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ADVERSE EVENT FOLLOWING IMMUNIZATION

AIDE-MÉMOIRE ON CAUSALITY ASSESSMENT

Purpose: This aide-mémoire serves as a guide to a systematic, standardized process of assessing whether serious adverse events following immunization (AEFI[1]) 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.

POSSIBLE CAUSES OF AEFI
Related to vaccine or vaccination
Vaccine product-related
Vaccine quality defect-related
Immunization error-related
Immunization anxiety-related
Coincidental adverse event

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**

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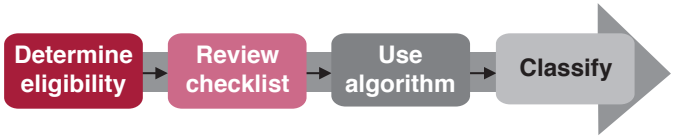
- **Signals** resulting from single or cluster cases
- Other AEFI as decided by the review committee or an investigation team such as **immunization errors**, significant **events of unexplained cause** occurring within 30 days after a vaccination (not listed in the product label), or events causing **significant parental or community concern.**

WHAT ARE THE STEPS[2] 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.



HOW ARE CASES CLASSIFIED AT THE END OF THE ASSESSEMENT?

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)

Underlying 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)

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.

A 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

Causality assessment of an AEFI - User manual for the revised WHO classification
http://www.who.int/vaccine_safety/publications/gvs_aefi/en/

WHO vaccine reaction rates information sheets
http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/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

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http://www.who.int/vaccine_safety/en/ E-mail: vaccsafety@who.int.

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Step 1 (Eligibility)

Name of the patient	Name of one or more vaccines administered before this event	What is the Valid Diagnosis? (The case diagnosis of the AEFI)	Does the diagnosis meet a case definition?

Create your question on causality here

Has the _____ vaccine/vaccination caused _____ ?(The event for review in step 2)

Step 2 (Event Checklist) [✔ check all boxes that apply]

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

Y: Yes. N: No. UK: Unknown. NA: Not applicable.

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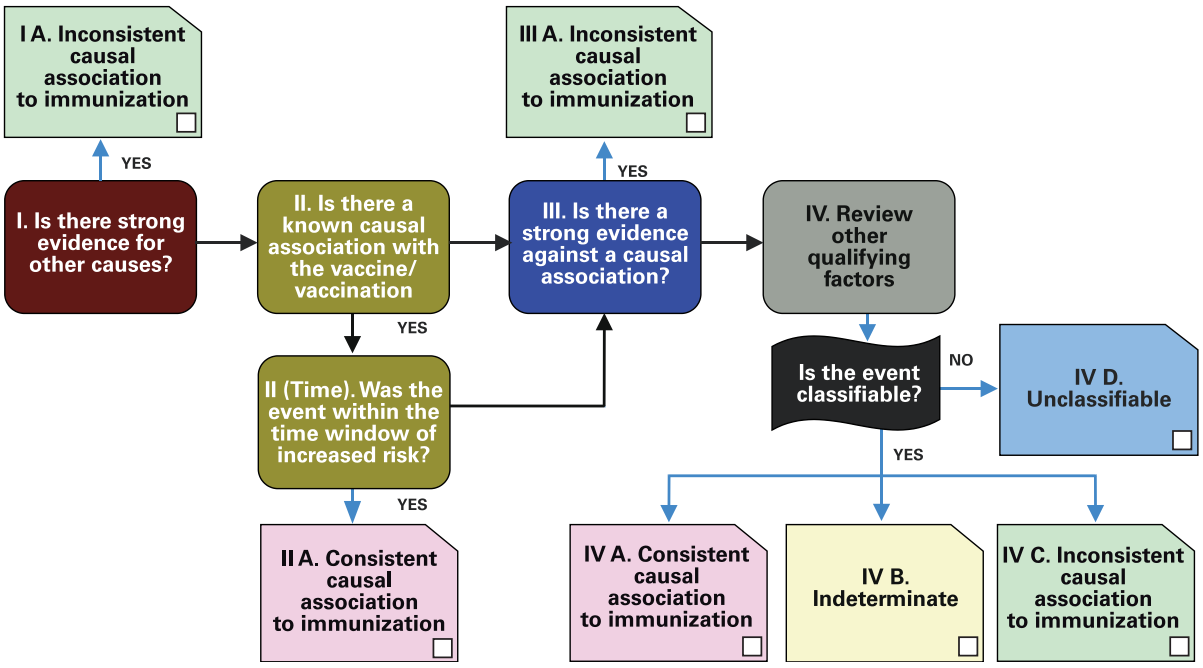
Step 3: (Algorithm) review all steps and ✓ all the appropriate boxes



Notes for Step 3:

Step 4: (Classification) ✓ all boxes that apply

	A. Consistent causal association to immunization	B. Indeterminate	C. Inconsistent causal association to immunization
Adequate information available	☐ A1. Vaccine product-related reaction (As per published literature) ☐ A2. Vaccine quality defect-related reaction ☐ A3. Imminization error-related reaction ☐ A4. Immunization anxiety-related reaction	☐ *B1. Temporary relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event) ☐ B2. Qualifying factors result in conflicting trends of consistency and inconstistency with causal association to immunization	☐ C. Coincidental Underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine
Adequate information not available	Unclassifiable ☐ Specify the additional information required for classification		

*B1: Potential signal and maybe considered for investigation

Summarize the classification logic

With available evidence, we could conclude that the classification is _____ because:

Feedback and corrective action recommended: