MODULE 5

Vaccine safety institutions and mechanisms
Overview

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

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

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

Module outcomes

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

1. List the main functions or services for vaccine safety, including national and international bodies, as well as manufacturers,

2. Describe the relevant areas of responsibility and (if applicable) the areas of collaboration between the National regulatory authority and immunization programmes within your own country,

3. Identify the mechanisms by which an AEFI seen in a clinic can be reported to the national regulatory authority,

4. Summarize information flows between institutions at national level (immunization clinics, NRAs, etc.) and international bodies.
Overview of functions

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

Global capacity building and harmonized tools
- Brighton Collaboration
- CIOMS/WHO working group
- Training providers

Global advice and response
- GACVS
- Other global or regional advisory bodies

National AEFI surveillance, investigation and response
- National regulatory authority
- National immunization programme
- AEFI review committee
- Other support groups

Global signal, evaluation and detection
- WHO PIDM
- Global Vaccine Safety DataNet
- Other partners

Product monitoring
- Vaccine manufacturers
- Licensing authorities in country of manufacture
- Procurement agencies

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

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

National AEFI surveillance systems

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

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

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

Mass vaccination campaigns

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

Key point

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

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

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

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

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

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

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

Core functions specific to vaccines

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

Strengthening NRAs

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

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

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

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

Functions depending on the source of vaccines

Of the six core functions, all NRAs are responsible for Function 1 (licensing vaccines) and Function 2 (AEFI surveillance). Both these functions should be coordinated with the National Immunization Programme.2,54 The NRAs can be responsible for Functions 3–6 depending on how its respective country obtains vaccines. Countries may:

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

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

NRA functions depending on source of vaccines

<table>
<thead>
<tr>
<th>Vaccine-specific NRA functions needed</th>
<th>Areas of activity by NRA (or WHO) depending on source of vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine procured by United Nations agency</td>
</tr>
<tr>
<td>FUNCTION 1 Marketing authorization and licensing activities</td>
<td>✓</td>
</tr>
<tr>
<td>FUNCTION 2 AEFI surveillance</td>
<td>✓</td>
</tr>
<tr>
<td>FUNCTION 3 NRA lot release</td>
<td></td>
</tr>
<tr>
<td>FUNCTION 4 Laboratory access</td>
<td></td>
</tr>
<tr>
<td>FUNCTION 5 Regulatory inspections</td>
<td></td>
</tr>
<tr>
<td>FUNCTION 6 Oversight of clinical trials</td>
<td></td>
</tr>
</tbody>
</table>
The graphic below shows some of the key capabilities enabling a NRA to implement the 6 core functions listed in the table above.

**NRA KEY CAPABILITIES**

- Review vaccine supplier qualifications and authorize release of vaccines
- Effectively communicate through communication systems informing healthcare workers, patients, and the public through the media
- Demonstrate sound regulatory competence, with the authority to enforce regulations
- Act based on government commitment (adequate sustained public funding)
- Have the epidemiological capacity to assess risk through AEFI surveillance
- Conduct research and training
- Understand critical components of the production process
- Demonstrate technical expertise necessary to evaluate documentation
- Ensure competency of inspectors (e.g., through trainings)

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**Vaccine procurement and lot release**

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

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

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

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

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

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

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

Key point

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

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

Regulation of drug safety

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

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

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

Pharmacovigilance is often conducted by national pharmacovigilance centres on behalf of NRAs. These centres, in collaboration with NRAs, have a significant role in the surveillance of adverse drug reactions after licensing, including for vaccines and have to be staffed with persons with experience in vaccinology or training in vaccine vigilance.
Influenza A (H1N1) vaccine example

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

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

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

National immunization programmes (NIP)

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

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

Key point

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

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

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

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

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

Safety of vaccine administration

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

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

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

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

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

■ Monitor persons receiving vaccines for 20 minutes after vaccination.

**AEFI Review Committee**

Every country should establish an AEFI Review Committee to:

■ Review individual serious and unusual AEFIs and other AEFIs referred to it by expert groups (e.g. the national immunization technical advisory groups) and/or national pharmacovigilance centres,

■ Assess potential causal links between AEFIs and a vaccine (or vaccine lot),

■ Monitor reported AEFI data for potential signals of previously unrecognized vaccine-related adverse events,

■ Provide recommendations for further investigation, education, corrective action and communication with interested parties, including the media,

■ Record its deliberations and decisions and feedback on each reviewed case to all relevant stakeholders.

