MODULE 4
Surveillance
Overview

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

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

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

Module outcomes

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

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

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

The specific aims of pharmacovigilance are to: 46

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

**Origins of pharmacovigilance**
The WHO Programme for International Drug Monitoring (PIDM)42 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)43 in Sweden, developed an international system for detecting previously unknown or poorly understood adverse drug reactions (ADRs). National regulatory authorities (NRAs) are responsible for reporting ADRs, particularly rare ones or new signals, to the UMC so that they can be monitored within the global population.46
In many countries, National pharmacovigilance centres are established or existing entities are designated to serve this function on behalf of the NRA. Such centres collect information about AEFI using standardized methodologies. They analyse this information and communicate regularly with NRAs to update the safety profiles of the products used in a country. You will learn more about vaccine safety institutions and reporting mechanisms in Module 5.

**NRA’s role in the regulation of drug safety**

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

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

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

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

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

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

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**Example for collaboration among institutions: Canada**

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

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

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

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

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

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

The number of National pharmacovigilance centres participating in WHO’s PIDM has increased from 10 in 1968 (when the programme started) to 108 as of June 2012. The centres vary considerably in size, resources, support structure and scope of activities. Collecting spontaneous reports of suspected ADRs remains their core activity.

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

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

Immunization safety requires a modified surveillance system

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

Immunization safety is the process of ensuring and monitoring the safety of all aspects of immunization, including:

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

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

¿Question 1¿
When parents bring their children for immunization, why may they have a low tolerance for any adverse events that follow?

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

Definition

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

“the science and activities relating to the
■ Detection,
■ Assessment,
■ Understanding and
■ Communication
of adverse events following immunization and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization”.

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.

Vaccine pharmacovigilance relies on three steps:

- Detect signals suggesting AEFI is related to a vaccine.
- Develop hypotheses about causal association between an AEFI and vaccination.
- Test hypotheses through appropriate epidemiological methods.

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).

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.

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?

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Special considerations for AEFI surveillance

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

Training for health workers

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

Determining causality

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

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

Independent review is needed

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

* The answer to all questions can be found at the end of this manual (page 202).
Interactions between AEFI and ADR surveillance systems

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>NRA</th>
<th>NIP</th>
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<tbody>
<tr>
<td>Monitoring safety of vaccines</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Integrating AEFI surveillance with system of vaccine delivery</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Clear distribution of roles in reporting and detection</td>
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<td>✔</td>
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</tbody>
</table>

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

Key point

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

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

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

The objectives for an effective AEFI surveillance system are to:

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

The following pages describe the following components of AEFI surveillance:

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

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

Stakeholders

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

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

Health workers should be trained to detect:

- All cases corresponding to locally suitable AEFI case definitions.
- Any clusters of AEFIs (i.e., two or more cases of the same adverse event related in time or place or to the vaccine administered).
- All other events believed to be due to immunization.

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 particular, health workers should 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.
- Swelling, redness, soreness at the injection site if it lasts for more than 3 days or swelling extends beyond nearest joint.
In addition to deciding which adverse events should be reported, it is essential that immunization programme managers define the roles and responsibilities of stakeholders, clarify on the process of reporting, and how to ensure/encourage reporting. The following questions should guide the immunization programme manager when setting up and maintaining a detection and reporting mechanism.

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

**Question 3**

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

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

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

Conducting an AEFI investigation

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

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

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

Practical issues for developing your AEFI investigation procedures

- Decide what should be investigated (develop the reporting system around these events), based on case definitions and identification of AEFI clusters (see below for cluster investigation).
- Decide who should conduct investigations and in what timeframe.
- Design the investigation procedure and forms to collect all relevant information for determining cause and assessing causality.
- Have a system in place for collecting and testing any samples of suspect vaccines and diluents.
- Have a system in place to conduct post mortems and testing 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 AEFS, 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 AEFS,
- Signals and events associated with newly introduced vaccines,
- Other AEFS as recommended by WHO:
  - AEFS 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 AEFS),
  - 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 AEFS occurring in similar age groups and populations with genetic predisposition or disease.

Examples of AEFI clusters

**Example 1**
An outbreak of lymphadenitis 3 months after BCG immunization was traced to a switch to a different strain of vaccine. The investigation also highlighted a number of immunization errors (vaccines not properly reconstituted, and injections not given intradermally).

*Cause: vaccine reaction compounded by immunization errors.*

**Illustration 2**
Four children died and a fifth was hospitalized after receiving measles vaccine from the same vial. The vaccine was not refrigerated, and was transported from house to house for immunization. Reactions began 4-5 hours after vaccination, with vomiting, unconsciousness, and meningeal irritation. *Staphylococcus aureus* bacteria were cultivated from the incriminated vial.

*Cause: sepsis caused by inappropriate vaccine handling.*

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

1. Identify the immunization history of the cluster cases including details of when, where and which vaccines were given, by collecting and recording:
   - Detailed data on each patient,
   - Programme-related data (storage and handling, etc.),
   - Immunization practices and the associated health workers' practices.
2. Identify any common exposures among the cases, for example:
   – All data on vaccine(s) used (name, lot number, etc.),
   – Data on other people in the area (also non-exposed).

**Including vaccine testing in an AEFI investigation**

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

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

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

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

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

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

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

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

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

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

The quality of a causality assessment depends on:

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

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

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

**Strength of association**: The association between the AEFI and the vaccine should be strong in terms of magnitude and also in the dose-response relationship of the vaccine with the adverse event.
Specificity: The association should be distinctive. The adverse event should be linked uniquely or specifically with the vaccine concerned rather than occurring frequently, spontaneously or commonly in association with other external stimuli or conditions.

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

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

**Risk/benefit assessment**

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

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

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

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

**Question 4**

Think about this example:

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

Should the measles campaign be suspended?

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

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

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

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

### Risk Evaluation

- 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 administering the vaccine/drug.
☐ E. Expectations towards substance’s safety.

Question 2

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

Which of the following statements is not correct?
Select one or more.

☐ A. Health workers have the responsibility to detect AEFIs and report AEFIs when they first occur.
☐ B. Health workers should be able to detect all cases corresponding to locally suitable AEFI case definitions.
☐ C. Health workers should be trained to detect clusters of AEFI and all other events believed to be due to immunization.
☐ D. Health workers must report serious AEFIs only.
☐ E. To support reporting in their countries, immunization programme managers should establish appropriate criteria for detecting AEFIs by identifying adverse events of importance to the programme in their country.
Question 3

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

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

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

Question 4

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

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

Question 5

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

Is this statement true or false? Select one.

- □ True
- □ False

You have completed Assessment 4.
Assessment solutions

**Question 1**

Answers A, B, D and E are correct.

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

**Question 2**

Answer D is incorrect.

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

In particular, health workers must report:

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

**Question 3**

Answers A, C and D are correct.


**Answers A – D**

Reported events requiring the initiation of an investigation are:

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

**Answer E**

Vaccine testing is not an integral part of an investigation. It is only appropriate if the working hypothesis about the possible causes of an AEFI suggests there may be a problem with vaccine quality, e.g. bacterial contamination, damage due to inadequate maintenance of the cold chain, a reconstitution error, etc.
**Question 4**

Answer C is incorrect.

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

- **Consistency**
- **Strength of association**
- **Specificity**
- **Temporal relation**
- **Biological plausibility**

**CAUSALITY**

**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.