

Causality assessment of an adverse event following immunization (AEFI)

User manual for the revised WHO classification



**World Health
Organization**

**CAUSALITY ASSESSMENT
OF
AN ADVERSE EVENT FOLLOWING
IMMUNIZATION
(AEFI)**

**User manual for the revised WHO
classification**

WHO/HIS/EMP/QSS. MARCH 2013



WHO Library Cataloguing-in-Publication Data

Causality assessment of adverse event following immunization (AEFI): user manual for the revised WHO classification.

1. Adverse drug reaction reporting systems. 2. Immunization programs. 3. Vaccines – adverse effects. I. World Health Organization.

ISBN 978 92 4 150533 8

(NLM classification: QW 805)

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ACKNOWLEDGEMENT: The definitions and the concepts of this revised WHO AEFI Causality Assessment scheme have been largely adapted from *Definition and application of terms for vaccine pharmacovigilance. Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance*

(<http://www.cioms.ch/index.php/component/booklibrary/?task=view&Itemid=&id=45&catid=58>).

The protocol for the causality assessment of an adverse event following immunization (AEFI) has been developed by a subgroup of the Global Advisory Committee on Vaccine Safety (GACVS) that included Alberto Tozzi, Barbara Law, Brigitte Keller-Stanislowski, Edwin Asturias, Michael Gold, Jerry Labadie and Neal Halsey with inputs provided by Stephen Evans and Ananda Amarasinghe. The WHO secretariat supporting the work included Madhava Ram Balakrishnan and Patrick Zuber

PURPOSE: This user manual serves as a guide to a systematic, standardized global causality assessment process for serious adverse events following immunization (AEFI). It is intended to be used by staff at national level (such as members of national AEFI committees) and at subnational level, as well as immunization programme managers and others. It also serves as an educational tool for trainers and researchers and as a ready reference guide on AEFI causality assessment.

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Glossary

Adverse event following immunization (AEFI)	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.
Causal association	A cause-and-effect relationship between a causative factor and a disease with no other factors intervening in the process.
CISA	Clinical Immunization Safety Assessment Network.
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.
Cluster	Two or more cases of the same event or similar events related in time, geography, and/or the vaccine administered. National programme managers may decide upon a more precise definition.
Data mining	A field at the intersection of computer science and statistics that attempts to discover inapparent patterns in large data sets. Data mining utilizes methods at the intersection of artificial intelligence, machine learning, statistics and database systems. The overall goal of the data mining process is to extract information from a data set and transform it into an understandable structure for further use.
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization.
Immunization error-related reaction (formerly programmatic error)	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus, by its nature, is preventable.
Immunization safety	The public health practices and policies dealing with the various aspects of the correct administration of vaccines, focusing on minimizing the risk of transmission of disease with the injection and maximizing the effectiveness of the vaccine. The term encompasses the spectrum of events from proper manufacture to correct administration.
Minor AEFI	An event that is not “serious” and that has no potential risk to the health of the recipient of the vaccine.
Signal (safety signal)	Information (from one or multiple sources) which suggests a new and potentially causal association, or a new aspect of a known association, between an intervention and an event or set

of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

Surveillance	The continuing, systematic collection of data that is analysed and disseminated to enable decision-making and action to protect the health of populations.
Vaccine	A biological substance that is administered to individuals to elicit immunity (protection) against a specific disease.
Vaccination failure	Vaccination failure is based on clinical endpoints or immunological criteria, where correlates or surrogate markers for disease protection exist. Vaccination failure can be due to vaccine failure (either “primary” when immune response is inadequate or “secondary” when the immune response wanes) or failure to vaccinate (i.e. when an indicated vaccine was not administered appropriately for any reason).
Vaccine pharmacovigilance	The science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.
Vaccine product	All components of a given vaccine formulation, including the immunogen (part of the vaccine that stimulates an immune response) and others that may be present such as the adjuvant, preservative and other additives used during the manufacturing process to confirm product quality/stability (e.g. potassium or sodium salts, albumin, gelatin), support growth and purification of specific immunogens (e.g. egg or yeast proteins, antibiotic) or inactivate toxins (e.g. formaldehyde).
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, whether the active component or one of the other components of the vaccine (e.g. adjuvant, preservative or stabilizer).
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.

Acronyms

ADR	Adverse drug reaction
AEFI	Adverse event(s) following immunization
AFP	Acute flaccid paralysis
AIDS	Acquired immune deficiency syndrome
BCG	Bacille Calmette–Guérin
CIOMS	Council for International Organizations of Medical Sciences
DTP	Diphtheria, tetanus and pertussis (vaccine)
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barré syndrome
HIV	Human immunodeficiency virus
IPV	Inactivated poliovirus vaccine
ITP	Idiopathic thrombocytopenic purpura
LMIC	Low- and middle-income countries
MMR	Measles, mumps and rubella vaccine
OPV	Oral polio vaccine
SAE	Severe adverse event
VAPP	Vaccine-associated paralytic polio
WHO	World Health Organization

Introduction and rationale

Immunization is among the most successful and cost-effective public health interventions. It has led to the global eradication of smallpox as well as the elimination of poliomyelitis in regions of the world. Immunization currently averts an estimated 2 to 3 million deaths from diphtheria, tetanus, pertussis (whooping cough), and measles every year in all age groups.¹ More people than ever before are being reached with immunization. In 2011, in children under the age of one year, about 83% (an estimated 109 million infants) were vaccinated with three doses of diphtheria-tetanus-pertussis (DTP3) vaccine, about 84% (an estimated 110 million) with measles vaccine, and about 88% (an estimated 114 million) with the BCG vaccine.

Immunization safety has become as important as the efficacy of the national vaccine-preventable disease control programmes. Unlike drugs, the expectations from vaccinations are much higher and problems arising from the vaccine or vaccination are less acceptable to the general public. Vaccines are usually administered to healthy people, including entire birth cohorts of infants and in vast numbers. The settings in which they are administered vary from sophisticated tertiary care hospitals to primitive settings in remote, inhospitable and inaccessible terrain. In many countries, specific vaccinations are mandatory for school admission as well as international travel. The assessment, licensure, control and surveillance of biological medicinal products, including vaccines, are major challenges for national regulatory authorities confronted by a steadily increasing number of novel products, complex quality concerns, and new technical issues arising from rapid scientific advances.

The benefits of immunization are often not visible, particularly if the target disease incidence is low. In contrast, adverse effects that follow immunization are promptly noticeable, especially when the vaccinee was apparently healthy at the time of immunization. Although other factors may have contributed to or even been totally responsible for the event, they may not be considered or investigated. Fear of vaccine reactions, real or perceived, deters many people from undergoing vaccination. The problems of vaccine reaction and reluctance to be vaccinated have been known for many years in industrialized countries and are often raised after most of the benefits from immunization have been obtained. As immunization programmes have expanded in low- and middle-income countries (LMICs) in recent decades, the problems have become familiar there too.

Allegations that vaccines/vaccination cause adverse events must be dealt with rapidly and effectively. Failure to do so can undermine confidence in a vaccine and ultimately have dramatic consequences for immunization coverage and disease incidence long after proof is generated that the adverse event was not caused by vaccine (e.g. autism and MMR, encephalopathy and pertussis). On the other hand it must always be remembered that vaccines are not 100% safe and harm can result from errors in immunization practice. Thus vaccine-associated adverse reactions and error-related immunization events may affect healthy individuals and should be promptly identified for further response. Appropriate action(s) must be taken to respond promptly, efficiently, and with scientific rigour to vaccine safety issues. This will minimize adverse effects to the health of individuals and

¹ World Immunization Week 2012. Geneva, World Health Organization, 2012. See: http://www.who.int/immunization/newsroom/events/immunization_week/2012/further_information/en/index1.html (accessed 28 February 2013).

entire populations and in turn help to maximize the benefits of immunization programmes. Causality assessment of AEFI is thus a vital component of AEFI risk assessment, decision-making and the initiation of action.

Definitions of adverse events following immunization

A number of key terms used in this document are defined here for the sake of clarity.

General definition

Adverse event following immunization (AEFI): *This is* defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the use of the vaccine. The adverse event may be any unfavourable or unintended sign, an abnormal laboratory finding, a symptom or a disease.

Cause-specific definitions

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.

Vaccine quality defect-related reaction: An AEFI that is caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including the administration device, as provided by the manufacturer.

Immunization error-related reaction: An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and that thus, by its nature, is preventable.

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

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

The need for causality assessment of adverse events

Causality is the relationship between two events (the cause and the effect), where the second event is a consequence of the first. A direct cause is a factor in absence of which the effect would not occur (necessary cause). Sometimes there are multiple factors that may precipitate the effect (event) or may function as co-factors so that the effect (event) occurs. Many challenges are involved in deciding whether an adverse event is actually caused by a vaccine. Vaccines are often administered to children at ages when many underlying diseases become evident. Vaccines administered to adults can also coincide with an entirely different risk factor for an event. The fact that a vaccine was administered within a reasonable time period of the occurrence of an event does not automatically suggest that the vaccine caused or contributed to the event.

The evidence of a link between a vaccine as a potential cause and a specific event is derived from epidemiological studies that follow the scientific method and try to avoid biases and confounders. An example is a patient who is a smoker but also has a family history of breast cancer: is tobacco the cause of the cancer or only a co-factor? In the same way, to perform causality assessment in individual cases after vaccination, even where evidence for a causal link exists for some vaccines and AEFI (e.g. measles vaccine and thrombocytopenia), it is important to consider all possible explanations for the event and the degree of likelihood of each before attributing the event to the vaccine product, a vaccine quality defect, an error in the immunization process, immunization anxiety or coincidence.

AEFI causality assessment in practice

Causality assessment is the systematic review of data about an AEFI case; it aims to determine the likelihood of a causal association between the event and the vaccine(s) received. For individual cases, one tries to apply the evidence available on the basis of the history and time frame of the event to arrive at a causal likelihood. The quality of the causality assessment depends upon:

- the performance of the AEFI reporting system in terms of responsiveness, effectiveness and quality of investigation and reports;
- the availability of adequate medical and laboratory services and access to background information;
- the quality of the causality review process.

Causality assessment usually will not prove or disprove an association between an event and the immunization. It is meant to assist in determining the level of certainty of such an association. A definite causal association or absence of association often cannot be established for an individual event.

With inadequate or incomplete data, an AEFI can be deemed unclassifiable. However, it should also be noted that AEFI causality may be indeterminate due to lack of clear evidence for a causal link, or conflicting trends, or inconsistency with causal association to immunization. It is nevertheless important not to disregard the above reports of AEFI because at some point they may be considered a signal and may lead to hypotheses regarding a link between a vaccine and the event in question, with specific studies designed to test for a causal association. Pooling of data on individual cases is very helpful in

generating hypotheses. The case of rotavirus vaccine and intussusception is a good example. In 1998 a rotavirus vaccine (RotaShield®) was licensed for use in the USA. Initial clinical trials with the vaccine showed that it had been effective in preventing severe diarrhoea caused by rotavirus A, and researchers had detected no statistically significant serious adverse effects. After RotaShield® was licensed, however, some infants vaccinated developed intussusception. At first it was not clear if the vaccine or some other factor was causing the bowel obstructions. The results of investigations showed that RotaShield® vaccine caused intussusception in some healthy infants younger than 12 months of age who normally would be at low risk for this condition. The United States Advisory Committee on Immunization Practices (ACIP) voted on 22 October 1999 to no longer recommend use of the RotaShield® vaccine in infants because of an association between the vaccine and intussusception.¹

¹ See: <http://www.cdc.gov/vaccines/vpd-vac/rotavirus/vac-rotashield-historical.htm> (accessed 20 January 2013).

Levels of causality assessment and their scientific basis

Causality assessment of AEFI should be performed at several different levels. The first is the population level, where it is necessary to test if there is a causal association between the use of a vaccine and a particular AEFI in the population. Secondly, at the level of the individual AEFI case report, one should review previous evidence and make a logical deduction to determine if an AEFI in a specific individual is causally related to the use of the vaccine. The third level of assessment is in the context of the investigation of signals.