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

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

**Other support groups**

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

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

**Pharmacovigilance centres**

The AEFI surveillance functions of pharmacovigilance centres relate to the reporting and investigation of adverse events associated with vaccines as well as medicinal drugs. Many countries now operate a decentralized pharmacovigilance system, with a national pharmacovigilance centre functioning as the
focal point for a network of regional and/or local centres. These may be located in a range of organizations, including relevant government departments, hospitals, academic environments, or hosted by a professional body such as a national medical association.

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

**National immunization technical advisory groups (NITAGs)**

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

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

NITAGs also serve to:

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

Global vaccine safety stakeholders and services

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

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

WHO and other partners are supporting various global initiatives that aim to strengthen and support national AEFI surveillance, investigation and response. The following graphic shows some of the initiatives at global level that support countries on vaccine safety issues. Move your mouse over each group to find out about its overall role.
Components of 21st century global vaccine systems

GACVS

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

WHO and partners

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

Brighton collaboration

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

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

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

WHO Programme for International Drug Monitoring (PIDM)


Other support groups

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

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

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

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

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

- **Are independent and unbiased:** They take decisions free of vested interests, including the interests of WHO itself or of other organizations. Each committee member signs a declaration of interest accordingly.
- **Offer broad expertise:** They have the expertise to evaluate and make decisions in the field of vaccine safety. They are familiar with drug regulatory processes, with special reference to the needs of the low-income countries.
- **Take decisions with scientific rigour:** All decisions of the Committee are based on the best available scientific evidence and expertise. It is authoritative, defensible and explicable in terms of fact, scientific evidence and process.
Since its establishment, GACVS has discussed a broad range of vaccine safety issues either causing, or with a potential to cause, public concern. These include general issues relevant to all vaccines, such as the safety of adjuvants, as well as vaccine-specific issues relating to long-standing vaccines and to new vaccines and vaccines under development.

GACVS example

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

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

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

Interactive excercise

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

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* in infants symptoms of HIV-infection rarely appear before several months of age.
**Question 1**

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

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

**Key point**

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

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**Good information practices – Vaccine Safety Net**

The internet is a mine of useful information on various topics, but also contains websites of dubious quality. Although many quality websites offer science-based information about vaccine safety, other sites provide unbalanced and misleading information. This can lead to undue fears, particularly among parents and patients.

To assist readers in identifying websites providing information on vaccine safety that comply with good information practices, the Global Advisory Committee on Vaccine Safety (GACVS) recommended a list of criteria that sites providing information on vaccine safety should adhere to.\(^4^5\) The recommended criteria fall into four categories:

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

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

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

* The answer to all questions can be found at the end of this manual (page 202).
From March 2010, more than 30 websites successfully met the GACVS criteria and are listed on the WHO website. Listed sites are re-evaluated for their adherence to the credibility and content criteria every two years. Evaluation dates are included within each site description.45

Global Capacity building and harmonized tools

Global advice and response
GACVS
Other global or regional advisory bodies

National AEFI surveillance, investigation and response
National regulatory authority
National immunization programme
AEFI review committee
Other support groups

Global signal, evaluation and detection
WHO PIDM
Global Vaccine Safety DataNet
Other partners

Product monitoring
Vaccine manufacturers
Licensing authorities in country of manufacture
Procurement agencies

Brighton Collaboration – setting standards in vaccine safety

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

The main objectives of the collaboration are.40

■ To raise global awareness of the availability of standardized case definitions and guidelines for data collection, analysis and presentation, and to educate about the benefit of and monitor their global use and to facilitate access,

■ To develop single standardized case definitions86 for specific AEFIs,

■ To prepare guidelines for data collection, analysis and presentation for global use,

■ To develop and implement study protocols for evaluation of case definitions and guidelines in clinical trials and surveillance systems.
Case definitions

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

Key point

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

CIOMS/WHO working group

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

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

To propose standardized definitions relevant to the monitoring of safety of vaccines intended for the prevention of infectious diseases during clinical trials and for the purposes of vaccine pharmacovigilance after licensing,

To contribute to the development, review, evaluation and approval of AEFI case definitions as developed by the Brighton Collaboration process, and to contribute to their dissemination, including their translation into additional languages,

To collaborate with other CIOMS Working Groups, especially that on Standardized MedDRA Queries (MedDRA is the Medical Dictionary for Regulatory Activities) and the CIOMS Working Group VIII on Signal Detection on issues relevant to vaccine safety.

