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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# Table of Contents

**Introduction** ...................................................................................................................................... 7

**Getting starting** ................................................................................................................................ 8

**MODULE 1: Introduction to vaccine safety** ........................................................................................ 9

Overview .................................................................................................................................................. 10
Importance of immunization programmes ......................................................................................... 10
History of vaccine development .......................................................................................................... 11
Expectations towards safety of vaccines ............................................................................................. 13
How the immune system works .......................................................................................................... 14
How vaccines work .............................................................................................................................. 16
Vaccine-preventable diseases ............................................................................................................... 17
Types of vaccine .................................................................................................................................... 18
Adverse events ....................................................................................................................................... 19
  - Classification .................................................................................................................................... 19
  - Causes .............................................................................................................................................. 20
  - Frequency and severity .................................................................................................................. 21
Vaccine safety in immunization programmes ...................................................................................... 23
Vaccine regulations .............................................................................................................................. 25
Pre-licensure vaccine safety ................................................................................................................ 25
  - Post licensure surveillance options .............................................................................................. 27
Balancing efficacy and safety .............................................................................................................. 29
Summary .............................................................................................................................................. 31

**ASSESSMENT 1** ................................................................................................................................... 32

Assessment solutions ............................................................................................................................ 36

**MODULE 2: Types of vaccine and adverse reactions** ...................................................................... 38

Overview ............................................................................................................................................... 39
Types of vaccine ..................................................................................................................................... 40
  - Live attenuated vaccines ................................................................................................................ 41
  - Inactivated whole-cell vaccines ................................................................................................... 44
  - Subunit vaccines ............................................................................................................................ 45
  - Toxoid vaccines .............................................................................................................................. 49
Combination vaccines .......................................................................................................................... 50
AEFI surveillance components

Detection and reporting
Investigation
Causality assessment of AEFIs
Risk/benefit assessment
Summary

ASSESSMENT 4
Assessment solutions

MODULE 5: Vaccine safety institutions and mechanisms
Overview
Overview of functions

NATIONAL LEVEL
National AEFI surveillance systems
National regulatory authority
Core functions specific to vaccines
Functions depending on the source of vaccines
Vaccine procurement and lot release
Regulation of drug safety
National immunization programmes (NIP)
Core functions specific to vaccine safety
Safety of vaccine administration
AEFI Review Committee
Other support groups

INTERNATIONAL LEVEL
Global vaccine safety stakeholders and services
Global analysis and response
Global Advisory Committee on Vaccine Safety (GACVS)
Good information practices – Vaccine Safety Net
Global Capacity building and harmonized tools
Brighton Collaboration – setting standards in vaccine safety
CIOMS/WHO working group
Vaccine safety training opportunities
INTRODUCTION

Goal

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

Rationale

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

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

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

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

Modules

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

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

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

Assessments

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

- Training questions within the module,
- Assessments testing your knowledge at the end of each module,
- A general assessment testing your understanding at the end of the whole course. This assessment is only accessible online. Please visit: www.vaccine-safety-training.org, click “Start course” and “General assessment” to register. Should you pass the general assessment, you will be provided with a downloadable document confirming your successful participation in the exam.
MODULE 1

Introduction to vaccine safety
Overview

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

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

Module outcomes

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

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

Importance of immunization programmes

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

Why are vaccines so special?

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

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

History of vaccine development

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

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

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

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

For vaccine-safety-training.org/tl_files/who/ivb_09_10_eng.pdf

Question 1

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

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

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

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

* The answer to all questions can be found at the end of this manual (page 202).
that every child received protection against six childhood diseases (i.e. tuberculosis, polio, diphtheria, pertussis, tetanus and measles) by the time they were one year of age and to give tetanus toxoid vaccinations to women to protect them and their newborns against tetanus.

