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

**USER MANUAL FOR THE REVISED WHO CLASSIFICATION  
SECOND EDITION**

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

**User manual for the revised WHO classification  
Second edition**

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Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification (Second edition)  
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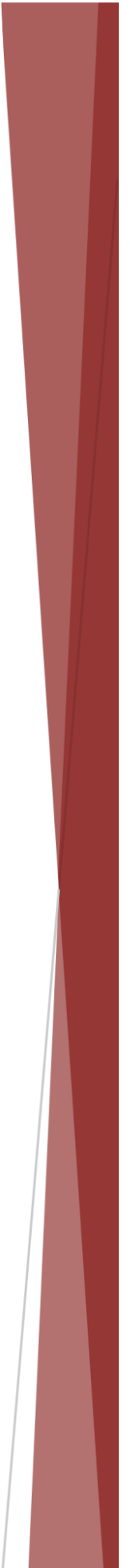
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## **PURPOSE:**

This user manual serves as a guide to a systematic, standardized global causality assessment process for individual 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.



# The second edition and what is new

## Background

Since the 2013 publication of the “Causality assessment of an adverse event following immunization (AEFI), user manual for the revised WHO classification”, there has been extensive global interest in adopting the new revised causality assessment methodology for vaccine pharmacovigilance systems. WHO provided technical support and helped build capacity in countries of all WHO Regions who wanted to use the revised methodology. An AEFI causality assessment software was developed, translated to six UN languages and made available online.

Recently, the new methodology has been scientifically evaluated. In April 2017, WHO coordinated an India - Zimbabwe project entitled “*Inter-country study to assess the inter-rater reliability of the WHO AEFI causality assessment methodology and the utility of the new WHO AEFI causality assessment software*”. The quantitative aspect of the study determined that there was realistic agreement between assessors in their findings. The qualitative aspect of the study identified areas of the methodology that could be made even more robust by the use of more accurate and clearer language, semantics and graphics.

In the meanwhile, feedback from surveillance systems and other research studies have shed new evidence on areas such as, “substandard and falsified vaccines”, “immunization anxiety” and “immunization triggered stress responses” that need to be incorporated into new guidance documents.

## What is new?

- Greater clarity on “AEFI cases ineligible for classification” and “unclassifiable cases”
- A broader consideration on a spectrum of stress responses to immunization when assessing causality for immunization anxiety related AEFI
- Attention to “falsified vaccines” during AEFI causality assessment.
- Use of clearer language and semantics in the checklist questions
- Better graphics in the algorithm with emphasis on the mandatory path
- Updated examples with current information throughout the entire document.





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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.
Falsified vaccines	Vaccines that deliberately/fraudulently misrepresent their identity, composition or source
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.
Immunization Triggered Stress Response (ITSR)	Stress response to immunization that can be triggered and may manifest just prior to, during, or after immunization.

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.
Substandard vaccines	Authorized vaccines that fail to meet either their quality standards or specifications
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
IOM	Institute of Medicine
IPV	Inactivated poliovirus vaccine
ITP	Idiopathic thrombocytopenic purpura
ITSR	Immunization triggered stress response
LMIC	Low- and middle-income countries
MMR	Measles, mumps and rubella vaccine
NRA	National regulatory authority
OPV	Oral polio vaccine
SAE	Severe adverse event
VAPP	Vaccine-associated paralytic polio
WHO	World Health Organization



# I. 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. More people than ever before are being reached with immunization. During 2016, about 86% of infants worldwide (116.5 million infants) received 3 doses of diphtheria-tetanus-pertussis (DTP3) vaccine, 85% of children had received one dose of measles vaccine by their second birthday and 85% of infants around the world received three doses of polio vaccine <sup>1</sup>.

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 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.

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<sup>1</sup> Immunization coverage fact sheet updated in July 2017 <http://www.who.int/mediacentre/factsheets/fs378/en/> (accessed 2 January 2018).

## Adverse events following immunization – Key definitions<sup>1</sup>

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.

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<sup>1</sup> *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.who.int/vaccine\\_safety/initiative/tools/CIOMS\\_report\\_WG\\_vaccine.pdf](http://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf) (accessed 2 January 2018).



## II. Key considerations for causality assessment of AEFI

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 either ineligible for causality assessment or 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 healthy infants younger than 12 months who had received the RotaShield® vaccine were at higher 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.<sup>1</sup>

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<sup>1</sup> See: <http://www.cdc.gov/vaccines/vpd-vac/rotavirus/vac-rotashield-historical.htm> (accessed 2 January 2018).

