Monitoring and responding to AESI
Learning objectives: The learner should be able to

1. Define an AESI & describe its practical applications in the country context
2. Explain the process of implementing AESI through Active Vaccine Safety Surveillance (AVSS) systems
3. Plan the application of AESI in special populations and unique situations
Presentation structure

Define and understand the difference between AEFI and AESI

Implement AESI in the field level

Apply the concept of Active vaccine safety surveillance (AVSS) to AESI

AESI in special situations
Definition: Adverse events of special interest (AESI)

• An AESI is a pre-specified medically-significant event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further special studies.
AESIs identified through active vaccine safety surveillance (AVSS) systems if there is proven association with immunization that is true for most, if not all, vaccines.  

01

proven association with a known vaccine platform or adjuvant that is being used in any COVID-19 vaccine.

02

theoretical concern related to viral replication during COVID-19 infection.

04

theoretical concern based on immunopathogenesis of COVID-19 disease.

03

05
# Differences between AEFI/AESI and practical implications

<table>
<thead>
<tr>
<th>AEFI</th>
<th>AESI in the context of COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What</strong></td>
<td>Any untoward medical occurrence that follows immunization, and that 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.</td>
</tr>
<tr>
<td><strong>Purpose of collecting information</strong></td>
<td>To identify all events after vaccination – determine if serious, investigate (serious) and do causality assessment.</td>
</tr>
<tr>
<td><strong>Identification method</strong></td>
<td>Identified via spontaneous reporting by vaccine recipients or their parents, or health care workers or other persons who first notice the event.</td>
</tr>
</tbody>
</table>
## Differences between AEFIs and AESIs and practical implications

<table>
<thead>
<tr>
<th></th>
<th>AEFI</th>
<th>AESI in the context of COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case definitions</strong></td>
<td>Important</td>
<td>Critical</td>
</tr>
<tr>
<td><strong>Type of reporting</strong></td>
<td>All events that follow immunization and are notified to the health care system.</td>
<td>All events identified through active surveillance that fit the case definition, irrespective of immunization status</td>
</tr>
<tr>
<td><strong>Training</strong></td>
<td>All frontline immunization staff in health care facilities (public and private); and other relevant staff for reporting, investigation, data analysis, and causality assessment</td>
<td>Immunization staff and other health care workers in sentinel sites and predefined active surveillance systems, NIP/EPI managers, NRA, research staff, national AEFI committee</td>
</tr>
<tr>
<td><strong>Users</strong></td>
<td>Health care workers, NIP/EPI managers, NRA, surveillance and information managers, epidemiologists, surveillance and information managers, vaccine safety partners including the community</td>
<td>Sentinel site staff, NIP/EPI managers, NRA, epidemiologists, national AEFI committees, study teams</td>
</tr>
</tbody>
</table>
Active vaccine safety surveillance (AVSS) systems aim to collect complete, accurate information about adverse events following immunization (AEFIs) and their risk factors in a defined population via a continuous organized process.
Benefits of active vaccine safety surveillance

1. AVSS systems can be used for signal detection

2. Determine the rate of an event in a defined population

3. Determine the relative risk of the event
   - the chance of the event occurring in those who were vaccinated with the specific vaccine, compared with those who were not
   - the change in the event rate over time
Types of AESIs identified with AVSS systems

- Delayed AESIs
- Severe and serious AESIs
- AESIs in priority target groups
- Surveillance of AESIs during mass COVID-19 immunization campaigns
Key considerations - Implementing AVSS systems for COVID-19 vaccine-related AESIs

- Complementary to existing passive surveillance systems
- When significant knowledge gaps cannot be addressed through passive surveillance
- Have sufficient funding and robust governance systems
- Have systems in place to share collected data widely and transparently

- When it is important to define the risk and risk factors in the population immunized with COVID-19 vaccines
- Use harmonized protocols wherever possible
- Operate independently without conflicts of interests.
AVSS: Resources, governance and ethical considerations

collaborative approach, involving stakeholders eg manufacturers, the Ministry of Health, the national immunization technical advisory group, multilateral and non-governmental organizations, the national regulatory authority and pharmacovigilance centres.

Ethical and privacy clearances will be required to collect and analyse identifiable data.
Co-ordination of AVSS systems

Coordination will avoid duplication of effort and increase the size of the population under surveillance, thus enabling the assessment of very rare events and making comparisons.