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

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

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

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

Strengthening immunization: WHO’s Expanded Programme on Immunization

Although around 24 million infants are still not receiving the full complement of EPI vaccines in the first year of life, the success of the EPI can be judged by the reduction in worldwide cases of measles and poliomyelitis (see graphics). These two diseases are among several (including neonatal tetanus) targeted by the WHO for elimination through vaccination.
Vaccines used in NIPs are safe and effective. However, like other pharmaceutical products, vaccines are not completely risk-free and adverse events will occasionally result from vaccination. Although most adverse events are minor (e.g. redness at injection site, fever), more serious reactions (e.g. seizures, anaphylaxis) can occur albeit at a very low frequency.
The general public has low tolerance to any adverse events following vaccination, because vaccines are given to healthy persons to prevent disease. For this reason, a higher standard of safety is expected of immunizations compared with medications that are used to treat people who are sick (e.g. antibiotics, insulin). This lower tolerance for risks from vaccines translates into a greater need to detect and investigate any adverse event following immunization (AEFI) than is generally expected for other pharmaceutical products.

**Low public tolerance requires safe vaccination**

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

**How the immune system works**

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

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

- **Bacteria** are single-celled life-forms that can reproduce quickly on their own.

- **Viruses**, on the other hand, cannot reproduce on their own. They are ultramicroscopic infectious agents that replicate themselves only within cells of living hosts.
The immune system responds to bacteria and viruses in a very complex way: it recognizes unique molecules (antigens) from bacteria and viruses and produces antibodies (a type of protein) and special white blood cells called lymphocytes that mark the antigens for destruction.

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

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.

**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

- Immunization triggers an immune system response by which the vaccinee develops long-term protection (immunity) that would normally follow recovery from (sometimes several) naturally occurring infections.
- Vaccinee does not endure the illness
- Low risk of adverse reaction greatly outweighs the risk of complications by natural infection.
**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, diarrhoeal disease caused by rotaviruses, and pneumonia and other respiratory tract infections caused by *Haemophilus influenzae* type B and pneumococcal bacteria. Others, such as the vaccine against yellow fever, are recommended in countries where the disease burden is significant.

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

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

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

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

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

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

### Types of Vaccine

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Live attenuated (LAV)       | - Tuberculosis (BCG)  
- Oral polio vaccine (OPV)  
- Measles  
- Rotavirus  
- Yellow fever |
| Inactivated (killed antigen)| - Whole-cell pertussis (wP)  
- Inactivated polio virus (IPV) |
| Subunit (purified antigen)  | - Acellular pertussis (aP),  
- Haemophilus influenzae type b (Hib),  
- Pneumococcal (PCV-7, PCV-10, PCV-13)  
- Hepatitis B (HepB) |
| Toxoid (inactivated toxins) | - Tetanus toxoid (TT),  
- Diphtheria toxoid |

Vaccine manufacturers strive to develop vaccines that:

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

Classification

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

- **Vaccine product-related reaction**
  
  An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
  
  **Example:** Extensive limb swelling following DTP vaccination.

- **Vaccine quality defect-related reaction**
  
  An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.
  
  **Example:** Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio.

- **Immunization error-related reaction**
  
  An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
  
  **Example:** Transmission of infection by contaminated multidose vial.

- **Immunization anxiety-related reaction**
  
  An AEFI arising from anxiety about the immunization.
  
  **Example:** Vasovagal syncope in an adolescent during/following vaccination.

- **Coincidental event**
  
  An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.
  
  **Example:** A fever occurs at the time of the vaccination (temporal association) but is in fact caused by malaria.

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

**Key point**

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

Trusted and well-informed health care providers are best suited to provide such information. Information about the immunization(s) should be provided well ahead of the immunization visit. This gives parents the time to understand the information well and ask questions that will increase their trust.
Question 3*

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

☐ A. An adverse vaccine reaction is a vaccine-related event caused or precipitated by a vaccine when given correctly.

☐ B. An adverse vaccine reaction can be caused by errors in the administration of the vaccine.

☐ C. An adverse vaccine reaction can be the result of unrelated coincidence.

☐ D. An adverse event following immunization can be due to all of the causes stated in A, B, and C.

Causes

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

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

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

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

Routes of administration of several vaccines

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

* The answer to all questions can be found at the end of this manual (page 202).
Question 4

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

- [ ] Antigens
- [ ] Antibiotics
- [ ] Preservatives
- [ ] Adjuvants
- [ ] Stabilizers

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

**Frequency and severity**

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

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

**Key point**

Vaccine adverse events are expected to occur with a certain frequency.

