WHO Vaccine Safety Basics

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

Module 1
Introduction to vaccine safety

Key Points

Explain the importance of vaccination in the control of infectious diseases,
Describe the basic principles of vaccination,
Explain how the public are less tolerant of the risks associated with vaccines (although very low) than they are of those associated with drugs used to treat disease,
List the main types of vaccine and illustrate them with examples,
Describe the importance of post marketing vaccine safety surveillance,
Identify some vaccines that have been associated with adverse vaccine reactions.
• 1796, Development of first smallpox vaccine
• By 1900, there were two human virus vaccines, against smallpox and rabies, and three bacterial vaccines against typhoid, cholera and plague
• During the 20th century, other vaccines that protect against once commonly fatal infections such as pertussis, diphtheria, tetanus, polio, measles, rubella, and several other communicable diseases were developed.
• A worldwide case detection and vaccination programme against smallpox gathered pace and, in 1979, the World Health Assembly officially declared smallpox eradicated
Based on the emerging success of the smallpox programme, in 1974, the World Health Organization (WHO) launched the Expanded Programme on Immunization (EPI).

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

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

Although around 24 million infants are still not receiving the full complement of EPI vaccines in the first year of life, the success of the EPI can be judged by the reduction in worldwide cases of measles and poliomyelitis (see graphics). These two diseases are among several (including neonatal tetanus) targeted by the WHO for elimination through vaccination.
• Around 24 million infants are still not receiving the full complement of EPI vaccines in the first year of life
• the reduction in worldwide cases of measles and poliomyelitis

Key point
Although vaccines used in national immunization programmes (NIPs) are considered safe and effective, vaccines are not risk-free and adverse events will occasionally occur following vaccination. Public trust in vaccine safety is key to the success of vaccination programmes.
Expectations towards safety of vaccines

General public has low tolerance to adverse events as vaccines are usually given to healthy persons.

Expectation to safety standard is higher with vaccines compared to medicines for sick people.

National regulatory authorities (NRAs) rigorously ensure the quality, safety, & effectiveness of vaccines and pharmaceutical products.

- Once introduced, vaccines are thoroughly and continuously reviewed.
- NRAs monitor and investigate AEs to ensure safety for population.
- Before being introduced, vaccines are assessed in clinical trials.

Low public tolerance requires safe vaccination
CIOMS/ WHO Cause-Specific Definition of AEFIs

1. 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.

2. 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.

3. Immunization error-related reaction
   - An AEFI that is caused by inappropriate vaccine handling, prescribing or administration.

4. Immunization anxiety-related reaction
   - An AEFI arising from anxiety about the immunization.

5. Coincidental event
   - An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.
Examples

1. Vaccine product-related reaction
   EXAMPLE: Extensive limb swelling following DTP vaccination.

2. Vaccine quality defect-related reaction
   EXAMPLE: Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio.

3. Immunization error-related reaction
   EXAMPLE: Transmission of infection by contaminated multidose vial.

4. Immunization anxiety-related reaction
   EXAMPLE: Vasovagal syncope in an adolescent following vaccination.

5. Coincidental event
   EXAMPLE: A fever after vaccination (temporal association) and malarial parasite isolated from blood.
Adverse events: Causes

Vaccines contain different components: add a potential risk of an adverse reaction.

- Different types of antigens: using different scientific methods such as attenuation, inactivation, and recombination DNA technology.
- Adjuvants and conjugated proteins: enhance immune response.
- Antibiotics, stabilizers, and preservatives: reduce contamination during the manufacturing process and to maintain their effectiveness during transport and storage.
Please note that routes of administration (intradermal, subcutaneous or intramuscular injection, drops given orally, or intranasal administration) also contribute to the risk of an adverse reaction: They are recommended by the manufacturer for each vaccine and are determined to maximize vaccine effectiveness and limit adverse reactions.
Progress in Vaccine regulations

includes shifts towards…

• strictly defined procedures for vaccine consistency, reliance on Good Manufacturing Practices (GMPs) rather than final product testing and

