MODULE 3
Adverse events following immunization
Overview

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

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

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

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

Module outcomes

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

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

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

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

AEFIs are grouped into five categories.

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

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

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

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

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

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

**Serious event**

An AEFI will be considered serious, if it:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
is a congenital anomaly/birth defect, or
- requires intervention to prevent permanent impairment or damage.

Severe event

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

<table>
<thead>
<tr>
<th><strong>Adverse events following immunization (AEFI)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>The pandemic influenza A (H1N1) vaccine was an example of where the AEFI classification was used to describe events.</td>
</tr>
<tr>
<td>The European Medicines Agency (EMEA) publication “Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine” states that there should be “protocols in place […] to ensure that immunogenicity, effectiveness and safety of the final pandemic vaccine are adequately documented during use in the field (i.e., during the pandemic), since there will be only limited immunogenicity and safety data and no efficacy data at the time of licensing”. This publication directed health workers to prioritize reports of the following adverse events:</td>
</tr>
<tr>
<td>- Fatal or life-threatening adverse reactions,</td>
</tr>
<tr>
<td>- Serious unexpected adverse reactions. This refers to the classification of AEFIs that is discussed in more detail later in this module,</td>
</tr>
<tr>
<td>- AEFI: neuritis, convulsion, anaphylaxis, syncope, encephalitis, thrombocytopenia, vasculitis, Guillain-Barré syndrome and Bell’s palsy.</td>
</tr>
<tr>
<td>For each of the above AEFI, standard case definitions from the Brighton Collaboration were used if available. This helped compare data from different countries.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th><strong>Key point</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>It is important to note that ‘serious’ and ‘severe’ are often used as interchangeable terms but they are not.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th><strong>Question 1’</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>True or false?</strong></td>
</tr>
<tr>
<td>An anaphylactic reaction following immunization that results in the death of the patient is considered a serious event.</td>
</tr>
</tbody>
</table>

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* The answer to all questions can be found at the end of this manual (page 202).
A vaccine reaction is an individual’s response to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly. From the 5 causes for AEFI from the previous page, vaccine reactions comprise vaccine product-related reactions and vaccine quality defect-related reactions.

Vaccine reactions can be classified into two groups:

<table>
<thead>
<tr>
<th>Minor reactions</th>
<th>Severe reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually occur within a few hours of injection.</td>
<td>Usually do not result in long-term problems.</td>
</tr>
<tr>
<td>Resolve after short period of time and pose little danger.</td>
<td>Can be disabling.</td>
</tr>
<tr>
<td>Local (includes pain, swelling or redness at the site of injection).</td>
<td>Are rarely life threatening.</td>
</tr>
<tr>
<td>Systemic (includes fever, malaise, muscle pain, headache or loss of appetite).</td>
<td>Include seizures and allergic reactions caused by the body’s reaction to a particular component in a vaccine.</td>
</tr>
</tbody>
</table>

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

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

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

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

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

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Local reactions (pain, swelling, redness)</th>
<th>Systemic reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fever &gt; 38°C</td>
</tr>
<tr>
<td>BCG²</td>
<td>90–95%</td>
<td>–</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Adults up to 15%</td>
<td>1–6%</td>
</tr>
<tr>
<td></td>
<td>Children up to 5%</td>
<td></td>
</tr>
<tr>
<td>Hib</td>
<td>5–15%</td>
<td>2–10%</td>
</tr>
<tr>
<td>Measles/MR/MMR</td>
<td>~ 10%</td>
<td>5–15%</td>
</tr>
<tr>
<td>OPV</td>
<td>None</td>
<td>Less than 1%</td>
</tr>
<tr>
<td>Pertussis (DTwP)⁻</td>
<td>up to 50%</td>
<td>up to 50%</td>
</tr>
<tr>
<td>Pneumococcal conjugate*</td>
<td>~ 20%</td>
<td>– 20%</td>
</tr>
<tr>
<td>Tetanus/DT/aTd</td>
<td>~ 10%*</td>
<td>– 10%</td>
</tr>
</tbody>
</table>

**Treatment**  
- Cold cloth at injection site  
- Paracetamol  
- Give extra oral fluids  
- Wear cool clothing  
- Tepid sponge or bath  
- Paracetamol

