategy[97] 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;

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

https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/aefi

- the third goal looks to establish a global vaccine safety support structure so that countries can benefit from international collaboration, training and information exchange.

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:

Directly relating to vaccine system (VS)	Supporting elements ensuring effectiveness of VS
1 Strengthen vaccine safety monitoring.	**5** Establish a legal, regulatory and administrative framework at all levels.
2 Strengthen ability to evaluate vaccine safety signals.	**6** Strengthen regional and global technical support platforms for vaccine pharmacovigilance.
3 Develop vaccine safety communication plans, understand perceptions of risk, and prepare for managing any AEFI and crises promptly.	**7** Make international expert scientific advice on vaccine safety issues available.
4 Develop internationally harmonized tools and methods for vaccine pharmacovigilance.	**8** Put in place systems for appropriate interaction between national governments, multilateral agencies, and manufacturers.

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 Oberved 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 natses 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)