Implemented though global coordination of AVSS systems, as well as regional or national coordination, through the proposed or existing governance and research structures.
Core and complete data sets to be collected for the AVSS system

<table>
<thead>
<tr>
<th>Complete data set</th>
<th>Core data set</th>
<th>Vaccination data</th>
<th>Health events or outcomes</th>
<th>Demographic data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vaccine brand name</td>
<td>Adverse event(s)</td>
<td>Age at onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lot number</td>
<td>Date of onset of symptoms</td>
<td>Gender</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Date of vaccination</td>
<td>Serious</td>
<td>Medical conditions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose number</td>
<td>Outcome</td>
<td>Medication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Site of vaccination</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Place of vaccination</td>
<td>Place of care</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vaccine antigens</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concomitant vaccines</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Route administration</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
### Key resources available and being developed for COVID-19 vaccine listed AESIs

<table>
<thead>
<tr>
<th>Description</th>
<th>Purpose</th>
<th>Setting to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brighton case definitions</td>
<td>To provide a standard case definition so safety data are comparable</td>
<td>See <a href="https://brightoncollaboration.us/covid-19/">https://brightoncollaboration.us/covid-19/</a> for latest list and definitions</td>
</tr>
<tr>
<td>AESI confirmation and Interpretation forms</td>
<td>Detailed data form to facilitate standardized data collection and interpretation focused on the Brighton criteria to assess LOC.</td>
<td>case investigation and assessment — AEFI signal / cluster investigation — outcome validation for analytic and epidemiological studies</td>
</tr>
<tr>
<td>Tabular checklist and algorithm to determine certainty</td>
<td>Abbreviated tabular form to summarize available case data and assign LOC</td>
<td>same as above but where data have been collected and data abstraction is not needed</td>
</tr>
<tr>
<td>Automated tool to determine LOC for cases</td>
<td>To replace the previous Brighton online ABC tool</td>
<td>— training for LOC determination — causality assessment where first step is to determine LOC — any setting where LOC needs to be assessed</td>
</tr>
</tbody>
</table>
Key resources available and being developed for COVID-19 vaccine listed AESIs

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<thead>
<tr>
<th>Description</th>
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<th>Setting to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background rates and risk factors of AESI</td>
<td>To provide summarized data on incidence of event as coincidental events by age, gender and geography</td>
<td>— epidemiologic studies where expected versus observed are compared &lt;br&gt;— public reassurance in terms of ‘expected’ coincidental events</td>
</tr>
<tr>
<td>ICD and MedDRA codes</td>
<td>To assist in identifying or coding events from or for health care or pharmacovigilance databases</td>
<td>— AEFI MedDRA coding &lt;br&gt;— coded database searches</td>
</tr>
<tr>
<td>Template protocols</td>
<td>Assess background rates, conduct active surveillance</td>
<td></td>
</tr>
</tbody>
</table>

Important Links

- [https://docs.google.com/spreadsheets/d/1QgF35nYcsaFN3DZTOtV_IP0TYqQzsDMUQBAd5M9brrM/edit#gid=1666959512](https://docs.google.com/spreadsheets/d/1QgF35nYcsaFN3DZTOtV_IP0TYqQzsDMUQBAd5M9brrM/edit#gid=1666959512)
- [https://brightoncollaboration.us/](https://brightoncollaboration.us/)
- [https://brightoncollaboration.us/covid-19/](https://brightoncollaboration.us/covid-19/)
In-country reporting and processing of AESIs

Active surveillance for AESI

Prospective

Clinical case diagnosis

Retrospective

Active surveillance system of the country

Matches one of the predefined and pre-identified conditions (Chapter 2, Table 2.1)

AESI reporting form

National AEPI committee to review all AESI for signals

Special analyses of AESI data

AEN LineList from active surveillance center/site

All Dossiers include details vaccinated and unvaccinated cases

Dossiers for each case with Reporting form, AESI confirmation form, Clinical case record, lab reports, autopsy report etc. (AEFI investigation form only for vaccinated case)

Corporate Regulatory Authority, Expanded Program on Immunization, Ministry of Health

Feedback to AEPI

* Data flow can be customized according to the active surveillance methods adopted by the country
Detecting & processing AESIs though AVSS

Through cohort event monitoring (CEM), sentinel surveillance (SS) and data linkage (DL) using case definitions

Specific electronic AVSS tools (e.g. m-health (MH) and e-health (EH))

Vaccine exposure information should be obtained

Use AESI reporting form AESI confirmation form for the specific, AESI, detailed clinical records and results of additional tests must be collated & AESI linelist

Dossiers for each AESI should be submitted to the national level (NRA/NIP/EPI/MoH) in compliance with the country protocol and shared with specially trained national AEFI committee.
Initial causality assessment of Covid19 vaccinated AESI

After confirming the absence of programmatic errors, Immunization stress related responses or coincidental events, Covid19 vaccinated AESI cases will have to be categorised by the committee as

“'B1 -Indeterminate' because the temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing the event (it may be a new vaccine-linked event)”
Data analyses for AESI cases from AVSS

The causality assessment committee trained to review population-based scientific data needs to compare the incidence of the AESI among the COVID-19 vaccinated and unvaccinated individuals within a specific population and identification of signals for further characterization.

