



AIDE MEMOIRE

Purpose: This *aide-mémoire* serves as a guide to a systematic, standardized causality assessment process for serious adverse events following immunization (including clusters). It is intended to be used by staff at the national (or first sub-national) level.

AEFI causality assessment overview

All reported AEFIs require verification of the diagnosis, coding, review, collation and storage; if an AEFI is serious, it requires triage for systematic, standardized causality assessment. Many AEFIs, including serious ones, may be coincidental while others are well known to be vaccine related (e.g., oral polio vaccine-associated paralytic polio [VAPP]).

Causality assessment is the systematic review of data about an AEFI case to determine the likelihood of a causal association between the event and the vaccine(s) received.

Causality assessment is a critical part of AEFI monitoring and enhances confidence in national immunization programmes. Whether an AEFI is, or is not, attributable to the vaccine or the vaccination programme determines what, if any, steps need to be taken to address the event.

Causality assessment is important for:

- 1) identification of urgent problems for investigation/action;
- 2) identification of programmatic and batch problems;
- 3) detection of signals for potential follow up and research;
- 4) basis for estimation of rates of serious AEFIs;
- 5) comparison of AEFIs between vaccine products;
- 6) validation of pre-licensure AEFI data.

Causality assessment outcomes help raise awareness of vaccine-associated risks among health-care workers; this, combined with knowledge of benefits of immunization, forms the basis of vaccine information for parents and/or vaccinees.

The quality of the causality assessment depends upon (1) the quality of the AEFI case report and the effectiveness of the reporting system, and (2) the quality of the causality review process. Poor quality causality assessment can lead to erroneous conclusions, crises and loss of confidence in the national immunization programme.

Causality assessment of adverse events with vaccines versus drugs

Many safety monitoring systems deal with vaccines and drug products together yet there are important differences between them that affect causality assessment.

- **Vaccines** are given to healthy populations and mostly (infants) at a vulnerable age; they are elective, have a complex composition (biological products), immunological considerations in addition to pharmacological, may cause the illness they are meant to prevent (e.g., VAPP), have a short duration of exposure, a “long” time for response, and “minor” adverse events are important as they may indicate programme error.
- **Drugs** are given to ill populations and mostly adults, they are rarely elective, challenge/dechallenge/rechallenge, chemical products, pharmacological considerations mainly, longer exposure, many adverse events reported, many classes of drugs, and minor adverse events rarely important.

Expertise needed for causality assessment of vaccine adverse events is different from that needed for causality assessment of drug adverse events.

Routine AEFI review and triage

All AEFIs need to be screened and triaged by trained immunization programme staff to determine the subsequent steps needed (follow up, action, addition to database, analysis, reference for systematic causality assessment, etc.).

AEFI must be reviewed to verify the diagnosis and the timing with respect to immunization, and to classify them on the basis of standardized national case definitions.¹

¹ Standardized case definitions for some AEFIs are available from the Brighton Collaboration at (<http://www.brightoncollaboration.org>). Use of these definitions is encouraged, especially for serious cases where systematic standardized causality assessment is required.

Systematic causality assessment

All *serious AEFIs* and *signals*, defined below, require systematic causality assessment (see *Checklist, Section C, page 2*).

Serious AEFI¹:

- 1) WHO standard definition for drug and vaccine adverse events is “any untoward medical occurrence that results in death, hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity, or is life threatening”.
- 2) Additional AEFIs that need systematic causality assessment are:
 - AEFIs that may be caused by a programme error, e.g., a *cluster*² of bacterial abscesses;
 - serious *unexplained AEFI* occurring within 30 days after vaccination and not listed in product label;
 - events causing significant parental or community concern.

Signal: Reported information on possible causal relationship between AEFI and vaccine; relationship previously unknown or incompletely documented.

WHO categories for causality³

Use step-by-step guide (see *Checklist, Section C, page 2*) to determine category.

Very likely/Certain⁴: A clinical event with a plausible time relationship to vaccine administration and which cannot be explained by concurrent disease or other drugs or chemicals.

Probable: A clinical event with a reasonable time relationship to vaccine administration; is unlikely to be attributed to concurrent disease or other drugs or chemicals.

Possible: A clinical event with a reasonable time relationship to vaccine administration, but which could also be explained by concurrent disease or other drugs or chemicals.

Unlikely: A clinical event whose time relationship to vaccine administration makes a causal connection improbable, but which could be plausibly explained by underlying disease or other drugs or chemicals.

Unrelated: A clinical event with an incompatible time relationship and which could be explained by underlying disease or other drugs or chemicals.

Unclassifiable: A clinical event with insufficient information to permit assessment and identification of the cause.

¹ “Severe” is not synonymous with “serious”.

² A “cluster” is two or more AEFIs related in time, place and/or by vaccine.

³ Adapted for vaccines from original WHO categories available at <http://www.who-umc.org/indes2.html>

⁴ Can be certain in rare instances where there is a demonstrated relationship e.g., VAPP or mumps vaccine-related aseptic meningitis with isolation of the vaccine strain.