### III. Levels of AEFI 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. This manual will be focusing on this aspect of causality assessment. 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?”). Population level assessments are done through epidemiological studies. 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 published peer reviewed literature that this vaccine may cause such an event if administered correctly?” and “In this patient, did the event occur within a plausible time window after vaccine administration?”<sup>1</sup>

It is important to consider the background rates for the occurrence of an event of interest and then after a population has received vaccine, determine if the observed rate of that event is in excess of the background rates. WHO information sheets on observed rates of vaccine reactions that summarize known reactions to existing single antigen vaccines or combination products are available online.<sup>2</sup>

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<sup>1</sup> The detailed document can be downloaded free at: <https://www.nap.edu/catalog/13164/adverse-effects-of-vaccines-evidence-and-causality> (accessed 2 January 2018).

<sup>2</sup> See: [http://www.who.int/vaccine\\_safety/initiative/tools/Guide\\_Vaccine\\_rates\\_information\\_sheet\\_.pdf](http://www.who.int/vaccine_safety/initiative/tools/Guide_Vaccine_rates_information_sheet_.pdf) (accessed 2 January 2018).

## 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 assessing this relationship in order to identify a possible new vaccine product-related reaction, 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:
  - pre-existing 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 in the vaccinee. 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)<sup>1</sup>.

### 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. A review of the corresponding adverse event reports should be performed to verify that the available documentation is strong enough to suggest a new potential causal association, or a new aspect of a known association, in order to justify further evaluation of the signal. The objective of signal evaluation is to draw conclusions on the presence or absence of a suspected causal association between an adverse event and a vaccine, and to identify the need for additional data collection or for risk minimisation measures. This may also prompt the regulatory authorities to request the marketing authorisation holder (MAH) for an additional analysis of its available data on a particular event under investigation.

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<sup>1</sup> Relapsing neuropathy due to tetanus toxoid. Report of a case. J Neurol Sci. 1978 Jun;37(1-2):113-25. Pollard JD, Selby G. <https://www.ncbi.nlm.nih.gov/pubmed/308529> (accessed 2 January 2018)

## IV. Case selection for AEFI causality assessment

The selection of cases for causality assessment should focus on:

- serious AEFI<sup>1</sup> 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 are important. The information and evidence that is collected during a good quality AEFI investigation holds the key for a successful evaluation of the event, the circumstances of its occurrence and provides vital clues for the probable cause of its occurrence.

The WHO standard investigation form<sup>2</sup> and the WHO aide memoire for AEFI investigation<sup>3</sup> can provide guidance for an investigation. However it is critical to remember that these guidance documents may not address all circumstances and situations that may emerge during the investigation. Good investigators provide additional evidence to the assessors by their critical thinking and problem solving abilities, rigorous attention to detail to ensure that nothing is missed, excellent oral communication skills when interviewing stakeholders and the ability to document and prepare good reports and dossiers of investigations.

An AEFI should fulfill four 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.

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<sup>1</sup> *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.who.int/vaccine\\_safety/initiative/tools/CIOMS\\_report\\_WG\\_vaccine.pdf](http://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf) (accessed 2 January 2018).

<sup>2</sup> [http://www.who.int/vaccine\\_safety/initiative/investigation/AEFI\\_Investigation\\_form\\_2Dec14.pdf](http://www.who.int/vaccine_safety/initiative/investigation/AEFI_Investigation_form_2Dec14.pdf) (accessed 2 January 2018).

<sup>3</sup> [http://www.who.int/vaccine\\_safety/initiative/investigation/New\\_aide-memoire\\_AEFI.pdf](http://www.who.int/vaccine_safety/initiative/investigation/New_aide-memoire_AEFI.pdf) (accessed 2 January 2018).

- There must be a “valid diagnosis” (as explained below) for the unfavourable or unintended sign, abnormal laboratory finding, symptom or disease in question.
- All vaccines that were administered before the event should be identified

### **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 whose areas of expertise could include paediatrics, neurology, general medicine, forensic medicine, pathology, microbiology, immunology and epidemiology. Other external medical experts should be invited for the review of specific events<sup>1</sup>. The committee needs to be independent and have support from, and work in close communication with both the immunization programme and the National Regulatory Authority (NRA). 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.

A drug safety committee evaluating Adverse Drug Reactions (ADR) may need to be specifically trained on AEFI causality assessment before the committee acquires sufficient expertise in assessing the causality of AEFI.

Countries requiring special technical expertise (such as special training on AEFI causality assessment or advice on laboratory tests) in causality assessment should contact the respective WHO country office or WHO regional office. Assistance is also available from WHO at global level.<sup>2</sup>

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<sup>1</sup> WHO | Global Manual on Surveillance of Adverse Events Following immunization [http://www.who.int/vaccine\\_safety/publications/aeft\\_surveillance/en/](http://www.who.int/vaccine_safety/publications/aeft_surveillance/en/) (accessed 2 January 2018).