1. The population level

At the population level the aim is to answer the question “Can the given vaccine cause a particular adverse event?” (i.e. “Can it?”) Several criteria are relevant to establishing causality but only the first criterion is absolutely essential:

- Temporal relationship: The vaccine exposure must precede the occurrence of the event.
- Strength of association: The association should meet statistical significance to demonstrate that it was not simply a chance occurrence.
- Dose–response relationship: Evidence that increasing exposure increases the risk of the event supports the suggestion of a causal relationship. However, one should keep in mind that, in the case of vaccines, dose and frequency tend to be fixed.
- Consistency of evidence: Similar or the same results generated by studies using different methods in different settings support a causal relationship.
- Specificity: The vaccine is the only cause of the event that can be shown.
- Biological plausibility and coherence: The association between the vaccine and the adverse event should be plausible and should be consistent with current knowledge of the biology of the vaccine and the adverse event.

One should also consider the presence of systematic bias (analytic bias) in study methods as this weakens conclusions that a causal association exists.

The United States Institute of Medicine (IOM) has applied these criteria and has published literature that addresses (in detail) two critical questions in the revised WHO causality algorithm, namely: “Is there evidence in literature that this vaccine(s) may cause the reported event even if administered correctly?” and “Did the event occur within an appropriate time window after vaccine administration?”¹

WHO information sheets on observed rates of vaccine reactions that summarize known reactions to existing single antigen vaccines or combination products are available online.²

¹ The detailed document can be downloaded free at: <http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx> (accessed 23 February 2013).

² See: http://www.who.int/vaccine_safety/initiative/tools/Guide_Vaccine_rates_information_sheet_.pdf (accessed 23 February 2013).

2. The individual level

At the individual level it is usually not possible to establish a definite causal relationship between a particular AEFI and a particular vaccine on the basis of a single AEFI case report. However, it is important to try in order to identify a possible new vaccine product-related AEFI, as well as to determine if the event is preventable or remedial – such as a product-related quality defect or immunization error. Identifying a coincidental AEFI that is falsely attributed to a vaccine product is vital as otherwise the coincidence may result in loss of public confidence in the vaccine, with the consequent return of vaccine-preventable disease.

The aim of causality assessment at the individual level is to address the question “Did the vaccine given to a particular individual cause the particular event reported?” (i.e. “Did it?”). As noted, it is seldom possible to achieve a straightforward answer to this question, so in most cases the assessment involves systematic consideration of all possible causes of an AEFI in order to arrive at a conclusion that the evidence is consistent with the vaccine being a cause, or is inconsistent with this conclusion, or is indeterminate.

The scientific basis for the criteria which are assessed in the process include:

- Temporal relationship: The vaccine exposure must precede the occurrence of the event.
- Definitive proof that the vaccine caused the event: Clinical or laboratory proof that the vaccine caused the event is most often found for live attenuated vaccines. (For instance, in a case of aseptic meningitis after immunization with Urabe mumps vaccine virus, isolation of the Urabe virus from the cerebrospinal fluid is definitive proof that it caused the meningitis. Another example is isolation of the BCG agent from a focus of osteomyelitis.)
- Population-based evidence for causality – i.e. what is known about “Can it?”
 - A definitive “yes” at the population level is consistent with causality at the individual level.
 - A strong “no” at the population level is inconsistent with causality at the individual level.
 - If there is no clear answer to the question at the population level, this will often lead to an indeterminate conclusion at the individual level. If there are significant numbers of individual cases, however, this clearly points to the need to try to answer the question at the population level.
- Biological plausibility: In situations where the “Can it?” question has no clear “yes” or “no” answer, biological plausibility may provide support for or against vaccine causality. In other words, the association should be compatible with existing theory and knowledge related to how the vaccine works.
- Consideration of alternative explanations: In doing causality assessment on an individual case report, it must be remembered that in essence one is conducting a differential diagnosis. Thus it is important to consider “coincidental AEFI” – i.e. an AEFI due to something other than the vaccine product, immunization error or immunization anxiety. All reasonable alternative etiological explanations should be considered, including:
 - preexisting illness;
 - newly acquired illness;
 - spontaneous occurrence of an event without known risk factors;
 - emergence of a genetically programmed disease;

- other exposures to drugs or toxins prior to the event;
 - surgical or other trauma that leads to a complication;
 - a manifestation of, or complication of, a coincidental infection that was present before or at the time of immunization, or was incubating, but was not apparent at the time of immunization.
- Prior evidence that the vaccine in question could cause a similar event. The concept of “rechallenge”, which is more commonly used in the assessment of causality in medicines, has been helpful for certain vaccine event considerations (e.g. Guillain-Barré syndrome (GBS) after tetanus toxoid vaccination, where GBS occurred on three separate occasions in the same individual within weeks of administration of tetanus toxoid).

3. Investigation of signals

The assessment of whether a particular vaccine is likely to cause a particular AEFI takes into account all evidence from individual cases of AEFI, as well as surveillance data and, where applicable, cluster investigations and nonclinical data.

Case selection for causality assessment

The selection of cases for causality assessment should focus on:

- serious AEFI¹ that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect;
- the occurrence of events above the expected rate or of unusual severity;
- signals generated as a result of individual or clustered cases as these could signify a potential for large public health impact.

WHO recommends that other AEFI should also be assessed if the reviewing team or review committee decides that causality needs to be determined as a special case or in order to conduct special studies. Such AEFI could include:

- AEFI that may have been caused by immunization error (e.g. bacterial abscess, severe local reaction, high fever or sepsis, BCG lymphadenitis, toxic shock syndrome);
- significant events of unexplained cause occurring up to 30 days after a vaccination (and that are not listed on the product label);
- events causing significant parental or community concern (e.g. hypotonic hyporesponsive episode (HHE), febrile seizures).

Prerequisites for causality assessment

AEFI are usually reported through passive or stimulated passive surveillance, and less frequently from active surveillance systems. Timely reporting of AEFI followed by appropriate and detailed investigation is the key to successful causality assessment and signal detection. An AEFI report should fulfill three prerequisites before causality assessment, namely:

- The AEFI case investigation should have been completed. Premature assessments with inadequate information could mislead the classification of the event.
- All details of the case should be available at the time of assessment. Details should include documents pertaining to the investigation as well as laboratory and autopsy findings as appropriate.
- There must be a “valid diagnosis” (as explained below) for the unfavourable or unintended sign, abnormal laboratory finding, symptom or disease in question.

Who should do causality assessment?

To ensure that the prerequisite criteria described above are met and to ensure broader acceptance of the findings, causality assessment of AEFI should ideally be performed by a reviewing team or committee of reviewers from relevant specialties. However, in many countries and situations this broad level of expertise may not be available and existing human resources need to be used for the causality assessment of AEFI.

¹ *Definition and application of terms for vaccine pharmacovigilance. Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance.* Geneva, Council for International Organizations of Medical Sciences, 2012. See: <http://www.cioms.ch/index.php/component/booklibrary/?task=view&Itemid=&id=45&catid=58> (accessed 4 March 2013).

Countries requiring special technical expertise (such as special laboratory tests or training) in causality assessment should contact the respective WHO country office or WHO regional office. Assistance is also available from WHO at global level.¹

¹ Contact: Immunization, Vaccines and Biologicals, World Health Organization, 20 avenue Appia, 1211 Geneva 27, Switzerland. Tel: +41 22 791 4468; Fax: +41 22 791 4227; e-mail: vaccines@who.int. The web link is http://www.who.int/immunization_safety/en/.

Steps for causality assessment of an individual adverse event

The revised process envisages the causality assessment of an individual AEFI case in relation to a particular vaccine. If multiple vaccines are given simultaneously, the reviewers will have to assess causality separately for each suspected vaccine.

Causality assessment has four steps, as follows:

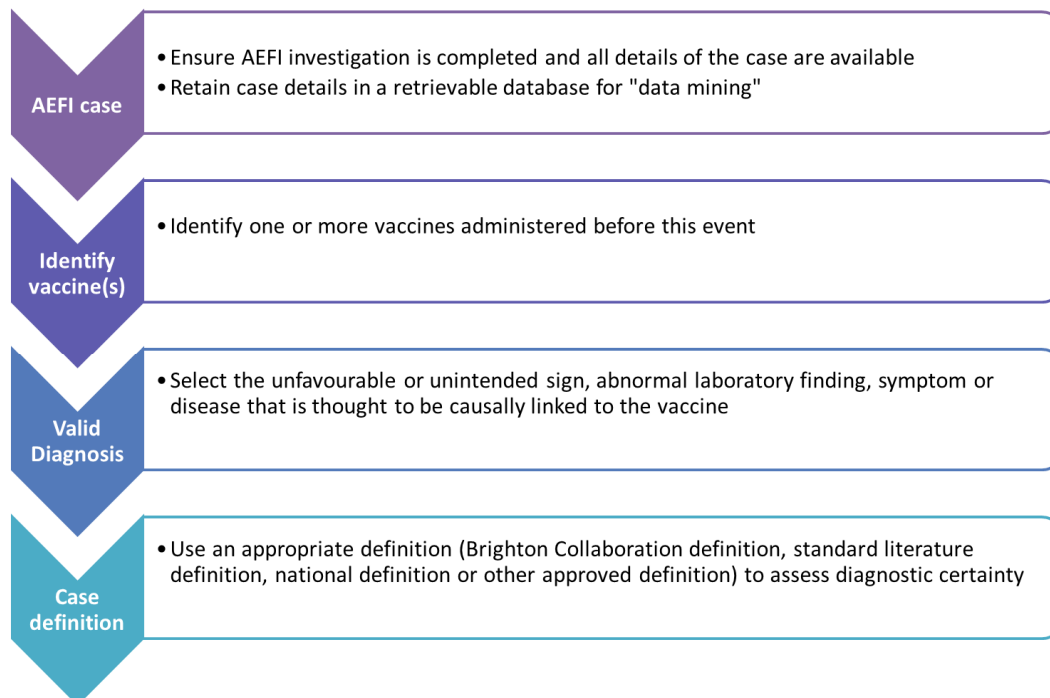
- Step 1: Eligibility. The first step aims to determine if the AEFI case satisfies the minimum criteria for causality assessment as outlined below.
- Step 2: Checklist. The second step involves systematically reviewing the relevant and available information to address possible causal aspects of the AEFI.
- Step 3: Algorithm. The third step obtains a trend as to the causality with the information gathered in the checklist.
- Step 4: Classification. The fourth step categorizes the AEFI's association to the vaccine or vaccination on the basis of the trend determined in the algorithm.

The worksheet used for the causality assessment of an individual AEFI case is presented in Annex 1. This can be used by the reviewers to arrive at a decision on causality.

Step 1: Eligibility

Before proceeding with causality assessment, it is necessary first to confirm that the vaccine was administered *before* the event occurred (Fig. 1). This can be ascertained by eliciting from the relevant informants a very detailed and careful history and physical findings. It is also essential to have a valid diagnosis for the reported AEFI, which could be an unfavourable or unintended sign, an abnormal laboratory finding, a symptom or a disease.

Fig. 1. Causality assessment – Eligibility



The valid diagnosis refers to the extent to which the unfavourable or unintended sign, abnormal laboratory finding, symptom or disease is defined, and whether it is well founded and corresponds accurately to the event being assessed. Validity can help determine what types of tests and tools to use, and can help to make sure that the methods used are not only correct but that they also truly measure the event in question.

For instance, a diagnosis of “altered consciousness” can be defined by a spectrum of terms by various observers. Among such terms are: clouding of consciousness, confusional state, delirium, lethargy, stupor, dementia, hypersomnia, vegetative state, coma and brain death. Many of these terms mean different things to different people.¹ For a reliable and objective means of recording a person’s conscious status, the clinician uses a standard tool such as the Glasgow Coma Scale.

The valid diagnosis should meet a standard case definition (or it could also be a syndromic case definition). If available, it is best to adopt the Brighton Collaboration case definition which can be accessed online.² However, when a valid diagnosis exists but a case definition does not, case definitions can be adopted from standard medical literature or national guidelines, or may also be adopted locally by the reviewers. If the reported event does not have a valid diagnosis, the AEFI cannot be classified and additional information should be collected to arrive at a valid diagnosis.