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

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

CIOMS/WHO Report on Vaccine Pharmacovigilance:

Vaccine safety training opportunities

Global Vaccine Safety Resource Centre

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

Among the resources available are:

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

Overview of vaccine safety training opportunities for different target groups

Go to \url{www.who.int/vaccine_safety/initiative/tech_support} to access more information on the Global Vaccine Safety Resource Centre.
**Global signal evaluation and detection**

**WHO Programme for International Drug Monitoring**

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

The programme consists of a three-part network:

- National pharmacovigilance centres from WHO member countries are responsible for case reports sent to the WHO ICSR database (managed by the Uppsala Monitoring Centre (UMC) in Sweden),

- UMC oversees the WHO programme operations, including:
  - Collecting, assessing and communicating information from member countries about the benefits, harm, effectiveness and risks of drugs,
  - Collaborating with member countries in the development and practice of pharmacovigilance,
  - Alerting NRAs of member countries about potential drug safety problems via the WHO signal process.

- WHO headquarters in Geneva, Switzerland is responsible for policy issues.
As of June 2012, more than 100 countries had joined the programme, and more than 30 associate members were awaiting compatibility between the national and international reporting formats. Member countries are shown on the map below.42

Global Vaccine Safety DataNet (GVSD)

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

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

The goals of the meeting were to:

- Assess current capabilities and interest in establishing a global vaccine safety data network,
■ Explore the infrastructure and funding required to bring such a project to fruition,
■ Define how to best implement this project.

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

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

For example, if a vaccine safety issue is identified and validated in one site or country, the information can be rapidly communicated via the database to other countries using the same vaccine. Global collaborations would also enable the experience and expertise of the high-income countries to be extended to immunization programmes in the low-income countries, for example:
■ Training in data management, data sharing, data governance and data protection,
■ Developing ethical policies and procedures in collecting and reporting data, including guarding against conflicts of interest,
■ Sharing protocols, agreements and methods for evaluating local vaccine signals at global level.

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

Question 2
Think back to the example of the introduction of rotavirus vaccines (page 26) and detection of the post-licensure incidence of intussusception. How could the pooling of AEFI data from several countries via a global database have influenced the outcomes of surveillance in this example?

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

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

Procurement agencies

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

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

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

Licensing authorities in countries of manufacture

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

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

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

Vaccine manufacturers

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

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

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

Key point

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

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

The Global Vaccine Safety Blueprint has three main goals:

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

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

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

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

☑ The main functions and services that are present for vaccine safety, including national and international bodies, and manufacturers.

☑ The relevant areas that the NRA and NIP in your own country are responsible for, and (if applicable) the areas of collaboration between them.

☑ The main actors providing support on vaccine safety to countries at global level, as well as their areas support:
  1. Global capacity building and harmonized tools,
  2. Global analysis and response,
  3. Global signal evaluation and detection,
  4. Product monitoring.

☑ The Global Vaccine Safety Blueprint as the main strategic framework aiming at the establishment of effective vaccine pharmacovigilance systems in all countries.

You have completed Module 5.
We suggest that you test your knowledge!
ASSESSMENT 5
Question 1

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

Is this statement true or false? Select one:

- [ ] True
- [ ] False

Question 2

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

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

- [ ] A. National EPI Manager.
- [ ] B. A university professor of epidemiology.
- [ ] C. The director of the National Regulatory Authority.
- [ ] D. A senior investigator in immunology from the national research laboratory.
- [ ] E. A forensic physician.
- [ ] F. The transport manager of the company that distributes the vaccine.
Question 3

Reporting lines for AEFI:

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

A. A pharmacovigilance officer in the NRA

B. A person working in a vaccination centre

C. A Regional Health Officer

- Immunization programme manager
- The National Regulatory Authority
- The vaccine manufacturer

Question 4

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

1. Global Advisory Committee on Vaccine Safety (GACVS)

2. Vaccine manufacturers

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

4. Brighton collaboration

5. Global Vaccine Safety Data Link

- Global signal detection and evaluation
- National Immunization Technical Advisory Groups (NITAGs)
- Product monitoring
- Global capacity building and harmonized tools
- Global analysis and response
The Global Advisory Committee on Vaccine Safety (GACVS) is the main advisory body to WHO on vaccine-related safety issues. Which of the following actions are in the remit of this committee? Select one or more:

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

You have completed Assessment 5.
Assessment solutions

**Question 1**
The correct answer is ‘True’.

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

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

**Question 2**
Answers B, D and E are correct.

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

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

**Question 3**
Correct answers:

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

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

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

The National Regulatory Authority (NRA), is a national institution responsible for the regulatory procedures governing vaccine lot release and subsequent confirmatory testing, to ensure that all vaccines released for use within a country are safe, effective and of good quality.
National Immunization Technical Advisory Groups (NITAGs) are national advisory bodies responsible for strengthening evidence-based, locally-relevant policy and strategy decisions on issues of vaccine quality and safety, including the introduction of, or need for, new vaccines and immunization technologies.

**Question 4**

Correct answers:

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

**Question 5**

Answers A, C and D are correct.

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

**Answer B**

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

**Answer E**

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