The committee should review the national, regional and global epidemiological data to determine if there is a pattern in the profile of reports received e.g., clusters of similar events in space, time and vaccine administered.
Reconciling AESI data

Information about AESIs can be obtained from a passive AEFI surveillance system (spontaneous reporting) or from an AVSS system.

The data from both systems cannot be collated (merged) because the data collection methods are different, and they represent different cohorts of individuals and should, therefore, be analysed separately.
Prioritizing preparedness for AESI

1. At the time of vaccine authorization, countries need to review the RMP and discuss the risks and benefits with their respective in-country national immunization technical advisory groups (NITAGS) or regional immunization technical advisory groups (RITAGS).

2. They need to determine if they have the capacity to implement active surveillance for AESIs.

3. Then they should set priorities for which AESIs are most relevant to a given setting and adopt a system most suitable.
## Summary of tools recommended for AESI

<table>
<thead>
<tr>
<th>Description</th>
<th>Purpose</th>
<th>Status for COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detailed case definitions for AESI</td>
<td>To determine if clinical details comply with standard case definition by an expert</td>
<td>Available for some conditions and under development for others</td>
</tr>
<tr>
<td>Simplified case definitions for AESI</td>
<td>To determine if clinical details comply with standard case definition by a frontline health care provider</td>
<td>To be developed (some available)</td>
</tr>
<tr>
<td>AESI reporting form</td>
<td>To collect information for all AESI cases that have been notified in a standard common format for linelisting</td>
<td>Separate AESI reporting form developed for COVID-19</td>
</tr>
<tr>
<td>AESI linelist</td>
<td>To collate the AESI details from AESI reporting forms</td>
<td>Separate AESI linelist format developed for COVID-19</td>
</tr>
</tbody>
</table>
# Summary of tools recommended for AESI

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<thead>
<tr>
<th>Description</th>
<th>Purpose</th>
<th>Status for COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>AESI confirmation form</td>
<td>To collect confirmation information when AESI cases are identified. Separate form for each condition</td>
<td>To be developed</td>
</tr>
<tr>
<td>Investigation form for AESI cases that have history of COVID-19 vaccination</td>
<td>To collect detailed information when serious AEFI cases are investigated</td>
<td>Adapted to include COVID-19 specific questions</td>
</tr>
<tr>
<td>Causality assessment for AESI cases that have history of COVID-19 vaccination</td>
<td>To determine case classification of all AESI cases that have a history of COVID-19 vaccination reported from the passive surveillance system</td>
<td>Retain current method used for AEFI unchanged</td>
</tr>
<tr>
<td>Detailed analysis format of AESI as per protocol</td>
<td>Will depend on study protocol</td>
<td>Will depend on study protocol</td>
</tr>
</tbody>
</table>
AESI for pregnant women, neonates and immunocompromised individuals

The full impact of COVID-19 disease on pregnancy outcomes for mother and foetus as well as for new-borns is still unclear.

It is not yet clear whether vaccination will be recommended for pregnant or immunocompromised individuals. As a general rule, live vaccines are contraindicated for both.

It will be essential to plan to follow pregnancy outcomes with, for example, a registry of all such occurrences for any adverse outcomes to the mother, foetus or new-born.
Sudden unexpected death as an AESI

Sudden death has not yet been added to the AESI list. However, it will be essential to be prepared to enable rapid response.

A thorough field investigation should be conducted and autopsy performed according to the protocol for suspected COVID-19 cause of death. [https://pubmed.ncbi.nlm.nih.gov/32653819/](https://pubmed.ncbi.nlm.nih.gov/32653819/)

Knowing regional and age-specific background incidence of sudden deaths as well as relevant risk factors will be essential for causality assessment.

Appropriate communication at all stages of investigation, causality assessment and its outcomes will be critical.
Key points to remember

01
AVSS should be implemented complementary to the country’s passive surveillance (spontaneous reporting) system

02
AVSS for AESI can be implemented through Cohort event monitoring, sentinel site surveillance or data linkage

03
AESI should be prioritized and shortlisted for AVSS

04
Specific protocols and tools will need to be adopted by the country based on the local situation
References


• Data linkage https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html