At this stage it is also essential for the reviewers to define the “causality question” (Fig. 2). Examples of causality questions are:

- “Has the vaccine A caused hepatomegaly?” (an example of an unfavourable or unintended sign).
- “Has the vaccine B caused thrombocytopenia?” (an example of a laboratory finding).
- “Has the patient complained that the vaccine C caused itching and redness?” (an example of a symptom).
- “Has the vaccine D caused meningitis?” (an example of a disease).

Fig 2. Causality question

Create your question on causality here:

Has the _____ vaccine / vaccination caused _____?

(The event for review in step 2)

It is important that, if an AEFI is reported and does not meet the eligibility criteria, attempts should be made to collect additional information to ensure that the criteria are met. Additionally, all cases reported (including ineligible cases) should be stored in a repository (preferably electronic) so that they can be accessed when additional information becomes available through reports of similar cases or through periodic data mining.

Step 2: Checklist

The checklist (Table 1) contains elements to guide the reviewers as they collate the evidence needed for a case review.

¹ Tindall SC. Level of consciousness. Chapter 57 in: Walker HK, Hall WD, Hurst JW. *Clinical methods. The history, physical, and laboratory examinations*, 3rd edition. Boston, MA, Butterworths, 1990.

² See: <https://brightoncollaboration.org/public> (accessed 23 February 2013).

Table 1. The causality assessment checklist

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

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

The checklist is designed to assemble information on the patient-immunization-AEFI relationship in the following key areas:

- evidence for other causes;
- association of the event and the vaccine/vaccination with the vaccine product(s), immunization error or immunization anxiety (if there is an association, it is important to find out if the event occurred within an appropriate time window);
- evidence against a causal association;

- other qualifying factors for classification such as the background rate of the event, present and past health condition, potential risk factors, medication, biological plausibility etc.

The checklist and the questions are described in detail in Table 1, with some illustrative examples. It will be observed that sometimes the responses could be applicable to multiple questions; therefore it is essential that the “Remarks” column is used to explain the reasons. Please note that the list of examples and illustrations provided are not exhaustive.

I. Is there strong evidence for other causes?

In judging whether a reported association is causal, it is necessary to determine the extent to which researchers have taken other possible explanations into account and have effectively ruled out such alternative explanations.

Does a clinical examination or laboratory tests on the patient confirm another cause?

Clinical examination and laboratory tests may help to identify other conditions such as other diseases and congenital anomalies that could have caused the event. For example:

The death of a teenage girl in the United Kingdom following vaccination with the human papilloma virus (HPV) vaccine was initially attributed to the vaccine. A post-mortem found it to be due to a malignant mediastinal tumour.¹

- Japanese encephalitis vaccine was blamed for a viral encephalitis outbreak in Uttar Pradesh, India in 2007. Investigations (into the seasonality as well as the epidemiological, clinical and laboratory profile of cases) later proved that accidental consumption of the *Cassia occidentalis* beans by the children concerned was responsible for the disease which was not encephalitis as initially believed but a syndrome of acute hepato-myoenkephalopathy.²

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

Most vaccine adverse events are minor and temporary, such as a sore arm or mild fever. More serious adverse events occur rarely (of the order of one case per thousands of doses to one case per millions of doses), and some are so rare that risk cannot be accurately assessed. Most AEFI, and particularly those related to vaccines that have been used for several decades, are available in the literature. WHO information sheets on rates of vaccine reactions are available online.³ It is important to be alert in order to detect new events (signals). AEFI may be related to the vaccine product, immunization error or immunization anxiety.

Vaccine product(s)

Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?

It is rare for vaccines to produce adverse events due to the vaccine’s inherent properties when administered correctly. However, such cases have occurred. For example:

¹ See *HPV vaccine in the clear* at: <http://www.nhs.uk/news/2009/09September/Pages/Cervical-cancer-vaccine-QA.aspx> (accessed 23 February 2013).

² *Cassia occidentalis* toxicity causes recurrent outbreaks of brain disease in children in Saharanpur. *Indian Journal of Medical Research*, 2008, 127:413–414. See: <http://icmr.nic.in/ijmr/2008/april/0421.pdf> (accessed 23 February 2013).

³ See: http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/index.html (accessed 23 February 2013).

- An extremely rare adverse event associated with OPV use is the vaccine-associated paralytic poliomyelitis (VAPP), which may occur in vaccine recipients or their contacts. The overall risk of VAPP is estimated at between 1 and 2.9 cases per million doses of trivalent OPV administered.

A causal association between measles–mumps–rubella (MMR) vaccine and idiopathic thrombocytopenic purpura (ITP) was confirmed using immunization/hospital admission record linkage. The absolute risk within six weeks of immunization was 1 in 22,300 doses.¹

Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?

- As an example, aseptic meningitis has been known to be a complication of mumps vaccination. Among 630 157 recipients of trivalent MMR vaccine containing the Urabe Am9 mumps vaccine, there were at least 311 meningitis cases suspected to be vaccine-related. In 96 of these 311 cases, Urabe Am9 mumps vaccine virus was isolated from cerebrospinal fluid.²

Immunization error

Immunization error describes an AEFI that is caused by inappropriate vaccine handling, prescribing or administration and that therefore, by its nature, is preventable. In many countries most AEFI are precipitated by immunization error. In such situations, immunization error has to be ruled out first during an AEFI investigation. An immunization error-related reaction may lead to a solitary event or a cluster of events associated with immunization.

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, wrong diluent etc.)?

It is essential that vaccines are used in accordance with the indications, contraindications, dosage, storage conditions, reconstitution procedures etc. outlined in the package insert. Each vaccine from a different manufacturer may have different specifications and failure to comply with them can result in AEFI. For example:

- systemic and/or local reactions following administration of an incorrect dose;
- systemic and/or local reactions following administration of the wrong product or administration to an individual in an incorrect age group;
- vaccine failure if a live attenuated product is given too soon after blood products or at an age when maternally transferred antibody could interfere with the replication required to induce an immune response

Was the vaccine (or any of its ingredients) administered unsterile?

Children immunized with contaminated vaccine (usually the bacterium *Staphylococcus aureus*) become sick within a few hours. Local tenderness and tissue infiltration, vomiting, diarrhoea, cyanosis and high temperature are the most frequent symptoms (toxic shock syndrome). Bacteriological examination of the vial, if still available, or of local tissue can confirm the source of the infection.³

¹ Miller E et al. Idiopathic thrombocytopenic purpura and MMR vaccine. *Archives of Disease in Childhood*, 2001, 84:227–229 (doi:10.1136/adc.84.3.227)

² Sugiura A. Aseptic meningitis as a complication of mumps vaccination. *Pediatric Infectious Disease Journal*, 1991, 10(3):209–213. See: <http://www.ncbi.nlm.nih.gov/pubmed/2041668> (accessed 23 February 2013).

³ Simon PA et al. Outbreak of pyogenic abscesses after diphtheria and tetanus toxoids and pertussis vaccination. *Pediatric Infectious Disease Journal*, 1993, 12(5):368–371. See: <http://www.ncbi.nlm.nih.gov/pubmed/8327295> (accessed 23 February 2013).

Was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal at the time of administration?

Abnormal colour, turbidity or presence of visible contaminants may be the first indication that the vaccine contents are abnormal and may have caused the AEFI.

Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?

AEFI have resulted because of accidental use of the wrong product or the wrong diluent. This may occur because of improper storage and/or improper selection.¹ Vaccine failure can result if the entire content is not dissolved when freeze-dried vaccines are used or if the cold chain is not maintained properly. Errors in drawing up vaccine into syringes may result in AEFI due to excess filling or vaccine failure due to inadequate filling.

Was there an error in vaccine handling (e.g. a break in cold chain during transport, storage and/or immunization session etc.)?

Exposure to excess heat or cold as a result of inappropriate transport, storage or handling of the vaccine (and its diluent where applicable) may result in:

- vaccine failure as a result of inactivation of the active vaccine components;
- systemic or local reactions due to changes in the physical nature of the vaccine, such as agglutination of aluminium-based excipients in freeze-sensitive vaccines.

Reconstituted vaccines used beyond the prescribed time and recommended maintenance conditions can result in vaccine failure and/or disease in the recipient (e.g. toxic shock syndrome).

Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?

A variety of AEFI may result from incorrect administration of a vaccine. For example:

- neurological, muscular, vascular or bone injury from the use of an incorrect injection site, equipment or technique;
- systemic and/or local reactions following administration of an incorrect dose;
- sterile abscess following subcutaneous instead of intramuscular injection of alum adjuvanted vaccines – usually a result of using a needle that is too short to reach the muscle layer.

Immunization anxiety

Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?

The types of reactions caused by immunization anxiety include, but are not limited to, vasovagal-mediated reactions, hyperventilation-mediated reactions or stress-related psychiatric disorders. For example:

- In September 1998, more than 800 young people in Jordan believed they had suffered from the side-effects of tetanus-diphtheria toxoid vaccine administered at school; 122 of them were admitted to hospital. For the vast majority of the young people, the symptoms did not result from the vaccine but arose from mass psychogenic illness. A review of the literature showed, however, that this mass

¹ Bundy DG et al. Pediatric vaccination errors: application of the "5 rights" framework to a national error reporting database. *Vaccine*, 2009, 27(29):3890–3896 (Epub 2009 Apr 23). See: <http://www.ncbi.nlm.nih.gov/pubmed/19442422> (accessed 23 February 2013).

reaction was similar in many ways to previous outbreaks, even though the underlying causes varied.¹

Adolescents, especially if immunized in mass clinical settings, are more prone to have anxiety-related vasovagal reactions resulting in fainting, sometimes accompanied by tonic-clonic seizure-like movements (not a seizure).²

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?

It is important to confirm if the event took place in an “appropriate” time window of increased risk. This is applicable to all questions under II. For example:

- The “appropriate” time window for VAPP is between 4 and 40 days. A case classified as a recipient VAPP is a person who has onset of acute flaccid paralysis (AFP) 4–40 days after receiving OPV, isolating Sabin virus and with neurological sequelae compatible with polio 60 days after the onset of paralysis.³ Thus cases with AFP onset less than 4 days or over 40 days after receiving OPV and isolating Sabin virus in the stool are not classified as recipient VAPP.

III. Is there strong evidence against a causal association?

Is there strong evidence against a causal association?

An AEFI that is initially thought to be due to a vaccine may, after investigation, be found to be explained by a similar manifestation caused by another factor. For example:

- In recent years, some researchers hypothesized that measles vaccine may be associated with autism. A series of studies were reviewed by the GACVS and also the IOM Committee to review adverse effects of vaccines. Both groups concluded that no evidence exists of a causal association between MMR vaccine and autism or autistic disorders.^{4 5}

IV. Other qualifying factors for classification

Sections I to III outline the strong evidence for or against causality for most cases of AEFI. Below are some additional factors that support the above observations. If the AEFI is still unclassified, these qualifying factors provide reviewers with indications on causality.

Could the event occur independently of vaccination (background rate)?

¹ Kharabsheh S et al. Mass psychogenic illness following tetanus-diphtheria toxoid vaccination in Jordan. *Bulletin of the World Health Organization*, 2001, 79(8):764–770. See: <http://www.who.int/docstore/bulletin/pdf/2001/issue8/vol79.no.8.764-770.pdf> (accessed 23 February 2013).

² Syncope after vaccination – United States, January 2005–July 2007. *Morbidity and Mortality Weekly Report*, 2008, 57(17):457–460. See: <http://www.ncbi.nlm.nih.gov/pubmed/18451756> (accessed 23 February 2013).

³ *Case definition: poliomyelitis*. Pan American Health Organization. See: <http://www.paho.org/english/ad/fch/im/PolioCaseDefinition.htm> (accessed 23 February 2013).

⁴ *MMR and autism*. World Health Organization. See: http://www.who.int/vaccine_safety/topics/mmr/mmr_autism/en/ (accessed 23 February 2013).

⁵ *Adverse effects of vaccines: evidence and causality*. United States Institute of Medicine. See: <http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx> (accessed 23 February 2013).