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a. Local reactogenicity varies from one vaccine brand to another, depending on the strain and the number of viable antigen in the vaccine.

b. Diarrhoea, Headache and/or muscle pains.

c. When compared with whole cell pertussis (DTwP) vaccine, acellular pertussis (DTaP) vaccine rates are lower.

d. Rate of local reactions are likely to increase with booster doses, up to 50–85%.

e. Source: [http://www.cdc.gov/vaccines/hcp/acip-recs/](http://www.cdc.gov/vaccines/hcp/acip-recs/)

f. Paracetamol dose: up to 15mg/kg every 6–8 hours, maximum of 4 doses in 24 hours.

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### Severe vaccine reactions

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

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**Key point**

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

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

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

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

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Reaction*</th>
<th>Onset interval#</th>
<th>Frequency per doses given</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG26</td>
<td>Fatal dissemination of BCG infection</td>
<td>1–12 months</td>
<td>0.19–1.56/1,000,000</td>
</tr>
<tr>
<td>OPV29</td>
<td>Vaccine associated paralytic poliomyelitis (VAPP)b</td>
<td>4–30 days</td>
<td>2–4/1,000,000</td>
</tr>
<tr>
<td>DTwP30</td>
<td>Prolonged crying and seizuresc</td>
<td>0–24 hours</td>
<td>&lt; 1/100</td>
</tr>
<tr>
<td></td>
<td>HHE</td>
<td>0–24 hours</td>
<td>&lt; 1/1,000–2/1,000</td>
</tr>
<tr>
<td>Measles31</td>
<td>Febrile seizures</td>
<td>6–12 days</td>
<td>1/3,000</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>15–35 days</td>
<td>1/30,000</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis</td>
<td>1 hour</td>
<td>1/100,000</td>
</tr>
</tbody>
</table>

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

b. VAPP risk higher for first dose (1 in 750,000 compared with 1 in 5.1 million for subsequent doses), and for adults and immunocompromised patients.

c. Seizures are mostly febrile. The risk of having a seizure depends on the persons age. The risk is much lower in infants < 4 months of age.
The difference between *serious* and *severe* adverse events

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

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

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**Immunization error-related reaction**

<table>
<thead>
<tr>
<th>Key point</th>
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</thead>
<tbody>
<tr>
<td>Immunization errors often constitute the greatest proportion of AEFIs. They can include deaths associated with the reconstitution of vaccines with an incorrect diluent or a drug (e.g. insulin).</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Immunization error</th>
<th>Possible AEFI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-sterile injection</strong></td>
<td>• Local injection site reactions (e.g., abscess, swelling, cellulitis, induration),</td>
</tr>
<tr>
<td>• Reuse of disposable syringe or needle leading to contamination of the vial, especially in multi-dose vials,</td>
<td></td>
</tr>
<tr>
<td>• Improperly sterilized syringe or needle,</td>
<td>• Sepsis,</td>
</tr>
<tr>
<td>• Contaminated vaccine or diluent.</td>
<td>• Toxic shock syndrome,</td>
</tr>
<tr>
<td></td>
<td>• Blood-borne transmission of disease, e.g., hepatitis B, HIV,</td>
</tr>
<tr>
<td></td>
<td>• Death</td>
</tr>
<tr>
<td><strong>Reconstitution error</strong></td>
<td>• Local abscess,</td>
</tr>
<tr>
<td>• Inadequate shaking of vaccine,</td>
<td>• Vaccine ineffective*</td>
</tr>
<tr>
<td>• Reconstitution with incorrect diluent,</td>
<td>• Effect of drug, e.g., insulin, oxytocin, muscle relaxants,</td>
</tr>
<tr>
<td>• Drug substituted for vaccine or diluent,</td>
<td>• Toxic shock syndrome,</td>
</tr>
<tr>
<td>• Reuse of reconstituted vaccine at subsequent session.</td>
<td>• Death.</td>
</tr>
<tr>
<td><strong>Injection at incorrect site</strong></td>
<td>• Local reaction or abscess or other local reaction,</td>
</tr>
<tr>
<td>• BCG given subcutaneously,</td>
<td>• Local reaction or abscess or other local reaction,</td>
</tr>
<tr>
<td>• DTP/DTT/T too superficial,</td>
<td>• Sciatic nerve damage.</td>
</tr>
<tr>
<td>• Injection into buttocks.</td>
<td>• Increased local reaction from frozen vaccine,</td>
</tr>
<tr>
<td></td>
<td>• Ineffective vaccine*</td>
</tr>
<tr>
<td><strong>Vaccine transported/stored incorrectly</strong></td>
<td></td>
</tr>
<tr>
<td>• Freezing vaccine during transport,</td>
<td></td>
</tr>
<tr>
<td>• Failure to keep vaccine in cold chain, exposing to excessive heat or cold.</td>
<td></td>
</tr>
</tbody>
</table>