AEFI surveillance monitors adverse events and follows up severe events that may have been due to the vaccine.

Question 5

Which of the following statements is wrong:

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

* The answer to all questions can be found at the end of this manual (page 202).
Frequency and severity of adverse vaccine reactions

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Occurrence among persons vaccinated in percent</th>
<th>Severity of reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥ 10%</td>
<td>Common and usually minor reactions:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Are part of the immune response to vaccine,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reactions settle on their own,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Examples include:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Fever,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Malaise.</td>
</tr>
<tr>
<td>Common (frequent)</td>
<td>≥ 1% and &lt; 10%</td>
<td>Rare, usually more severe reactions:</td>
</tr>
<tr>
<td>Uncommon (infrequent)</td>
<td>≥ 0.1% and &lt; 1%</td>
<td>1. Usually require clinical management,</td>
</tr>
<tr>
<td>Rare</td>
<td>≥ 0.01% and &lt; 0.1%</td>
<td>2. Examples include:</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt; 0.01%</td>
<td>- Severe allergic reaction (e.g., anaphylaxis) including an exaggerated response to the vaccine antigen or component,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Vaccine specific reactions, such as BCG osteitis.</td>
</tr>
</tbody>
</table>

Background rates

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

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

Example: Fever following vaccination

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

Key point

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

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

Potential stages in the evolution of an immunization programme


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

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

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

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

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

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


Key point

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

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

- Monitor the incidence of AEFI,
- 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.\textsuperscript{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.\textsuperscript{12}

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

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

Pre-licensure vaccine safety

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

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

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

<table>
<thead>
<tr>
<th>Key point</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
<tr>
<td>The sensitivity of detection of uncommon or rare adverse events, or those with delayed onset is, however, low in these trials.</td>
</tr>
<tr>
<td>As a result, continuous post-licensure monitoring of vaccine safety is needed to identify and evaluate such adverse events.</td>
</tr>
</tbody>
</table>
Clinical trials and assessment of vaccine safety

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

**Introduction**

Involves making the vaccine available for use.

Rotavirus vaccine example

In August 1998 the first rotavirus vaccine, RotaShield®, was licensed in the USA. Pre-licensure literature noted a suspicion of an increased risk of intussusception. After RotaShield® was licensed for routine use by the public (approximately one million children vaccinated within the first nine months licensure) the American vaccine safety surveillance, Vaccine Adverse Event Reporting System (VAERS), began to receive reports of intussusception following administration of the vaccine. About 100 (0.01%) of the one million children vaccinated developed intussusception, 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. 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.

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

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

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

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

**Rotateq® vaccine example**

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

One year following introduction, ACIP reviewed available data to evaluate the rate of reports of intussusception following RotaTeq® vaccination and found that it did not exceed expected background rates in the absence of vaccination. Additionally, active surveillance among a population of insured children did not identify any reports of intussusception within 30 days of more than 28,000 administered doses. 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. Since introduction, the use of second generation rotavirus vaccines in routine immunization has reduced hospitalizations for severe diarrhoea by 70 to 80% and may have prevented illness in unvaccinated children by limiting the infections that spread the virus to others.

**Post licensure surveillance options**

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

A range of surveillance options can be used to monitor the safety of vaccines and immunizations post-licensure.
<table>
<thead>
<tr>
<th>Passive surveillance systems</th>
<th>Passive surveillance systems (or spontaneous reporting systems) are the cornerstone of most post-licensure safety monitoring systems because of their relative ease of implementation, their cost and ability to capture unexpected events. 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.</th>
</tr>
</thead>
</table>
| 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. 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 enrollee populations numbering from thousands to millions, they can detect very rare adverse events. With denominator data on doses administered and the ready availability of appropriate comparison (i.e. unvaccinated) groups, these large databases provide an economical and rapid means of conducting post-licensure studies of the safety of drugs and vaccines. They also represent powerful tools to allow for testing hypotheses when signals or allegations create suspicions of a possible vaccine safety issue. 
The Vaccine Safety Datalink (VSD) project is an example of a LLDB between the USA’s Centers for Disease Control and Prevention (CDC) and eight HMOs. The VSD project was established in 1990 to monitor immunization safety and to address the gaps in scientific knowledge about rare and serious events following immunization. |
| **Clinical centers, including the Clinical Immunization Safety Assessment (CISA) centers** | More recently, tertiary clinical centers have been used to conduct research on immunization-associated health risks. The USA’s Clinical Immunization Safety Assessment (CISA) Network is a national network of six medical research centers with expertise in immunization safety conducting clinical research on immunization-associated health risks. Established in 2001 as a collaborative project between the CDC, six medical research centers, and American Health Insurance Plans, CISA conducts clinical research on vaccine adverse events and the role of individual variation. |
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.