Knowledge of the background incidence of events which may occur in temporal relationship with a vaccine is essential for assessing a cluster of events in terms of the strength of the signal it may provide. For example:

- In Israel, during the early phases of the annual influenza immunization campaign in October 2006, four deaths occurred among elderly vaccinees and the campaign was temporarily halted for an investigation. It was determined that the expected death rate among similarly aged vaccinees within seven days of a vaccine exposure was 0.01 to 0.02% and this rate had been constant for several years prior to the apparent signal. The background rate for death in the population was relatively high as a result of age (>75 years) and comorbid conditions (e.g. diabetes, cardiovascular disease, homebound status).¹
- The importance of understanding background rates of disease prior to a mass campaign were pointed out in a study published in October 2009. This provides many examples of how background rates can impact on temporally associated AEFI observed during immunization campaigns.²

Could the event be a manifestation of another health condition?

It is important to consider other health conditions that may have precipitated the AEFI. For example:

- Glutaric aciduria type I, a rare inborn error of metabolism, was identified after magnetic resonance imaging in monozygotic twin females with glutaric aciduria type I who were admitted with acute encephalopathic crisis symptoms three days after immunization for poliovirus.³

Did a comparable event occur after a previous dose of a similar vaccine?

The occurrence of an AEFI after a previous dose of a similar vaccine should be handled cautiously. In specialized settings, vaccination schedules can continue taking appropriate precautions. For example:

- Revaccinations have to be avoided in patients with a history of anaphylaxis after vaccine injection because of the potential risk of recurrent anaphylaxis. However, without diagnostic work-up, vaccine allergy remains a presumption and necessary vaccinations may be unjustifiably withheld. Diagnostic testing should be performed after suspected vaccination-induced anaphylaxis in order to rule out IgE-mediated allergy to the incriminated vaccine and its constituents and to enable future vaccinations with the tested compounds. Therefore, a history of anaphylaxis after vaccination may not be an absolute contraindication for revaccination.⁴

¹ Kokia ES et al. Deaths following influenza vaccination – background mortality or causal connection? *Vaccine*, 2007, 25(51):8557–8561. See: <http://www.ncbi.nlm.nih.gov/pubmed/18006121> (accessed 23 February 2013).

² Black et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. *Lancet*, 2009, 374:2115–2122. See: <http://download.thelancet.com/flatcontentassets/H1N1-flu/vaccination/vaccination-86.pdf> (accessed 23 February 2013).

³ Alkan A et al. Glutaric aciduria type I diagnosed after poliovirus immunization: magnetic resonance findings. *Pediatric Neurology*, 2002, 26(5):405–407. See: <http://www.ncbi.nlm.nih.gov/pubmed/12057806> (accessed 23 February 2013).

⁴ Seitz CS et al. Vaccination-associated anaphylaxis in adults: diagnostic testing ruling out IgE-mediated vaccine allergy. *Vaccine*, 2009, 27(29):3885–3889. See: <http://www.ncbi.nlm.nih.gov/pubmed/19428162> (accessed 23 February 2013).

- Revaccination of children who have a past history of an AEFI appears safe (with the exception of anaphylaxis and encephalopathy). A special immunization service should be part of a comprehensive immunization programme.¹

Was there exposure to a potential risk factor or toxin prior to the event?

Prior exposure to risk factors/toxins may be a clue to the possibility that an AEFI is a coincidental event. One should also consider the possibility of an interaction between a risk factor/toxin and vaccine in causing the AEFI. For example:

- A patient who undergoes a surgical procedure a week prior to vaccination (with an apparently normal post-operative period), may present with fever the day after immunization. One needs to determine if the fever (which is an AEFI) is a coincidental event (to vaccination) that occurred as a late complication of surgery or if it is due to the vaccine or vaccination (product-related, quality defect-related, or immunization error-related).
- An AEFI involving hair loss in a patient on chemotherapy who was given HBV vaccine may be a coincidental event due to the chemotherapy or may be a vaccine product-related reaction following immunization with HBV vaccine.
- Accidental ingestion and drug interaction are known causes of carbamazepine toxicity. Less well recognized is the possibility that influenza vaccination may significantly increase carbamazepine blood levels.²

Was there acute illness prior to the event?

About a quarter of patients with Guillain-Barré syndrome have had a recent *Campylobacter jejuni* infection.³ A prior history of a diarrhoeal illness a week or two before vaccination may be a clue that the GBS is a coincidental event relative to immunization because it was due to the same agent that caused the diarrhoeal illness prior to vaccination.

Did the event occur in the past independently of vaccination?

It is important to verify if a similar event occurred in the vaccinee and family in the past independent of immunization. For example:

- A 24-month-old child receives MMR immunization. Seven days later her pediatrician poses a diagnosis of atopic dermatitis. A careful clinical history, however, reveals that the child had signs of atopic dermatitis since five months of age.⁴

Was the patient taking any medication prior to vaccination?

¹ Gold M et al. Re-vaccination of 421 children with a past history of an adverse vaccine reaction in a special immunization service. *Archives of Disease in Childhood*, 2000, 83:128–131 (doi:10.1136/adc.83.2.128). See: <http://www.ncbi.nlm.nih.gov/pubmed/10906018> (accessed 23 February 2013).

² Robertson WC Jr. Carbamazepine toxicity after influenza vaccination. *Pediatric Neurology*, 2002, 26(1):61–63. See: <http://www.sciencedirect.com/science/article/pii/S0887899401003320> (accessed 23 February 2013).

³ Hughes RAC et al. Guillain-Barré syndrome. *Lancet*, 2005, 366(9497):1653–1666.

⁴ Hennino A et al. Influence of measles vaccination on the progression of atopic dermatitis in infants. *Pediatric Allergy and Immunology*, 2007, 18:385–390. See: <http://www.ncbi.nlm.nih.gov/pubmed/17617807> (accessed 23 February 2013).

Medications are known to cause adverse reactions and, when given concurrently with vaccine(s), must be considered as possible causes of an observed AEFI. For example

- Stevens-Johnson syndrome that occurs nine days after vaccination in an individual on a sulfa antibiotic could be a coincidental event (due to the sulfa drug) or a vaccine product-related reaction (due to the vaccine)

Is there a biological plausibility that the vaccine could cause the event?

Biological plausibility – or biological mechanisms as an additional qualifying factor – can be invoked only when a laboratory finding or a symptom/sign are similar and consistent with the natural history and physiopathology of the infection or antigen. Evidence regarding biological plausibility, however, can never prove causality. At best, biological plausibility adds an additional piece of supportive evidence. For example:

- Acute cerebellar ataxia is a proven complication of wild type varicella zoster virus (VZV) infection with an estimated incidence of five per 100 000 infections among children aged five years and under.¹ Since the wild virus causes acute cerebellar ataxia, it is biologically plausible that the attenuated vaccine virus could also result in this complication of VZV infection in certain vaccinees. However, existing evidence is still not sufficient to confirm or reject this hypothesis so it remains a theoretical possibility based on biological plausibility.²
- Some attenuated mumps vaccines, like mumps disease, are associated with aseptic meningitis. The lack of a standardized clinical case definition of aseptic meningitis and criteria for CSF evaluation complicates the interpretation of available data and may increase the probability of higher “case” ascertainment influenced by factors other than the vaccine strain.³

Step 3: Algorithm

After the checklist is completed, the AEFI case is ready to be applied to the algorithm. The algorithm aims to be a roadmap for the decision-making of the reviewers but it does not, and should not, take away the expert and deductive logical process inherent in linking a diagnosis to its potential cause. The stepwise approach of the algorithm helps to determine if the AEFI could be consistent or inconsistent with an association to immunization, an indeterminate outcome or unclassifiable (Fig. 3).

The algorithm allows the reviewers to focus logically and document their observations to the appropriate conclusions. “Yes” responses in the checklist should have corresponding conclusions in the algorithm. The boxes on the mandatory path correspond to the four major sections in the checklist (I to IV). It is essential that the reviewers evaluate all four boxes using the responses in the checklist. The conclusions are colour-coded green if the conclusion is inconsistent with a causal association to immunization; red if it is consistent with a causal association to immunization; yellow if it is indeterminate; and blue if the event is unclassifiable.

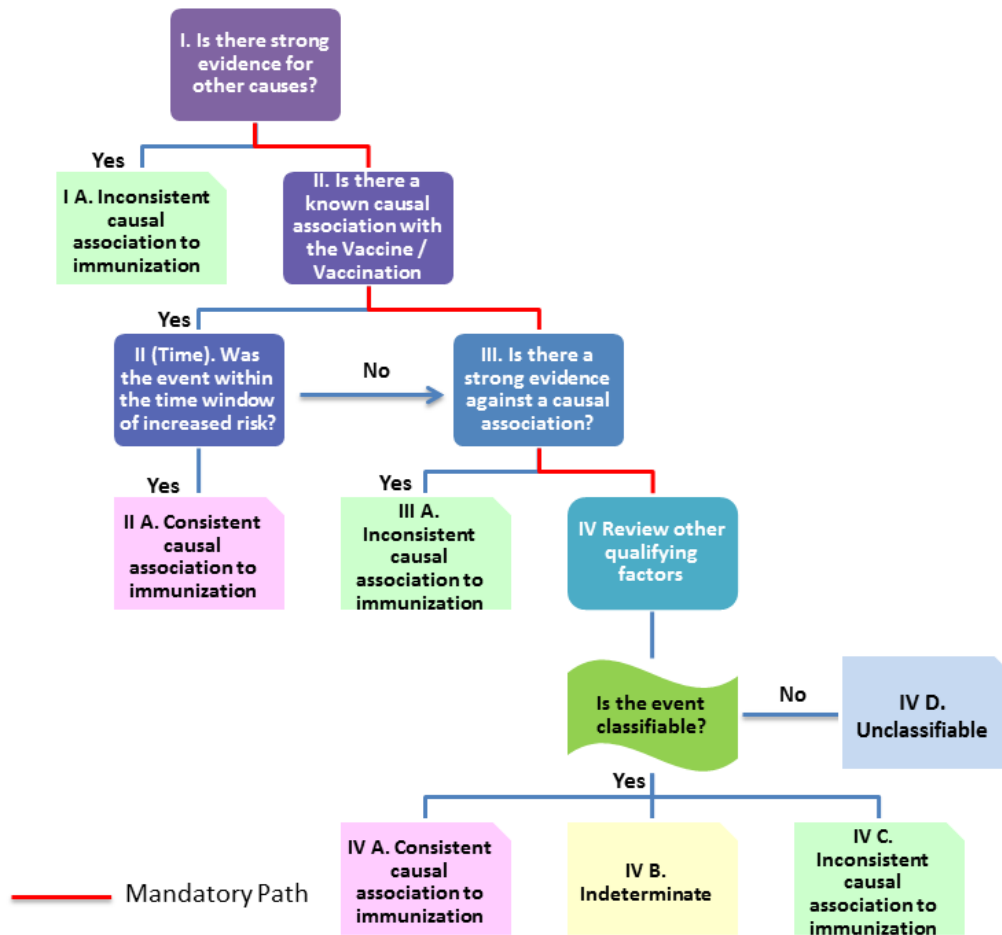
¹ Van der Maas NA et al. Acute cerebellar ataxia in the Netherlands: a study on the association with vaccinations and varicella zoster infection. *Vaccine*, 2009, 27(13):1970–1973 (Epub 2009 Jan 30). See: <http://www.ncbi.nlm.nih.gov/pubmed/19186201> (accessed 23 February 2013).

² Institute of Medicine. *Adverse effects of vaccines: evidence and causality*. Washington, DC, National Academies Press, 2012. See: http://www.nap.edu/catalog.php?record_id=13164 (accessed 23 February 2013).

³ Bonnet M-C et al. Mumps vaccine virus strains and aseptic meningitis. *Vaccine*, 2006, 24(49–50):7037–7045. See: <http://dx.doi.org/10.1016/j.vaccine.2006.06.049> (accessed 23 February 2013).

Summarizing the responses in the checklist adjacent to the corresponding conclusion or as a summary note at this point will enable the reviewers to have a transparent “dashboard view” of their conclusions and the logic for arriving at them.

