Purpose: This aide-mémoire serves as a guide to a systematic, standardized process of assessing whether serious adverse events following immunization (AEFI) are causally linked to vaccines/immunization or not.

Definition: AEFI causality assessment determines if a causal relationship exists between a vaccine (and/or vaccination) and an adverse event.

Rationale: Safety requirements for vaccines are stricter than those for drugs since vaccines are biological products that are more prone to lot variation and instability, they are used in healthy populations and the target groups are vulnerable. Vaccines therefore require a causality assessment process that responds in a timely manner and with scientific rigour to AEFI.

WHO SHOULD ASSESS AEFI CAUSALITY?

Ideally an AEFI review committee should be in place backed by written terms of reference. It should consist of independent experts who have no conflicts of interest. As far as possible, the experts should cover a broad range of expertise: infectious diseases, epidemiology, microbiology, pathology, immunology, neurology, forensics and vaccine programming. The committee should be supported by a secretariat (usually the national regulatory authority [NRA] and the immunization programme) that can provide supporting evidence and investigation findings to enable causality to be determined.

WHAT ARE PREREQUISITES FOR AEFI CAUSALITY ASSESSMENT?

- AEFI case investigation should be completed. Premature assessments may mislead classification.
- All relevant information should be available, including documents of investigation, laboratory and postmortem findings (if applicable).
- Valid diagnosis (unfavourable or unintended sign, abnormal laboratory finding, symptom or disease) for the AEFI must be defined, be well-founded and correspond accurately to the event being assessed.
- Information that could bias results (patient name, hospital name, etc.) should be anonymized.

AT WHAT LEVELS IS AEFI CAUSALITY ASSESSED?

AEFI causality assessment could be performed:

- At population level (is there a causal association between usage of a vaccine and a particular AEFI in the population?)
- For an individual (is the adverse event in the individual patient causally linked to the vaccine/vaccination?)

CONSIDERATIONS FOR ASSESSING CAUSALITY OF A SOLITARY AEFI:

- Temporal relationship: is it certain that the vaccination preceded the adverse event?
- Alternate explanations: is the event coincidental, i.e. is it due to something other than the vaccine product, immunization error or immunization anxiety?
- Proof of association: is there clinical or laboratory proof that the vaccine caused the event?
- Prior evidence: has a similar AEFI been previously reported in studies/literature or other sources?
- Population-based evidence: does the rate of event occurrence exceed the expected rate of the event in the population? (Refer to WHO information sheets on observed rates of known vaccine reactions.)
- Biological plausibility: can the association be explained by the natural history, biological mechanisms of the disease, laboratory evidence or animal studies? However this is not an important consideration.

WHICH AEFI TO SELECT FOR CAUSALITY ASSESSMENT?

All reported AEFI require verification of diagnosis, coding, review, information collation and storage. Causality assessment needs to be done for:

- Serious AEFI (i.e. events that are life-threatening or lead to death, hospitalization, significant disability or congenital anomaly)
- Clusters of AEFI (the cause for each case in the cluster should be determined separately). Line-listing of data may identify patterns that could constitute a signal
- Occurrence of events above the expected rate or of unusual severity

POSSIBLE CAUSES OF AEFI

<table>
<thead>
<tr>
<th>Related to vaccine or vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine product-related</td>
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<tr>
<td>Vaccine quality defect-related</td>
</tr>
<tr>
<td>Immunization error-related</td>
</tr>
<tr>
<td>Immunization anxiety-related</td>
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Coincidental adverse event
ADVERSE EVENT FOLLOWING IMMUNIZATION

WHAT ARE THE STEPS² OF A CAUSALITY ASSESSMENT?
- Determine the eligibility of the case
- Review the checklist to ensure that all possible causes are considered
- Use algorithm to determine trend of causality
- Classify causality.

WHAT ARE THE ACTIONS AFTER CAUSALITY ASSESSMENT?
They include providing feedback, training, modifying systems, refining tools, research, etc. to avoid and/or minimize recurrences. Based on outcomes of assessment, the following need to be considered:

A. Consistent with causal association to immunization
   A1 Vaccine product-related reaction: Follow protocols adopted by each country.
   A2 Vaccine quality defect-related reaction: Inform the NRA, manufacturer and relevant stakeholders. Take decision on existing vaccine stock.
   A3 Immunization error-related reaction: Training and capacity-building are critical to avoid recurrences.
   A4 Immunization anxiety-related reaction: Vaccinating in an ambient and safe environment.

B. Indeterminate
   B1 The temporal relationship is consistent but there is insufficient evidence for vaccine causing the event: A national database of such AEFI cases could help to identify signals.
   B2 Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization: If additional information becomes available, the classification can move into more definitive categories; if not, they are to be archived.

C. Inconsistent with causal association to immunization (coincidental)
   Confirm diagnosis; information on why the case is classified as coincidental to be provided to the patients, relatives, care provider and community.