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

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

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

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

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.
■ 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

<table>
<thead>
<tr>
<th></th>
<th>Measles infection&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Measles vaccine&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otitis</td>
<td>7–9%</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1–6%</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6%</td>
<td>0</td>
</tr>
<tr>
<td>Post-infectious encephalomyelitis</td>
<td>0.5/1,000</td>
<td>1/100,000 – million</td>
</tr>
<tr>
<td>SSPE</td>
<td>1/100,000</td>
<td>0</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0</td>
<td>1/100,000 – million</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Not properly quantified&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1/30,000&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Death</td>
<td>0.1 – 1/1,000 (up to 5 – 15%)</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Risks after natural measles are calculated in terms of events per number of cases.
<sup>b</sup> Risks after vaccination are calculated in terms of events per number of doses.
<sup>c</sup> Although there have been several reports of thrombocytopenia occurring after measles including bleeding, the risk has not been properly quantified.
<sup>d</sup> 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.


### Key point

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

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

☑️ With the exception of water safety, vaccines have the greatest potential to promote public health. They reduce morbidity and mortality from infectious disease, saving costs as well as lives.

☑️ Public trust in vaccines is easily undermined: there is a lower tolerance for adverse events than for other prescribed drugs.

☑️ The five categories of AEFIs are:
   1. Vaccine product-related reaction,
   2. Vaccine quality defect-related reaction,
   3. Immunization error-related reaction,
   4. Immunization anxiety-related reaction,
   5. Coincidental event.

☑️ Vaccines generate an immune response in the body, and the characteristics of a vaccine that increase the risk of an adverse reaction.

☑️ The four main types of vaccine are live attenuated, inactivated, subunit and toxoid and there are specific vaccines of each antigen type.

☑️ Vaccines are regulated from development, to licensure, to use, and national regulatory authorities play an important role in this process.

☑️ Post-licensure surveillance of a vaccine after its introduction to the market is critical as clinical trials may not detect rare or very rare reactions, or reactions with delayed onset.

☑️ The risks associated with vaccines are very low compared with the risks of the diseases they are designed to prevent.

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

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

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

Question 2

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

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

- Immunization anxiety-related reaction
- Coincidental event
- Immunization error-related reaction
- Vaccine product-related reaction
- 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.

<table>
<thead>
<tr>
<th>a</th>
<th>primary</th>
<th>e</th>
<th>adjuvants</th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td>secondary</td>
<td>f</td>
<td>immunity</td>
</tr>
<tr>
<td>c</td>
<td>antibodies</td>
<td>g</td>
<td>antigens</td>
</tr>
<tr>
<td>d</td>
<td>vaccine</td>
<td>h</td>
<td>memory cells</td>
</tr>
</tbody>
</table>

**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) ________________

<table>
<thead>
<tr>
<th>a</th>
<th>live attenuated</th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td>subunit (purified) antigen</td>
</tr>
<tr>
<td>c</td>
<td>inactivated toxin</td>
</tr>
<tr>
<td>d</td>
<td>inactivated (killed) antigen</td>
</tr>
</tbody>
</table>
An immunization programme can undergo several stages (Pre-vaccine, Increasing vaccination coverage, Loss of confidence, resumption of confidence, and eradication. Which of the following statements are correct? Select one or more:

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

You have completed Assessment 1.
Assessment solutions

Question 1

Answers A, C and D are correct.

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

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

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

Question 2

The correct choices are:

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

Question 3

The correct answers are:

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

The correct choices are:

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

Question 5

Answers A, C, D and E are correct.

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

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

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

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

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

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