Fig. 3. Causality assessment algorithm



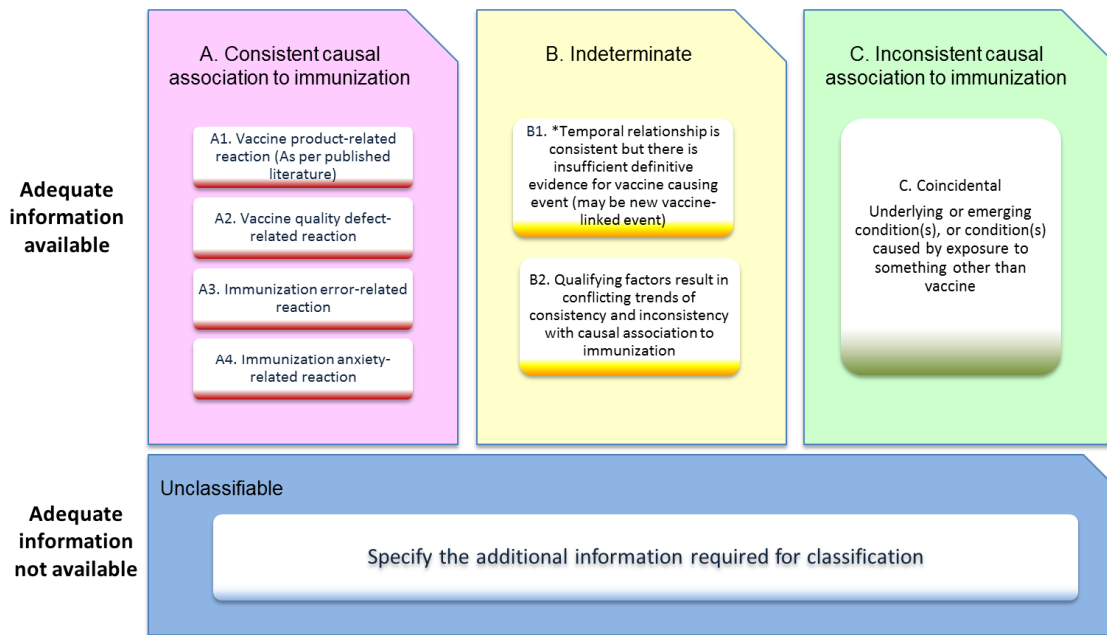
Responses IA, IIA and IIIA have greater strength and these conclusions have greater weight. When the conclusion is “unclassifiable”, the reviewers should determine the reasons why classification was not possible and all attempts should be made to obtain the necessary supporting evidence for classification.

Step 4: Classification

The final classification has been adapted from *Definition and application of terms for vaccine pharmacovigilance. Report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.*¹ The cause-specific definitions provide clarity on “A. Consistent causal association to immunization” and “C. Inconsistent causal association to immunization” (coincidental). The association is considered “B. indeterminate” when adequate information on the AEFI is available but it is not possible to assign it to either of the above categories. The details are presented in Fig. 4.

Fig 4. Causality assessment classification

¹ *Definition and application of terms for vaccine pharmacovigilance. Report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.* Geneva, Council for International Organizations of Medical Sciences, 2012.



*B1 : Potential signal and maybe considered for investigation

The final classification is based on the availability of adequate information.

I. Case with adequate information for causality conclusion

A case with adequate information for causality conclusion can be classified as follows:

A. Consistent causal association to immunization

- A1. Vaccine product-related reaction; or
- A2. Vaccine quality defect-related reaction; or
- A3. Immunization error-related reaction; or
- A4. Immunization anxiety-related reaction.

B. Indeterminate

- B1. Temporal relationship is consistent but there is insufficient definitive evidence that vaccine caused the event (it may be a new vaccine-linked event). This is a potential signal and needs to be considered for further investigation.
- B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization (i.e. it may be vaccine-associated as well as coincidental and it is not possible clearly to favour one or the other).

C. Inconsistent causal association to immunization (coincidental): This could be due to underlying or emerging condition(s) or conditions caused by exposure to something other than vaccine.

II. Case without adequate information for causality conclusion

This case is categorized as “unclassifiable” and requires additional information for further review of causality. The available information on unclassifiable cases should be placed in a repository or an electronic database which should be periodically reviewed to see if additional information is available for classification and to perform analyses for identifying signals.

Summarizing the logic of causality

Causality assessment is performed with the available information and resources that are at the reviewers' disposal at a given point in time. The information and resources may be adequate or inadequate. If the information is inadequate, causality assessment is not possible. Even with adequate information, the precision of causality is largely determined by the expertise, experience and skill of the reviewers (Fig. 5). Different cases, when systematically reviewed, may reveal conflicting findings that have to be debated by a group of experts before a clearer picture of causality emerges. It is possible that there may be more than one conclusion on causality by the same reviewers.

Fig. 5. Summary of classification logic

<p>Summarize the classification logic:</p> <p><i>With available evidence, we could conclude that the classification is _____ because:</i></p>

The categories “Consistent causal association to immunization” and “Inconsistent causal association to immunization” (coincidental) are clearly outlined in the *Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance*¹ and are described below. With available evidence, several cases would be classified as “indeterminate”. This must be discussed by the assessment team to determine if there is a signal or if additional investigation or special tests are needed.

Causality can change when additional information becomes available either about the same case or about similar cases. Resource constraints such as non-availability of autopsy facilities and special laboratory tests (such as the tryptase test as an indicator of mast cell activation in anaphylaxis) can modify interpretations.

¹ *Definition and application of terms for vaccine pharmacovigilance. Report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.* Geneva, Council for International Organizations of Medical Sciences, 2012.

Underlying mechanisms for the classification of adverse events

A. Consistent causal association to immunization

A1 and A2. Vaccine product-related and vaccine quality defect-related reactions

Vaccines are designed to induce a response by the immune system which involves a complex interaction between the vaccine antigens, the adjuvant (if present), antigen-presenting cells, lymphocytes and multiple immune mediators (cytokines). This interaction is important to the development of the desired immunity against the specific vaccine-preventable disease. However, the immune response in a vaccinee may manifest as relatively common and mild adverse reactions to the vaccine(s), such as redness and swelling at the injection site, or fever. Homeostatic mechanisms usually limit the inflammatory response so that such reactions are short-lived and have no lasting consequence. Uncommonly, the immune response to one or more vaccine components may result in a longer-lasting and more severe adverse reaction. Rarely, the immune response may cause a life-threatening allergic reaction.

It is important to note that vaccine product-related reactions may unmask a predisposition in certain high-risk individuals to other adverse events that would not occur in the majority of vaccinees. For example, fever is a relatively common inflammatory response following vaccination. For most vaccinees the fever is of short duration and there are no associated adverse reactions. However, in children with an underlying seizure disorder, or in infants and toddlers with a tendency to have febrile seizures, the fever may trigger a seizure. Other events that cause fever, such as respiratory infection, could also trigger a seizure. In such cases, the seizures result from a combination of an inherent property of the vaccine that caused fever and underlying factors in the vaccinee that lowered the threshold for seizure associated with fever.

Vaccine product-related and vaccine quality defect-related reactions are as follows:

- Reactions associated with the route and/or site of administration of the vaccine product or vaccinee-specific characteristics:
 - Bell's palsy following intranasal administration of a specific influenza vaccine where the causative mechanism was attributed to the vaccine composition combined with the mode of administration;
 - pain at the time of injection and associated physiological responses.
- Immune-mediated vaccine reaction:
 - local reactions, with involvement of the injection site, due to one or more vaccine components, i.e.
 - non-granulomatous inflammation with or without regional lymphadenitis
 - extensive limb swelling e.g. post-DTP vaccination,
 - mild, moderate or severe local inflammation, manifest as one or more of swelling, redness, pain, local tenderness and induration (examples of the mechanisms underlying more severe reactions include
 - subcutaneous injection of a vaccine [e.g. alum adsorbed] recommended for intramuscular administration,
 - localized antigen-antibody reaction [antibody excess],
 - aluminium adjuvant hypersensitivity, and

- infection),
 - granulomatous inflammation at the injection site with or without regional lymphadenitis (most commonly related to BCG vaccine);
- multisystem (generalized) reactions due to one or more vaccine components, i.e.
 - systemic inflammatory response (e.g. fever or lethargy)
 - mast cell degranulation
 - IgE mediated hypersensitivity (anaphylaxis),
 - non-IgE mediated hypersensitivity (reactions in this group are commonly referred to as anaphylactoid reactions),
 - disseminated granulomatous reaction (e.g. disseminated BCG in immunodeficient hosts)
 - immune complex mediated reaction (serum sickness reaction);
- organ-specific reactions due to one or more vaccine components, i.e.
 - auto-immune or undefined mechanism
 - central nervous system (e.g. demyelinating conditions such as GBS post-influenza vaccination),
 - blood (e.g. thrombocytopenia post-MMR vaccination),
 - skin (e.g. rashes after vaccination, including urticarial).
- Reactions as a consequence of replication of vaccine-associated microbial agent(s) in the vaccinee or in a close contact of the vaccinee. The microbial agent(s) could be:
 - an attenuated vaccine agent;
 - a wild-type vaccine agent due to insufficient inactivation during the manufacturing process;
 - a contaminant introduced into vaccine during the manufacturing process.
- Direct toxic effect of a vaccine component or contaminant (e.g. quality defect).

A3. Immunization error-related reaction

The emphasis for AEFI in this category is their preventable nature. Thus the classification mechanism focuses on the nature of the error rather than on the biological process(es) giving rise to the specific AEFI. Nevertheless, many of the AEFI in this category result from the same or similar processes as those that underlie vaccine product-related or vaccine quality defect-related reactions. Immunization error-related reactions are described below.

- Error in vaccine handling:
 - exposure to excess heat or cold as a result of inappropriate transport, storage or handling of the vaccine (and its diluent where applicable), resulting in:
 - failure to vaccinate as a result of inactivation of the active vaccine components
 - systemic or local reactions due to changes in the physical nature of the vaccine, such as agglutination of aluminium-based excipients in freeze-sensitive vaccines;
 - Use of a product after the expiry date, resulting in:
 - failure to vaccinate as a result of loss of potency or non-viability of an attenuated product.
- Error in vaccine prescribing or non-adherence to recommendations for use:
 - failure to adhere to a contraindication, resulting in:

- anaphylaxis following administration of a vaccine to an individual known to have an immune-mediated hypersensitivity to one or more components
- disseminated infection with an attenuated live vaccine agent following administration to an individual with a known immunodeficiency that contraindicated use of any live vaccines
- vaccine-associated paralytic polio in an immunocompromised household contact of a child given oral polio vaccine;
- failure to consider appropriately warnings or precautions for vaccine use;
- failure to adhere to vaccine indications or prescription (dose or schedule), resulting in:
 - systemic and/or local reactions following administration of an incorrect dose
 - systemic and/or local reactions following administration of the wrong product or administration to an individual in an incorrect age group
 - vaccine failure if a live attenuated product is given too soon after blood products or at an age when maternally transferred antibody could interfere with the replication required to induce an immune response
 - neurological, muscular, vascular or bone injury due to incorrect injection site, equipment or technique.
- Error in administration:
 - use of an incorrect diluent or injection of a product other than the intended vaccine, resulting in:
 - failure to vaccinate due to incorrect diluent
 - reaction due to the inherent properties of whatever was administered other than the intended vaccine or diluent;
 - incorrect sterile technique or inappropriate procedure with a multidose vial, resulting in:
 - infection at the site of injection due to a microbial contaminant introduced during administration of the vaccine
 - infection beyond the site of injection due to a microbial contaminant introduced during administration of the vaccine;
 - failure to ensure a safe environment during and immediately following immunization, resulting in:
 - head injury during a syncopal episode post-immunization;
 - inadvertent administration of vaccine to someone for whom it was not intended (e.g. via a needlestick injury or splash to the eye depending, on the vaccinee characteristics).

A4. Immunization anxiety-related reaction

The types of reactions caused by immunization anxiety include, but are not limited to:

- vasovagal mediated reactions;
- hyperventilation mediated reactions;
- stress-related psychiatric disorders.

B. Indeterminate

B1. Consistent temporal relationship but insufficient evidence for causality

In this case, the temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing the event (it may be a new vaccine-linked event). The details of such AEFI cases should be maintained in a national database. Over time, as more similar

vaccines are administered and if similar events are reported from one or multiple sources, the recorded cases will help to identify a signal suggesting a new potential causal association, or a new aspect of a known association, between a vaccine and an event or a set of related events.