KEY RESOURCES FOR CAUSALITY ASSESSMENT
WHO vaccine reaction rates information sheets http://www.who.int/vaccine_safety/initiative/tools/vacinfosheets/en/
Brighton Collaboration https://brightoncollaboration.org/public.html

1 AEFI definition: 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. http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf

2 For detailed description of the steps, please refer to the Causality assessment of an AEFI - User manual for the revised WHO classification shown in key resources

Contact us: Essential Medicines and Health Products (EMP) Department, World Health Organization, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland. Fax: +41 22 791 42 10 http://www.who.int/vaccine_safety/en/ E-mail: vaccsafety@who.int.

HOW ARE CASES CLASSIFIED AT THE END OF THE ASSESSMENT?

I. Case with adequate information
   A. Consistent with causal association to immunization
      A1. Vaccine product-related
      A2. Vaccine quality defect-related
      A3. Immunization error-related
      A4. Immunization anxiety-related
   B. Indeterminate
      B1 Consistent temporal relationship but insufficient definitive evidence for vaccine causing the event
      B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization
   C. Inconsistent with causal association to immunization (coincidental)
      Underslying or emerging condition(s) or condition(s) caused by exposure to something other than vaccine

II. Case without adequate information
   It is categorized as “unclassifiable” since it requires additional information to determine causality (the available information on such cases should be archived in a repository or an electronic database and classified when additional information becomes available)
### ADVERSE EVENT FOLLOWING IMMUNIZATION

#### Step 1 (Eligibility)

<table>
<thead>
<tr>
<th>Name of the patient</th>
<th>Name of one or more vaccines administered before this event</th>
<th>What is the Valid Diagnosis? (The case diagnosis of the AEFI)</th>
<th>Does the diagnosis meet a case definition?</th>
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<tbody>
<tr>
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#### Step 2 (Event Checklist) [✓ check all boxes that apply]

<table>
<thead>
<tr>
<th>I. Is there strong evidence for other causes?</th>
<th>Y</th>
<th>N</th>
<th>UK</th>
<th>NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does clinical examination, or laboratory tests on the patient, confirm another cause?</td>
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<table>
<thead>
<tr>
<th>II. Is there a known causal association with the vaccine or vaccination?</th>
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<tbody>
<tr>
<td>Vaccine product(s)</td>
</tr>
<tr>
<td>Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?</td>
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<tr>
<td>Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?</td>
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<table>
<thead>
<tr>
<th>Immunization error</th>
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<tbody>
<tr>
<td>Was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?</td>
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<tr>
<td>Was the vaccine (or any of its ingredients) administered unsterile?</td>
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<tr>
<td>Was the vaccine’s physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal at the time of administration?</td>
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<tr>
<td>Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?</td>
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<tr>
<td>Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?</td>
</tr>
<tr>
<td>Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?</td>
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<table>
<thead>
<tr>
<th>Immunization anxiety</th>
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<tbody>
<tr>
<td>Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?</td>
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<table>
<thead>
<tr>
<th>III. Is there strong evidence against a causal association?</th>
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<tbody>
<tr>
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<tr>
<th>IV. Other qualifying factors for classification</th>
</tr>
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<tbody>
<tr>
<td>Could the event occur independently of vaccination (background rate)?</td>
</tr>
<tr>
<td>Could the event be a manifestation of another health condition?</td>
</tr>
<tr>
<td>Did a comparable event occur after a previous dose of a similar vaccine?</td>
</tr>
<tr>
<td>Was there exposure to a potential risk factor or toxin prior to the event?</td>
</tr>
<tr>
<td>Was there acute illness prior to the event?</td>
</tr>
<tr>
<td>Did the event occur in the past independently of vaccination?</td>
</tr>
<tr>
<td>Was the patient taking any medication prior to vaccination?</td>
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<tr>
<td>Is there a biological plausibility that the vaccine could cause the event?</td>
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ADVERSE EVENT FOLLOWING IMMUNIZATION

**Step 3: (Algorithm) Review all steps and ✓ all the appropriate boxes**

I. Is there strong evidence for other causes? ✓

- Yes, proceed to Step II.
- No, move to Step IV D. Unclassifiable.

II. Is there a known causal association with the vaccine/vaccination? ✓

- Yes, proceed to Step III.
- No, move to Step IV B. Indeterminate.

II (Time). Was the event within the time window of increased risk? ✓

- Yes, proceed to Step IV A.
- No, move to Step IV D. Unclassifiable.

III. Is there a strong evidence against a causal association? ✓

- Yes, proceed to Step IV.
- No, move to Step IV A.

IV. Review other qualifying factors

- Is the event classifiable? ✓

- Yes, move to Step IV B. Indeterminate.
- No, move to Step IV D. Unclassifiable.

Notes for Step 3:

- Summarize the classification logic with available evidence. With available evidence, we could conclude that the classification is ________________ because:

**Step 4: (Classification) ✓ all boxes that apply**

A. Consistent causal association to immunization

- Adequate information available
  - A1. Vaccine product-related reaction (As per published literature)
  - A2. Vaccine quality defect-related reaction
  - A3. Immunization error-related reaction
  - A4. Immunization anxiety-related reaction

- Adequate information not available

- Unclassifiable
  - Specify the additional information required for classification

B. Indeterminate

- B1. Temporary relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event)

C. Inconsistent causal association to immunization

- C. Coincidental
  - Underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine

**Feedback and corrective action recommended:**

*B1: Potential signal and maybe considered for investigation