Checklist

A. Be prepared

- Develop a **centralized system** to verify diagnosis, review, code, collate, store reports and analyse AEFI data.
- Establish a **national (technical) advisory committee**. Ensure independence, breadth and depth of technical expertise needed for quality causality review. Provide administrative support to this committee.
- Adopt standard **case definitions** for AEFI (Brighton Collaboration definitions if available or national case definitions). Define **signal** for programme purposes.
- Define a **routine process** and adopt criteria for referral of AEFI cases for a systematic causality assessment by the committee.
- Define **frequency of meetings** for systematic causality assessment and triggers for exceptional (i.e., urgent) reviews.
- Develop a **process for action** on recommendations arising from causality assessment.

B. Receive and process reports at regional/national level

- Preliminary review of AEFI**: verify diagnosis, timing of event in relation to immunization, if event meets definition, if it fits criteria for referral for systematic standardized causality assessment (*see under Systematic causality assessment, page 1*). Code, collate, store reports and analyse data.
- For cases referred for systematic standardized causality assessment: verify case information and gather more data in a timely manner. Prepare case file for review, e.g., make information in the file anonymous.

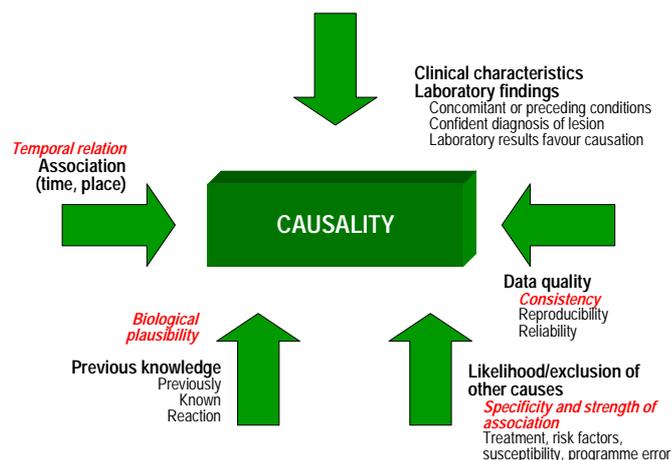
C. Conduct systematic standardized causality assessment using the step-by-step guide below

- 1. **Verify reason for reporting**: diagnosis; whether serious.
- 2. **Evaluate and assess factors**.
 - 2.1 Is this event known to be related to the vaccine? (**Consistency of findings, strength of association**.)
 - 2.2 What is the frequency of occurrence of this adverse event? Very common (>1/10); common (>1/100); uncommon (>1/1000); rare (>1/10 000); very rare (<1/10 000), or not previously reported.
 - 2.3 Are similar events known to occur with other diseases? (**Specificity of association**.)
 - 2.4 Is this event explainable by the biological properties of the vaccine? (**Biological plausibility**.)
 - 2.5 Is the vaccination-to-event interval compatible with the event? (**Temporal relation**.)
 - 2.6 Has the patient had similar symptoms in the past?
 - 2.7 Is there a history of concomitant or preceding drug therapy?
 - 2.8 Is there a history of a concomitant or preceding condition?
 - 2.9 Are there other factors that could affect the occurrence of the event?
- 3. **Determine causality category using WHO criteria** (*see page 1*).
 - 3.1 Is this an unknown event in relation to this vaccine?
 - 3.2 Is this a new event?
 - 3.3 Is there lack of sufficient data to reach a more definite conclusion?
 - 3.4 Would the case benefit from a second review if more data became available?
 - 3.5 Based upon answers to the questions above (in this Section), in which WHO category does the case fit best? N.B. not a numerical score.
- 4. **Prepare a brief case summary**.
- 5. **Take action on recommendation(s) from the review**.
- 6. **Consider the case for education purposes**.
- 7. **Communicate findings to immunization programme staff, national regulatory authority, and others (as appropriate)**.

D. Systematic causality assessment process for AEFI cluster

- Define case definition for cluster, verify if cases meet it.
- Conduct systematic causality assessment as per points 1–7 of section C above, including taking action.
- Determine if frequency of event is expected, increased, decreased, previously recognized or if it is a new event.

Causality assessment of serious AEFIs



Challenges and pitfalls to causality assessment

1. Causality assessment is not done, not systematic, not done by trained personnel and/or not done in a timely fashion.
2. Information in AEFI report is so limited that causality assessment cannot be done.
3. Lack of expertise and/or independence of the review committee responsible for formal causality assessment undermines credibility.
4. Non analysis of the AEFI in context after causality assessment may delay recognition of clusters and possible programme errors.
5. Lack of skilled communication of findings, not addressing all target audiences, or lack of diplomacy and/or cultural sensitivity.

All of these can damage the credibility of the immunization programme by reducing confidence in vaccine safety.

Words of advice

1. Ensure timely review of cases based on the best case information available: *solicit additional information on cases soon after receipt when memory is "fresh"*.
2. Ensure timely triage and referral of serious AEFI for expert systematic causality assessment.
3. Programme expertise is needed for credible quality review, assessment and analysis.
4. Act on recommendations following causality assessment to ensure programme safety and credibility.
5. Feedback and effective communication about the process and the outcomes to stakeholders and the media is vital to avoid misinterpretation.

Assistance for causality assessment is available from the World Health Organization through the Department of Immunization, Vaccines & Biologicals. Additional information on AEFI surveillance, investigation, management and causality assessment, and on vaccine safety communication can be found on the Web at http://www.who.int/immunization_safety/en/

Department of Immunization, Vaccines and Biologicals
World Health Organization
20 Avenue Appia, CH-1211 Geneva 27, Switzerland
Fax: +41 22 791 4210