B2. Conflicting trends of consistency and inconsistency with causality

Reviewing factors may result in conflicting trends of consistency and inconsistency with causal association to immunization. Even with adequate information, these AEFI cases cannot be clearly categorized because the outcomes of investigation may give contradictory conclusions. There could be clear pointers indicating that the event is related to the vaccine or the vaccination and at the same time there could also be clear evidence that the vaccine cannot be responsible.

C. Inconsistent causal association to immunization (coincidental)

AEFI can result from underlying or emerging conditions of the vaccine as well as from external exposures that can cause harm independent of immunization. These include, but are not limited to, the following:

Underlying or emerging condition(s) in the vaccine

Such underlying or emerging conditions could include:

- manifestation or complication of a congenital or inherited underlying disease condition or birth injury;
- manifestation or complication of an underlying acquired disease condition that may or may not have been diagnosed prior to immunization;
- psychogenic illness.

Conditions caused by exposure to external factors

Conditions caused by factors other than vaccine could include:

- infection due to agents such as bacteria, viruses, fungi or parasites;
- adverse reaction due to recent or concomitant medication or use of illicit substances;
- allergic and other hypersensitivity reactions due to exposure to allergens other than those present in the vaccine;
- injury due to exposure to environmental toxins;
- injury due to trauma, including surgery.

Initiating action after causality assessment

Determining causality is not an end in itself. The lessons learned from the assessment should provide insights for the technical, immunization programme and administrative managers on the causes and the next steps to take – including training, research, modifying systems, refining tools and so on – to avoid and/or minimize recurrences.

A. Consistent causal association to immunization

National immunization programmes need to establish standard protocols for responding to AEFI. These have to be decided by a national committee and approved by the existing decision-making system in the country.

A1. Vaccine product-related reaction

- It will be necessary to follow protocols adopted by each country when such cases are confirmed.

A2. Vaccine quality defect-related reaction

- If this reaction is related to a particular lot or batch, the distribution of the lot or batch has to be ascertained and specific instructions must be provided on the utilization or non-utilization of the lot or batch.
- It is important to inform the national regulatory authority and the marketing authorization holder about the AEFI. The event should be communicated to the manufacturer through these bodies.
- WHO should be contacted through the Organization's local country office or the WHO Uppsala Monitoring Centre (<http://www.who-umc.org/>) and the information communicated to ensure that other countries using the vaccine are alerted.

A3. Immunization error-related reaction

- Training and capacity-building are critical to avoid recurrences of such reactions.

A4. Immunization anxiety-related reaction

- Vaccination should take place in an ambient and safe environment.

B. Indeterminate

B1. Consistent temporal relationship but insufficient evidence for causality

- The details of such AEFI cases should be maintained in a national database. Later this can help to identify a signal suggesting a new potential causal association, or a new aspect of a known association, between a vaccine and an event or set of related events.

B2. Conflicting trends of consistency and inconsistency with causality

- These cases are classified on the basis of available evidence. If additional information becomes available, the classification can move into a more definitive category. During the assessment, the reviewers should clarify what additional information would be helpful to finalize the causality assessment and should seek information and expertise from national or international resources.

The GACVS can be approached for guidance through WHO, particularly when an event is likely to impact the immunization programme significantly.

C. Inconsistent causal association to immunization (coincidental)

- The information and confirmation should be provided to patients, their relatives, the care provider and the community.

Conclusion

It is important to recognize that causality assessment of an AEFI in an individual patient is an exercise in medical differential diagnosis. A good clinician does not diagnose diabetes or coronary artery disease on the basis of conflicting or vague information. In the same way, an AEFI should not be causally linked to a vaccine without adequate information.

In WHO's revised AEFI causality assessment process, end-users are encouraged to determine if the minimum criteria for causality assessment are reached, use a checklist to identify factors that could have caused the event, recognize a pattern through an algorithm and finally apply the human element in ascertaining causality.

In assessing causality of an AEFI, the human elements of experience, proficiency, resources and teamwork clearly play an important role. Tools like the one described above empower investigators to think about the rationale of an assessment, collect relevant data and help to improve consistency in assessments.

There are several models, algorithms and tools (including software) available for causality assessment, each with its own merits and with varying sensitivity and specificity. After a thorough review of the existing methodologies for assessing causality in adverse drug reactions and AEFI, and after pilot-testing of several approaches (including scoring scales, algorithms, questionnaires etc.), this revised scheme was developed by a GACVS working group in consultation with experts from around the world.

There was consensus that it is difficult to create a perfect system that clearly pinpoints the causality of AEFI. The basic steps in the algorithm developed by the Clinical Immunization Safety Assessment (CISA) Network was used by the GACVS working group and was developed into the present scheme to make it applicable in multiple settings.¹

¹ Halsey NA et al. Algorithm to assess causality after individual adverse events following immunizations. *Vaccine*, 2012, 30(39):5791–5798 (Epub 2012 Apr 14). See: <http://www.ncbi.nlm.nih.gov/pubmed/22507656> (accessed 23February 2013).

Annex 1. Worksheet for causality assessment

Step 1: Eligibility

Name of the patient	Name of one or more vaccines administered before this event	What is the valid diagnosis?	Does the diagnosis meet a case definition?

Create your question on causality here

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

Step 2: Event checklist

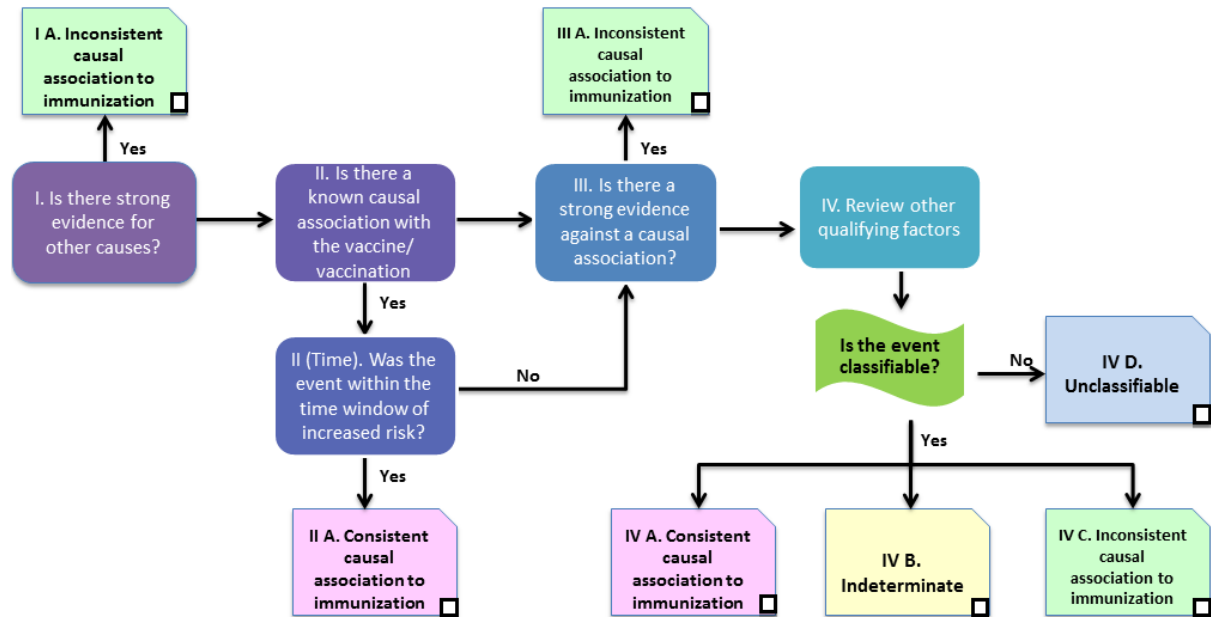
Check ✓ all boxes that apply

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

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

Step 3: Algorithm

Review all steps and check ✓ all the appropriate boxes



Notes for step 3:

Step 4: Classification

Check ✓ all boxes that apply

	<p style="text-align: center;">A. Consistent causal association to immunization</p> <p><input type="checkbox"/> A1. Vaccine product-related reaction (As per published literature)</p> <p><input type="checkbox"/> A2. Vaccine quality defect-related reaction</p> <p><input type="checkbox"/> A3. Immunization error-related reaction</p> <p><input type="checkbox"/> A4. Immunization anxiety-related reaction</p>	<p style="text-align: center;">B. Indeterminate</p> <p><input type="checkbox"/> B1. *Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event)</p> <p><input type="checkbox"/> B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization</p>	<p style="text-align: center;">C. Inconsistent causal association to immunization</p> <p><input type="checkbox"/> C. Coincidental Underlying or emerging condition(s), or conditions caused by exposure to something other than vaccine</p>
<p>Adequate information available</p>			
<p>Adequate information not available</p>	<p><input type="checkbox"/> Unclassifiable</p> <p>Specify the additional information required for classification : </p>		

*B1: This is a potential signal and maybe considered for investigation

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

ANNEX 2. Examples

Example 1: Meningococcal conjugate vaccine and seizures

Presenting problem: A five-month-old male (name PQ), given a second dose of Menjugate vaccine (first dose at age three months); two days post-immunization reported onset of fever – not documented. Five days post-immunization the infant had a right focal seizure and altered level of consciousness. The documented temperature was 39° C. The patient was treated with anticonvulsants and was admitted to hospital. He had persistent seizure activity on the third and fourth days in hospital. He was transferred to a tertiary-care referral paediatric hospital and admitted to the intensive care unit with status epilepticus. Seizures were controlled within 24 hours.

Past medical history: unremarkable good general health; no evidence of immune deficiency

- no prior history of seizures.

Investigations:

- CSF: 61 RBC; 144 WBC; 57% PMN; and 26% lymphocytes;
- protein 1.2; glucose 3.1;
- culture of CSF, pharynx and stool all negative;
- PCR positive for herpes simplex virus;
- MRI showed extensive inflammation of right frontal, parietal and temporal lobes, and a small amount of bleeding into the left temporal lobe;
- EEG showed paroxysmal lateral epileptiform discharges.

An investigation at the immunization session site confirmed the application of correct procedures in vaccine administration.

Treatment and course of illness: Treated with antibiotics and antiviral (acyclovir). The former was discontinued once PCR results were known; the latter was continued for 21 days. Good recovery in hospital on treatment. At discharge the infant was alert and active with normal tone. Home on anticonvulsants.

Note: The case meets the Brighton Collaboration case definition for encephalitis - at a level 2 of diagnostic certainty (evidence of encephalopathy with decreased level of consciousness and associated seizures; multiple indicators of CNS inflammation [temp 39C; CSF pleocytosis; EEG findings consistent with encephalitis; neuroimaging consistent with encephalitis]).

Step 1: Eligibility

Name of the patient	Name of one or more vaccines administered before this event	What is the valid diagnosis?	Does the diagnosis meet a case definition?
PO	Menjugate (Meningococcal Group C conjugate vaccine)	Meningoencephalitis	Yes (level 2)

Create your question on causality here
Has the Menjugate vaccine/vaccination caused meningoencephalitis ?