• continued vaccine pharmacovigilance and impact surveillance rather than individual, sporadic field studies.
Key point
Pre-licensure studies often identify common and acute negative reactions that occur with a frequency greater than 1 in 10,000 vaccinations, depending on total sample size of the study.
The sensitivity of detection of uncommon or rare adverse events, or those with delayed onset is, however, low in these trials.
As a result, continuous post-licensure monitoring of vaccine safety is needed to identify and evaluate such adverse events.
Key point
Spontaneous reporting is the cornerstone of most post-licensure safety monitoring systems because of its relative ease of implementation and ability to capture unexpected events.
Public confidence in vaccine safety is increased by clear communication of risk/benefit assessments, comparing the very low vaccine-associated risk with the very significant benefits of vaccination.

**Key point**
Risk/benefit assessments should be applied to most situations relating to the efficacy or safety of vaccines to ensure public safety and public health.
### Weighing the risks and benefits of a vaccine

#### Risk of acquiring illnesses following infection versus risk following vaccination

<table>
<thead>
<tr>
<th></th>
<th>Measles Infection</th>
<th>Measles Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otitis</td>
<td>7 – 9%</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 – 6%</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6%</td>
<td>0</td>
</tr>
<tr>
<td>Post-infectious encephalomyelitis</td>
<td>0.5/1 000</td>
<td>1/100 000 – million</td>
</tr>
<tr>
<td>SSPE</td>
<td>1/100 000</td>
<td>0</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0</td>
<td>1/100 000 – million</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Not properly quantified</td>
<td>1/30 000 $#$</td>
</tr>
<tr>
<td>Death</td>
<td>0.1 – 1/1 000 (up to 5 – 15%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Numbers per 100,000 doses. $\#$ Not properly quantified.
1. Explain the modes of action of live attenuated vaccines, conjugate vaccines, subunit vaccines, and toxoid vaccines,

2. List types of vaccine components, including adjuvants and preservatives, and explain their functions,

3. Explain the difference between live attenuated and inactivated vaccines,

4. Identify the contraindications for vaccination that may present an additional risk.
There are many types of vaccines, categorized by the antigen used in their preparation. Their formulations affect how they are used, how they are stored, and how they are administered. The globally recommended vaccines discussed in this module fall into four main types.
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Module 3
Adverse events following immunization

Key Points

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.
1. 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.

2. 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.

3. 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.

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

5. 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.
Mass Vaccination Campaigns

Challenge to AEFI surveillance.
Large population over a short period of time
→ adverse events may be more noticeable to staff and to the public.

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

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.
Rates of Adverse Vaccine Reactions

Differentiate *coincidental* events from events that are caused by a reaction to a *vaccine* or its *components*

Challenge in surveillance of AEFIs
WHO vaccine safety basics

Module 4
Surveillance
Key Points

1. Describe the basic principles of pharmacovigilance and the special considerations that apply to vaccination programmes,
2. Use AEFI case definitions to evaluate which AEFIs should be detected and reported to the National regulatory authority (NRA) or its equivalent,
3. Describe the principles of risk-benefit analysis relative to the protective effect of immunization and the importance of causality assessments to evaluate possible links between AEFIs and a vaccine or vaccine lot,
4. Explain how investigation of AEFI reports and vaccine testing can contribute to surveillance that ensures vaccine safety.
first two criteria must be met before any consideration can be given to approval for medical use, the issue of safety is more challenging.
Example for collaboration among institutions: Canada
Canada’s national regulatory authority (NRA) is Health Canada. The Public Health Agency of Canada (PHAC) conducts pharmacovigilance for vaccines in collaboration with public health authorities in the provinces and territories, and maintains the national database of reports of adverse events following immunization (AEFI).
Adverse Drug Reaction (ADR) surveillance

ADR surveillance is responsible for detecting and responding to adverse events associated with drugs.