Contraindication ignored

<table>
<thead>
<tr>
<th>Immunization error</th>
<th>Possible AEFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Vaccination staff ignoring or not becoming familiar with contraindications for a vaccine.</td>
<td>Avoidable severe reaction</td>
</tr>
</tbody>
</table>

**Question 2**

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

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

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

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

** The answer to all questions can be found at the end of this manual (page 202).
Individuals can react in anticipation to and as a result of an injection of any kind. These reactions are not related to the vaccine, but to fear of the injection. There are four reactions you may encounter.26

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

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

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

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

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

Vaccinations are normally scheduled in infancy and early childhood, when illnesses are common and congenital or early neurological conditions become apparent. Coincidental events are inevitable when vaccinating children in these age groups, especially during a mass campaign. Applying the normal incidence of disease and death in these age groups along with the coverage and timing of immunizations allows estimation of the expected numbers of coincidental events after immunization.

Estimates from the WHO Regional Office for the Western Pacific are presented in the table. For example, in Australia, each year there are likely to be 11 coincidental infant deaths the day after immunization.
**Influenza A (H1N1) vaccine example**

In response to the pandemic influenza A H1N1 strain, many countries had engaged in mass immunization against flu in 2009. Awareness of the expected background rates of possible adverse events was estimated crucial to the assessment of possible vaccine adverse reactions. Highly visible health conditions, such as Guillain-Barré syndrome, spontaneous abortion and death, can occur in close proximity to vaccination in substantial numbers when large populations are vaccinated. For example, for every 10 million individuals vaccinated in the United Kingdom, 21.5 cases of Guillain-Barré syndrome and 5.75 sudden deaths were expected to occur as unrelated coincidental events within 6 weeks of vaccination.

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

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

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

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

### Expected coincidental deaths following DTP vaccination in selected countries

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

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

\( nv = \text{number of immunization doses: assumed here to be three dose schedule; 3.} \)

\(ppv = \text{proportion of population vaccinated: assumed here to be 90% for each dose; 0.9.} \)
Additional information

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

Question 3*

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

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

Key point

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

Mass vaccination campaigns

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

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

- Staff unfamiliar with the vaccine or under pressure to vaccinate too many persons too quickly.
- If vaccinated group has different age compared to routine immunizations, different adverse events may occur.
- Interest groups may fuel concerns about AEFIs.
- Rumours rapidly damage the campaign.
- Increase in immunization errors.
- Staff may have less experience with adverse events (e.g. fainting with older children).
- Rumours jeopardize justification of campaign.
- If not dealt with immediately, rumours may not be countered sufficiently.

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

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

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

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

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

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

Key point

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

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

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

[Link to WHO aide-memoire]

Rates of adverse vaccine reactions

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

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

However, one of the main challenges in surveillance of AEFIs is to differentiate coincidental events from events that are caused by a reaction to a vaccine or its components.
To help strengthen the capacity to introduce vaccines in Member States, WHO has published *WHO Information Sheets on Observed Rates of Vaccine Reactions* online to provide details on selected vaccines that are relevant to the analysis of reported events. These cover, for example, vaccines such as Anthrax, BCG, Hep A, Hep B, Hib, HPV, Influenza, Pneumococcal, Rabies, Varicella Zoster.

**Key point**

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

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

**Example: Fever following vaccination**

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

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

### Expected rates of AEFIs following some childhood vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Estimated rate of severe reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>1 in 1,000 to 1 in 50,000 doses</td>
</tr>
<tr>
<td>OPV (oral polio vaccine)</td>
<td>1 in 2–3 million doses (or 1 in 750,000 doses for the first dose)</td>
</tr>
<tr>
<td>Measles</td>
<td>1 in 1 million doses</td>
</tr>
<tr>
<td>DTP</td>
<td>1 in 750,000 doses</td>
</tr>
</tbody>
</table>

**Question 4**

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

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

### Other factors to consider when comparing rates of AEFIs

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

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

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

*The answer to all questions can be found at the end of this manual (page 202).
**Vaccine doses**  
The same vaccine given as a 'primary dose' may have a different reactogenicity profile than when it is given as a 'booster dose'. For example, the DTaP vaccine given as a primary dose is less likely to result in extensive limb swelling when compared with this same vaccine given as a booster dose.

**Case definitions**  
Adverse event may be defined differently in research studies that do not stick to the same case definition. Not using standardized case definitions may consequently affect the estimation of the AEFI rate.

**Surveillance methods**  
The way that surveillance data is collected may alter the rate. For example, surveillance data may be collected actively or passively, using pre- or post-licensure clinical trials, with or without randomization and placebo controls.

**Background rate**  
The background rate of certain events may differ between communities. This can influence the observed rate even though the vaccine attributable rate is the same in both communities. For example, reports of death post-vaccination may be higher in a country that has a higher background rate of deaths due to coincidental infection.

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**Summary**

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

☑️ The characteristics of the five types of AEFI are Vaccine product-related reaction, Vaccine quality defect-related reaction, Immunization error-related reaction, Immunization anxiety-related reaction, Coincidental event.

☑️ The causes of the five types of AEFI and the practices that can minimize their occurrence.

☑️ Mass vaccination campaigns can lead to an increase in immunization errors, for example, because of staff inexperience in vaccinating a wider age group, and to the spread of unfounded rumours that may damage the campaign.

☑️ The importance of comparing background rates of adverse events with rates of vaccine-attributable reactions and taking account of factors that may confound the results of an AEFI investigation.

You have completed Module 3.  
We suggest that you test your knowledge!
ASSESSMENT 3
Question 1

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

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

Question 2

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

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

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

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

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

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

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

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

- Immunization error-related reaction
- Vaccine product-related reaction
- Immunization anxiety-related reaction
- Coincidental event
- Vaccine quality related reaction
Question 4

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

☐ A. Staff who are unfamiliar with the given vaccine and are under pressure to vaccinate many children in a short period of time.

☐ B. Different age groups receiving vaccines.

☐ C. Rumours spread by anti-vaccine lobbies. Nutritional status of the people/children receiving the vaccine.

☐ D. The nutritional status of a vaccinee.

Question 5

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

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

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

Select one:

☐ A. 0.2

☐ B. 26

☐ C. 10

☐ D. 16

☐ E. 1

You have completed Assessment 3.
Assessment solutions

Question 1

Answers C and D are correct.

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

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

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

Question 2

Answer D is incorrect.

Anaphylaxis has an onset interval of up to 1 hour following vaccination.
See the table “Severe vaccine reactions, onset interval, and rates associated with selected childhood vaccines” on page 73.

Question 3

Correct answers:

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

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

Question 4

Answers A, B and C are correct.

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

A. Staff who are unfamiliar with the given vaccine or mass campaign situations, or who are under pressure to vaccinate many children quickly may cause an increase in adverse events caused by immunization errors.
B. A wider age group may be targeted than for routine immunizations. Staff may have less experience with adverse events that occur in this age group (e.g. fainting among older children and teenagers).

C. Some sectors may antagonize against the campaign, for a variety of reasons. This may add fuel to concerns about AEFI during the efforts to justify the vaccination campaign. Rumours may spread rapidly and damage the campaign before there is a chance to counter them.

D. The nutritional status of a vaccinee is usually not a common issue with mass vaccination campaigns.

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

**Question 5**

**Answer A is correct.**

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

\[ 5,000,000 \times \frac{2}{100,000} \times \frac{8}{50} = 16 \]

The number observed is 26, therefore the excess is \( 26 - 16 = 10 \)

The excess incidence is \( \frac{10}{5,000,000} = \frac{0.2}{100,000} \) vaccinated individuals.

The correct answer is: 0.2.