Step 2: Event checklist

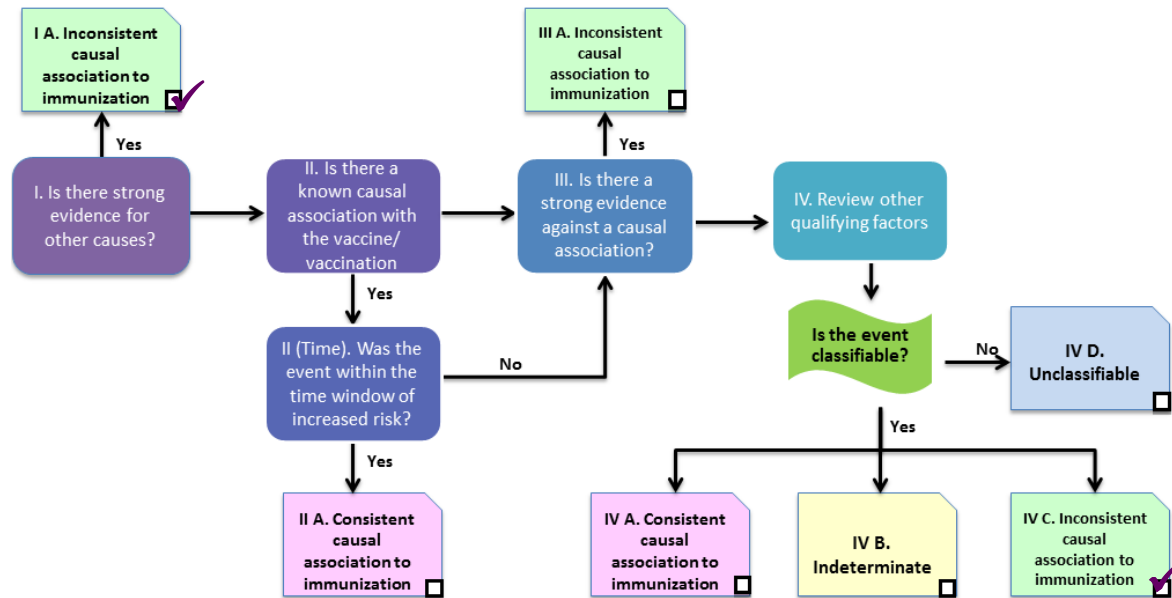
Y: Yes N: No UK: Unknown NA: Not applicable

Check ✓ all boxes that apply

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
Does a clinical examination, or laboratory tests on the patient, confirm another cause?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Yes – CSF PCR positive for herpes simplex virus
II. Is there a known causal association with the vaccine or vaccination?		
<i>Vaccine product(s)</i>		
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<i>Immunization error</i>		
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.)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Verified and found to be correct
Was the vaccine (or any of its ingredients) administered unsterile?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Verified and found to be correct
Was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal at the time of administration?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Verified and found to be correct
Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Verified and found to be correct
Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Verified and found to be correct
Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Verified and found to be correct
<i>Immunization anxiety</i>		
Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Anxiety cannot cause Meningoencephalitis
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?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
III. Is there strong evidence against a causal association?		
Is there strong evidence against a causal association?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	Unknown – hasn't been studied
IV. Other qualifying factors for classification		
Could the event occur independently of vaccination (background rate)?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Yes – several causes of meningoencephalitis in infants
Could the event be a manifestation of another health condition?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Yes – could be one of several different infections
Did a comparable event occur after a previous dose of a similar vaccine?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
Was there exposure to a potential risk factor or toxin prior to the event?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
Was there acute illness prior to the event?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
Did the event occur in the past independently of vaccination?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
Was the patient taking any medication prior to vaccination?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
Is there a biological plausibility that the vaccine could cause the event?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	Unknown – not reported so far in literature

Step 3: Algorithm

Review all steps and check ✓ all the appropriate boxes



Notes for step 3: I A: Because PCR positive for herpes simplex virus. IV C: because several causes of meningoencephalitis in infants. Could be one of several different infections.

Step 4: Classification

Check ✓ all boxes that apply

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

*B1: This is a potential signal and may be considered for investigation

Summarize the classification logic:

With available evidence, we could conclude that the classification is inconsistent (coincidental) because:

There is a clear alternative explanation for the meningoencephalitis (herpes simplex virus confirmed).

Example 2: OPV and acute flaccid paralysis

MA, a male child, was born on 29 December 2006 to a farmer couple in a polio endemic country. On 1 July 2009, he suddenly developed inability to use the left upper limb. This was reported by the local health worker to the medical officer on the same day and was investigated on 2 July 2009.

The medical officer obtained the details of the present illness from the parents. MA had a sudden onset of flaccid paralysis in the left arm on 1 July 2009. On the day of paralysis, there was no fever. The paralysis was static (neither ascending nor descending). There was no sensory loss. He did not travel outside his locality for 35 days preceding his illness. There was no history of trauma, no loss of consciousness and no convulsions. Within 30 days prior to the paralysis onset, he had injections in the gluteal region.

MA had a BCG scar. The health worker mentioned that MA had received three doses of OPV through routine immunization and the parents mentioned that he had over 10 doses of OPV through mass immunization campaigns. The last OPV before paralysis onset (and stool sample collection) was administered on 24 May 2009.

On clinical examination the medical officer observed that the tone was markedly diminished in the left upper limb. There was power of 0/5 in the muscles of the wrist, forearm and upper arm. The biceps, triceps and supinator jerks were diminished. Examination also showed that all other limbs were clinically within the normal range of expected findings. Using a measuring tape, he determined and recorded the circumference of all the limbs.

To test for the presence of enterovirus, two stool specimens were collected on 2 July 2009 and 4 July 2009. Both specimens were of adequate volume and were sent to a WHO-accredited laboratory in good condition (i.e. without desiccation or leakage, with adequate documentation, and with evidence that the cold chain was maintained). The second stool sample isolated Sabin type 1 and Sabin type 2 strains of poliovirus.

The medical officer re-examined MA on 9 September 2009 and observed that that the tone was diminished in the left upper limb compared to the right. There was improvement in the power in the muscles of the wrist (4/5), forearm (2/5) and upper arm (2/5). The biceps, triceps and supinator jerks were still diminished. Examination also showed that all other limbs were clinically within the normal range of expected findings. On measuring the limbs, the medical officer determined that there was wasting in the left upper arm.

Step 1: Eligibility

Name of the patient	Name of one or more vaccines administered before this event	What is the valid diagnosis?	Does the diagnosis meet a case definition?
MA	OPV	AFP	Yes http://www.who.int/immunization_monitoring/diseases/polio/myelitic

Create your question on causality here
 Has the OPV vaccine/vaccination caused AFP?
 (The event is for review in step 2)

Step 2: Event checklist

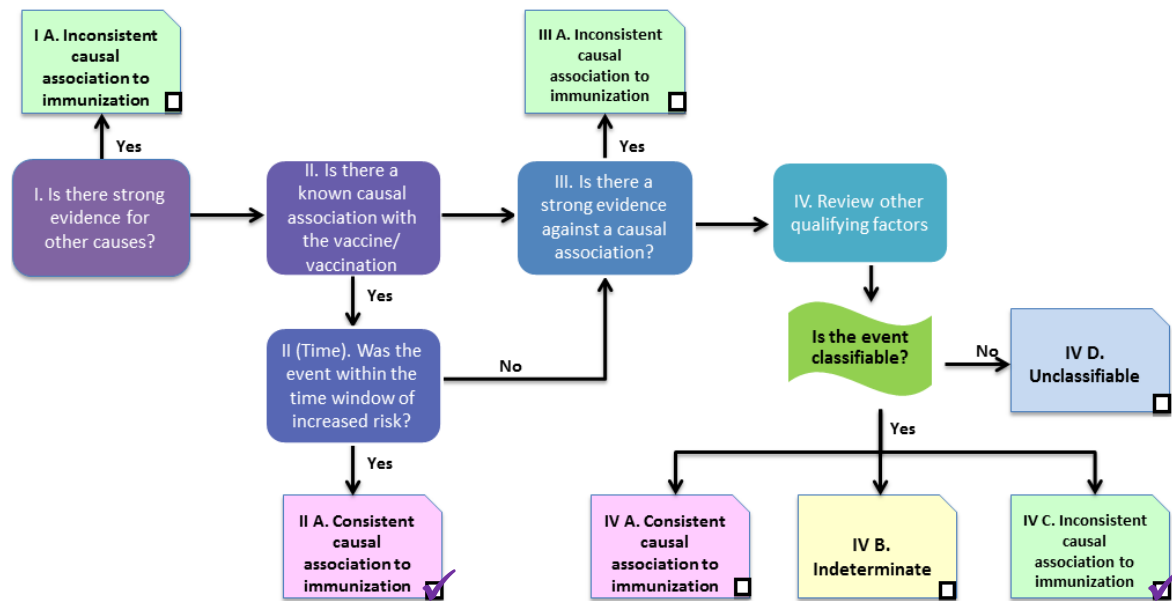
Check ✓ all boxes that apply

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

I. Is there strong evidence for other causes?		Y	N	UK	NA	Remarks
Does a clinical examination, or laboratory tests on the patient, confirm another cause?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<i>No details available on the other tests conducted on this child</i>
II. Is there a known causal association with the vaccine or vaccination?						
<i>Vaccine product(s)</i>						
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>VAPP is a recognized event</i>
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>Sabin 1 and 2 isolated</i>
<i>Immunization error</i>						
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)?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Was the vaccine (or any of its ingredients) administered unsterile?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc) abnormal at the time of administration?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc)?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc)?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc)?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Immunization anxiety</i>						
Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>Within 4–40 days</i>
III. Is there strong evidence against a causal association?						
Is there strong evidence against a causal association?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
IV. Other qualifying factors for classification						
Could the event occur independently of vaccination (background rate)?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>There are many causes for AFP</i>
Could the event be a manifestation of another health condition?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>Child received injection 30 days prior; there must have been an illness</i>
Did a comparable event occur after a previous dose of a similar vaccine?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Was there exposure to a potential risk factor or toxin prior to the event?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>Intramuscular injections within 30 days of immunization with oral poliovirus vaccine – a risk factor for vaccine-associated paralytic poliomyelitis</i>
Was there acute illness prior to the event?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<i>Inadequate information</i>
Did the event occur in the past independently of vaccination?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Was the patient taking any medication prior to vaccination?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is there a biological plausibility that the vaccine could cause the event?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>OPV can cause AFP</i>

Step 3: Algorithm

Review all steps and check ✓ all the appropriate boxes



Notes for step 3: II A: With available information, it seems likely that the vaccine caused the event. This is because OPV is known to cause the event and the time window is suitable. IV C: There are other causes of flaccid paralysis and the child was treated for an illness 30 days prior to paralysis; however, this information is inadequate.

Step 4: Classification

Check ✓ all boxes that apply

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

Summarize the classification logic:

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

With available information, it seems likely that the vaccine caused the event. (But we need to keep in mind that VAPP is more likely to occur after the first dose than after later doses.)

However, even though the trend is consistent we cannot completely rule out **inconsistent**, since information available on other causes is inadequate.

Example 3: AEFI after MMR vaccine

XX, a South Asian girl child was born on 1 December 2010 through LSCS (gestational age 38 weeks + 2 days). She was the first child to the parents. Birth weight was 3200g and Apgar at birth was 10.

On 22 May 2012 (at 18 months) between 9.30 and 10 a.m. she received 0.5ml MMR vaccine in the left arm with a 25mm 23G needle. She died 10 days after immunization.

She was not on any simultaneous medication. She had no antenatal complications, she had no food allergies, and her feeding and activities were normal. She had no history of hospitalization, no underlying congenital or acquired diseases or disorders, and no evidence of abuse, harm, neglect, accidental injury or previous need for child protection.

Previously she had the following immunizations: Penta (DTP Hep B and Hib) 1/OPV 1 on 9 August 2011, Penta 2/OPV 2 on 25 October 2011, and JE on 10 January 2012.

Prior to immunization, her feeding and activity were normal. She had an attack of fever one week prior which resolved. She was not receiving any medication at the time of vaccination.

After immunization with MMR, she developed mild fever on the same day (22 May 2012). On the third day after immunization (25 May 2012), she developed cough, high fever, vomiting and flushed face. On day 8 after immunization (30 May 2012), she was admitted to the local district hospital where tentative diagnosis of lower respiratory tract infection was made. Full blood examination showed that the initial WBC count was 3800 and platelets 152 000. The prescribed medications included Paracetamol, chlorpheniramine maleate, Cefaloxine, Salbutamol, Theophyllin, and Diclofenac sodium suppository.

She was later transferred to the district general hospital on 30 May 2012. The next day she developed fever, right hypochondrial tenderness and tenderness of the liver (1cm). Although she was haemodynamically stable, her WBC was 1300 and platelets 112 000. The condition was diagnosed as probable dengue illness. She further developed watery diarrhoea and convulsions and was treated for acute gastroenteritis with IV antibiotics and IV fluids. In the evening, the platelet count dropped from 112 000 (at 5:00 a.m.) to 77 000 (at 5:00 p.m.). Clinicians considered probable entry into the critical phase of dengue haemorrhagic fever, even though evidence of haemorrhages was not detected. At 8.00 p.m., there was a further drop in platelet count to 54 000 which clinicians considered as entry into the critical phase with haemodynamic instability (HR- >200; systolic BP – 60mmHg). She was then placed on IV fluids over six hours, exceeding the fluid quota (1330 ml given – 90.5%).