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

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

Immunization safety requires a modified surveillance system

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

• vaccine quality,
• adverse events,
• vaccine storage and handling,
• vaccine administration,
• disposal of sharps,
• management of waste.
1. Detect signals suggesting AEFI is related to a vaccine.
2. Develop hypotheses about causal association between an AEFI and vaccination.
3. Test hypotheses through appropriate epidemiological methods.
1. Health workers - usually the first responders to an AEFI
2. if not done correctly, can result in an adverse event. The possibility of immunization errors therefore must be investigated.

### Special considerations for AEFI Surveillance

**Three major factors:**

1. Training for health workers
2. Determining causality - challenging because:
   - Information on "dechallenge and rechallenge" - missing
   - Coincidental disease, Several vaccines administered at the same immunization visit,
   - Incorrect Vaccine storage, handling, transport and administration can result in an adverse event
3. Independent review is needed
   - independent review of AEs, causality assessment
Key point
A good collaboration between National Regulatory Authority and National Immunization Programme are usually critical components of a strong AEFI surveillance system.
In some countries where the NRA is not in a position to execute the aforementioned tasks, the National immunization programme may have taken over part of the activities of the NRA.
The objectives for an effective AEFI surveillance system are to:

- Identify problems with vaccine lots or brands
- Detect, correct and prevent immunization errors
- Prevent false blame arising from coincidental adverse events
- Reduce the incidence of injection reactions caused by anxiety or pain associated with immunization, by educating and reassuring
- Maintain confidence by properly responding to parent/community concerns
- Increasing awareness (public and professional) about vaccine risks
- Generate new hypotheses about vaccine reactions that are specific to the population of your country/region
- Estimate rates of occurrence of AEFIs in the local population compared with trial and international data

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

- Detection and reporting
- Investigation
- Causality assessment of AEFIs
- Risk benefit assessment
Any clusters of AEFIs (i.e., two or more cases of the same adverse event related in time or place or to the vaccine administered).

All vaccination staff must be able to diagnose adverse events.
| **Who should make the AEFI report and to whom?** | health workers |
| **How should reporting occur?** | Reporting should be as standardized |
| **What should be the route of reporting?** | depend on the local context. Reporting lines are simple and direct and clear to all stakeholders |
| **When should AEFIs be reported?** | Any AEFI that is of concern to the parents or to the health care worker |
AEFI Surveillance Components: Conducting an AEFI Investigation

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

- Serious AEFI s
- Clusters of minor AEFI s,
- Signals and events associated with newly introduced vaccines.
- Other AEFI s as recommended by WHO:
  - AEFI s that may have been caused by immunization error,
  - Significant events of unexplained cause occurring within 30 days after a vaccination,
  - Events causing significant parental or community concern.

Not all AEFI reports will need investigation
Be prompted by a newly identified risk, but must remain holistic (e.g. take into account the entire safety profile of a vaccine, not only the specific information relating to the event that was detected),
Example: Withdrawing a vaccine lot:

**Advantages:** reduces fear of vaccine, renews confidence in the vaccine or the campaign,

**Disadvantages:** cost, potential compromise of the campaign, loss of confidence in vaccine quality.
Considering the Options for Action (2/3)

The options analysis should describe the advantages and disadvantages of each option and the likely consequences.

Example: Withdrawing a vaccine lot:

- **Advantages:** reduces fear of vaccine, renews confidence in the vaccine or the campaign,
- **Disadvantages:** cost, potential compromise of the campaign, loss of confidence in vaccine quality.
It is essential to indicate the quality and quantity of any future evidence necessary to trigger reconsideration of the issue, and how the outcomes of any actions will be monitored and assessed.
List the main functions or services for vaccine safety, including national and international bodies, as well as manufacturers,
Describe the relevant areas of responsibility and (if applicable) the areas of collaboration between the National regulatory authority (NRA) and immunization programmes (NIP) within your own country,
Identify the mechanisms by which an AEFI seen in a clinic can be reported to the national regulatory authority,
Summarize information flows between institutions at national level (immunization clinics, NRAs, etc.) and international bodies.
There are many different organizations serving different purposes in vaccine safety and in the monitoring and support of national responses to adverse events. **Components of a 21st Century global vaccine safety monitoring, investigation, and response system.**
The National Regulatory Authority

- All countries should have a NRA to ensure all medicines including vaccines are safe, effective and of good quality.
- Responsible for ensuring vaccine safety and must meet by strong AEFI surveillance after licensure & vaccine introduction.
- Exchange information between NRA and NIP

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.
National Immunization Programme (NIP)

• Organizational component of Ministries of Health charged with preventing disease, disability, and death from vaccine-preventable diseases in children and adults.

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.
Safety of Vaccine Administration

NRAs and vaccine manufacturers provide guidance on how to prepare and administer vaccines correctly.

NIP (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.
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.
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.

National immunization technical advisory groups (NITAGs)

- Guide national governments and policy-makers to develop and implement evidence-based, locally relevant immunization policies and strategies that reflect national priorities.

National Pharmacovigilance centers.

- Collect, collate, analyze, and give advice on all information related to drug safety.
Components of 21st Century Global Vaccine Systems

- GACVS
- WHO and partners
- Brighton collaboration
- Council for International Organizations of Medical Sciences CIOMS/WHO working group
- WHO Programme for International Drug Monitoring (PIDM)
- Other support groups
1. Understand the need for improved communication on vaccine safety,
2. Critically evaluate and assess new information about vaccines before communicating to the target audience,
3. Gather information about the various target audiences, who they are, how they perceive vaccine risk and their knowledge about vaccines and safety,
4. Outline the fears and concerns of different groups associated with, or likely to be affected by, an immunization programme,
5. Design simple, clear and tailor-made messages to communicate information about vaccine safety to your target audience (e.g. parent, vaccinee, clinic staff, media, health professional, drug regulatory authority, health minister, etc.),
6. Identify the most suitable means and channels of communication to convey information to different target groups,
7. Understand the media as being an important ally in vaccine safety.
These concerns can be serious and are often misplaced. See the graphic below for some factors that may trigger public concerns.
We need to improve the quantity, quality and targeting of communication about vaccine safety if we are to increase acceptance of vaccination through improved awareness of the risks and benefits.
Good communication to all relevant stakeholders is essential to keep the trust of the public towards a transparent and accountable immunization service.
It is important to be clear about key messages and simple messages. To frame your communication simply and clearly, while covering all the essential points, you first need to know:

• Who is your intended audience?
• What is their background knowledge, attitudes and beliefs about vaccination?
Public perception

The public sees risk in terms of:
- Voluntariness of exposure,
- Familiarity of risk,
- Control over risk,
- Catastrophic potential,
- Fatal outcomes,
- Unequal balance between risk & benefit,
- Unequal distribution of risk.

Experts see risk in terms of:
- Morbidity and mortality levels
Personal Perspectives Influence Perception

- Religious beliefs
- Social contexts, including experience from media
- Prejudice or distrust of the medical system
- Fear over being injected with substance derived from disease-causing organisms
- Past adverse experiences
- Feelings of intimidation
- Technical concerns over distance or probability
- Financial concerns
Lack of information, or inadequate or misleading information about vaccine safety, increases the risk of the erosion of trust and confidence in health experts, immunization programmes and governments. Ultimately it can result in lost opportunities to protect health. WHO estimates that two million additional lives could be saved every year by the effective use of readily available vaccines.
Communicating in Public

General Principles to keep in mind

- Target audience
  - Concerns, age range, educational levels, gender, religious contexts.
- Communication objective
- Structured communication
- Interactive communication
Thank you