On day 10 following immunization, she was transferred to the intensive care unit. Her heart rate remained high and she continued to be haemodynamically unstable, with pupils wide, tachypnoea, peripheral cyanosis and fluid overload. She died at 9 a.m. on 1 June 2012.

Diagnosis of dengue illness was considered but no objective confirmation of dengue haemorrhagic fever was made (ultrasound, chest X-ray or virological examination). The primary cause of death was considered to be both prolonged shock and fluid overload. Her body was sent for autopsy.

No written autopsy report was available. The case (at the time of writing this report) was awaiting the pathological report. The medical officer who performed the autopsy unofficially communicated to the immunization programme manager that the appearance was compatible with a viral infection; however, there was no macroscopic evidence of bleeding or fluid leakage.

Field investigation by the immunization programme

Investigation on vaccine cold chain and vaccination technique at the Ministry of Health showed that the MMR vaccine, Batch number 065004 and expiry date February 2014 was given. It was manufactured by the manufacturer xyz. There was no breakdown in the cold chain after receipt of the stocks of vaccine at national level according to the daily temperature record. The VVM status was stage 1.

Further investigation showed that, of the 30 other children vaccinated on the same day at the same clinic, three were vaccinated with the same vaccine and there were no similar events.

Option 1 – MMR and thrombocytopenia

Step 1: Eligibility

Name of the patient	Name of one or more vaccines administered before this event	What is the valid diagnosis?	Does the diagnosis meet a case definition?
XX	MMR	Thrombocytopenia	Yes (Brighton level 2)

Create your question on causality here
Has the MMR vaccine / vaccination caused *Thrombocytopenia resulting in death*?

Step 2: Event checklist

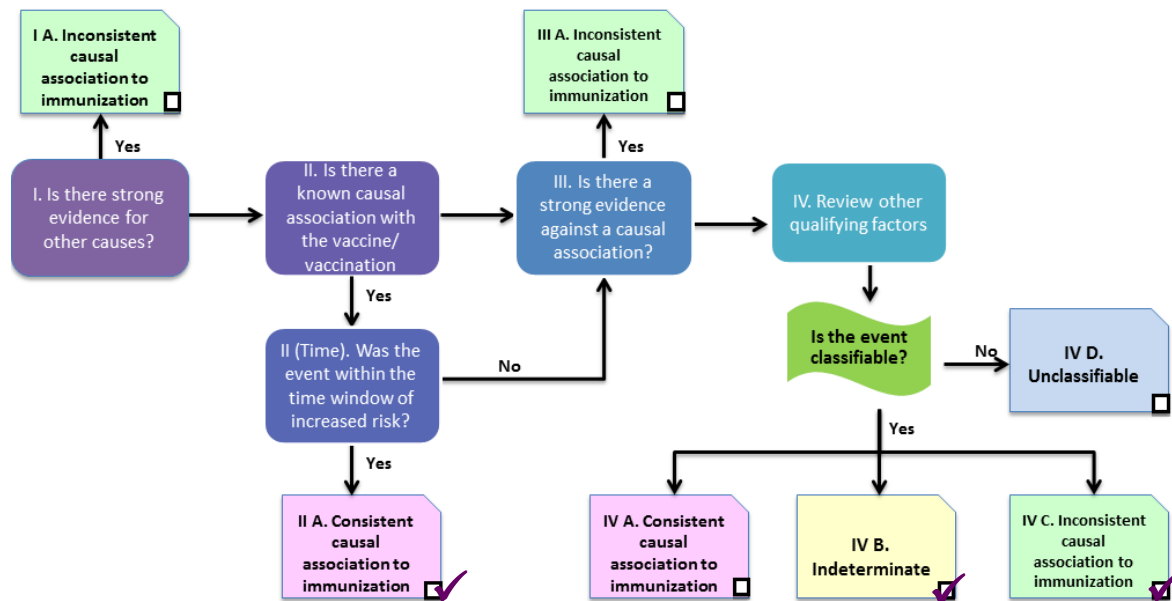
Check ✓ (check) all boxes that apply

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

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
Does a clinical examination, or laboratory tests on the patient, confirm another cause?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	With platelet count ↓ Liver enlarged, Dengue can affect liver. TWBC ↓ the tests may support dengue as a dx but don't confirm it
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?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Measles vaccine can cause thrombocytopenia but not severe enough for death
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Thrombocytopenia is a sign but not proof of causality
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.)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Verified and found correct
Was the vaccine (or any of its ingredients) administered unsterile?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Verified and found correct
Was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal at the time of administration?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
Was there an error in vaccine constitution or preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Verified and found correct
Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Verified and found correct
Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Verified and found correct
Immunization anxiety		
Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
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?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Within time (0–42 days) for measles vaccine to cause thrombocytopenia
III. Is there strong evidence against a causal association?		
Is there strong evidence against a causal association?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	Autopsy report compatible with viral infection. No evidence of bleeding
IV. Other qualifying factors for classification		
Could the event occur independently of vaccination (background rate)?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Dengue endemic country
Could the event be a manifestation of another health condition?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Other viral infection (H/o prior febrile illness +, present illness - fever, flushing
Did a comparable event occur after a previous dose of a similar vaccine?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/>	
Was there exposure to a potential risk factor or toxin prior to the event?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	H/o fever, unsure if there was an exposure.
Was there acute illness prior to the event?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Fever week prior to event – unclear etiology
Did the event occur in the past independently of vaccination?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
Was the patient taking any medication prior to vaccination?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
Is there a biological plausibility that the vaccine could cause the event?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Measles vaccine and thrombocytopenia but no evidence of bleeding

Step 3: Algorithm

Review all steps and check ✓ all the appropriate boxes



Notes for step 3: II A: Because measles vaccine can cause thrombocytopenia. The time window fits. Measles vaccine is associated with thrombocytopenia, but is not severe enough to cause death by bleeding. There is no evidence for bleeding on autopsy. IVB: Because other viral infection (H/o prior febrile illness +, present illness - fever, flushing cough and vomiting). IVC: Because we need to consider other viral infections (dengue cannot be ruled out).

Step 4: Classification

Check ✓ all boxes that apply

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

*B1: This is a potential signal and maybe considered for investigation

Summarize the classification logic:

With available evidence, we could conclude that the classification could be **indeterminate / inconsistent** because: With available evidence it is not possible to come to a conclusion as to whether the thrombocytopenia was caused by the vaccine, by dengue or by another viral disease. However, there is no evidence of bleeding on autopsy. Therefore, even if the MMR contributed to thrombocytopenia, it did not contribute to death.

EXAMPLE 3: Option 2 – MMR and sepsis

Step 1: Eligibility

Name of the patient	Name of one or more vaccines administered before this event	What is the valid diagnosis?	Does the diagnosis meet a case definition?
XX	MMR	Sepsis	Yes weblink: http://www.bmj.com/content/335/7625/879

Create your question on causality here
 Has the ___ *MMR* ___ vaccine / vaccination caused ___ sepsis resulting in death ___?
 (The event is for review in step 2)

Step 2: Event checklist

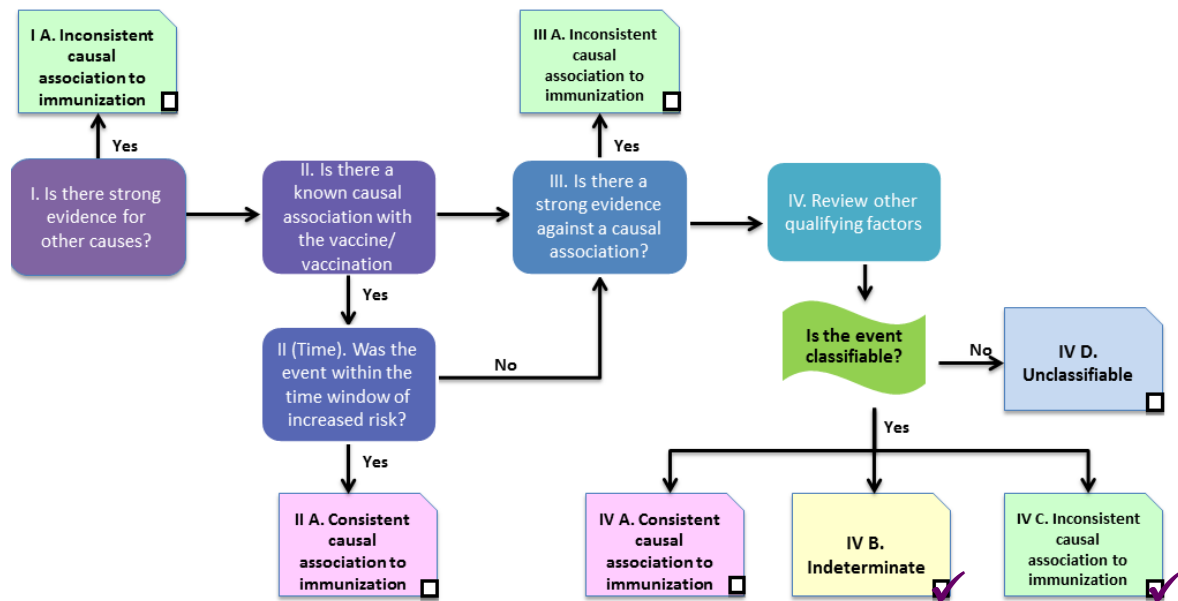
Check ✓ all boxes that apply

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

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
Does a clinical examination, or laboratory tests on the patient, confirm another cause?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	<i>Dengue is suspected but not confirmed. (Platelets ↓ TWBC ↓ liver ++)</i> IgM and virus isolation not done
II. Is there a known causal association with the vaccine or vaccination?		
<i>Vaccine Product(s)</i>		
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<i>Immunization error</i>		
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.)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Verified and found correct</i>
Was the vaccine (or any of its ingredients) administered unsterile?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Verified and found correct</i>
Was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal at the time of administration?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
Was there an error in vaccine constitution or preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Verified and found correct</i>
Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Verified and found correct</i>
Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Verified and found correct</i>
<i>Immunization anxiety</i>		
Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
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?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/>	
III. Is there strong evidence against a causal association?		
Is there strong evidence against a causal association?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>No evidence of bacterial</i>
IV. Other qualifying factors for classification		
Could the event occur independently of vaccination (background rate)?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>In this situation, it is possible that sepsis could be a complication of the respiratory tract infection</i>
Could the event be a manifestation of another health condition?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Other infections, probably dengue (unconfirmed)</i>
Did a comparable event occur after a previous dose of a similar vaccine?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/>	
Was there exposure to a potential risk factor or toxin prior to the event?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
Was there acute illness prior to the event?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Fever one week prior to immunization</i>
Did the event occur in the past independently of vaccination?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
Was the patient taking any medication prior to vaccination?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
Is there a biological plausibility that the vaccine could cause the event?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	

Step 3: Algorithm

Review all steps and check ✓ all the appropriate boxes



Notes for step 3:

IV C: In this situation, it is possible that sepsis causing death is a complication of the respiratory tract infection. IV B: Other infections, probably dengue (unconfirmed). Fever one week prior to immunization.

Step 4: Classification

Check ✓ all boxes that apply

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

*B1: This is a potential signal and may be considered for investigation

Summarize the classification logic:

*With available evidence, we could conclude that the classification is **indeterminate / inconsistent** because: The sepsis that caused the chain of events leading to the death of the child could have been due to a complication of respiratory tract infection or other viral disease (dengue suspected). The autopsy findings will give a better picture. We cannot rule out that the viraemia which is of low level with MMR may have made the viral infection already present worse. MMR is not the cause of death*

Technical assistance for AEFI causality assessment is available from the World Health Organization through the Essential Medicines and Health Products (EMP) Department.

Additional information on AEFI surveillance, investigation, management and causality assessment, as well as on vaccine safety communication, can be found online at http://www.who.int/immunization_safety/en/.

You can also contact us at

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