<sup>2</sup> Contact: Department of Essential Medicines and Health Products, World Health Organization, 20 avenue Appia, 1211 Geneva 27, Switzerland. Tel: +41 22 791 4468; Fax: +41 22 791 4227; e-mail: [gvs@who.int](mailto:gvs@who.int). The web link is [http://www.who.int/immunization\\_safety/en/](http://www.who.int/immunization_safety/en/).

## V. Steps for causality assessment of an individual AEFI

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:

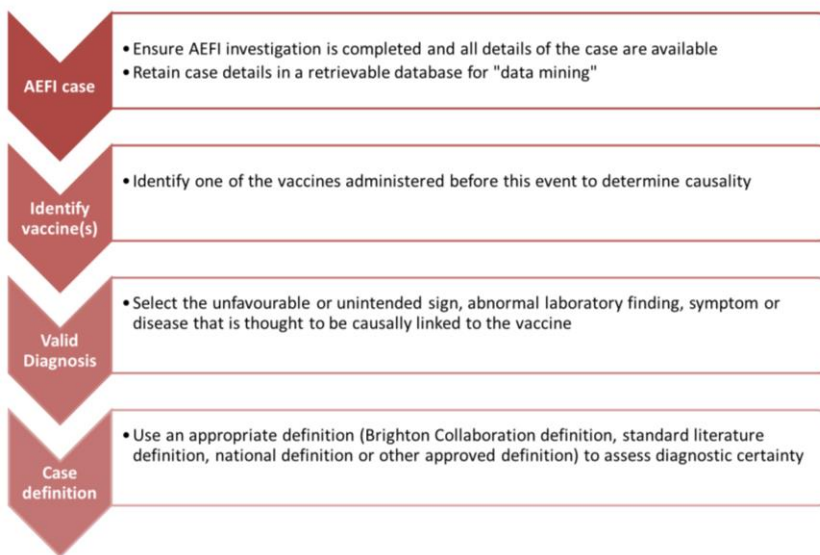
- Step 1: Eligibility. The first step aims to determine if the AEFI case satisfies the minimum criteria for causality assessment as outlined below.
- Step 2: Checklist. The second step involves systematically reviewing the relevant and available information to address possible causal aspects of the AEFI.
- 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. WHO has developed an e-tool that will help assessors perform an AEFI causality assessment both online (on computers) and both online and offline modes on tablets and iPads. Details are available at [http://www.who.int/vaccine\\_safety/causality-assessment-software-EN/en/](http://www.who.int/vaccine_safety/causality-assessment-software-EN/en/)

### 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.<sup>1</sup> 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.<sup>2</sup> 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.

Cases ineligible for causality assessment are those where the amount of information initially available to the assessor is so limited that the assessment cannot be initiated. For example if the name of the vaccine or the valid diagnosis are not available at the time of assessment.

Unclassifiable cases occur in instances where the reviewer is able to initiate an assessment, but during the process of discovers that some key elements are unavailable to permit a logical classification.

In either situation, reasons for not proceeding with the classification have to be provided

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?” (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 - valid diagnosis)

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. AEFI cases where the causality question cannot be created by an assessor is categorized as “ineligible”. 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.

<sup>1</sup> 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.

<sup>2</sup> See: <https://www.brightoncollaboration.org/> (accessed 2 January 2018).

For a given assessment only one valid diagnosis and one vaccine administered can be assessed at one time. If multiple vaccines are administered to the patient at the same time, each vaccine should be assessed separately; when faced with multiple presumptive diagnoses, the reviewer should consider doing a separate causality assessment for each diagnosis. Likewise for a cluster of AEFI, each individual case must be assessed separately. One cannot gather a group of cases within a cluster and attempt a collective causality assessment of such a group within a cluster of cases.

At this point of the assessment, the assessor has to make a decision if the information that is available at hand is sufficient to proceed (eligibility for assessment), if not the assessment should be temporarily kept in abeyance until the basic information is obtained.

## Step 2: Checklist

The checklist (Table 1) contains elements to guide the reviewers to collate the evidence

**Table 1. The causality assessment checklist**

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
1. In this patient, does the medical history, clinical examination and/ or investigations, confirm another cause for the event?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>II. Is there a known causal association with the vaccine or vaccination?</b>		
<b>Vaccine product</b>		
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
2. Is there a biological plausibility that this vaccine could cause such an event?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
3. In this patient, did a specific test demonstrate the causal role of the vaccine ?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>Vaccine quality</b>		
4. Could the vaccine given to this patient have a quality defect or is substandard or falsified?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>Immunization error</b>		
5. In this patient, 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"/>	
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
8. When this patient was vaccinated, 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"/>	
9. In this patient, 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"/>	
10. In this patient, 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"/>	
<b>Immunization anxiety (Immunization Triggered Stress Response - ITSR)</b>		
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>II (time). If "yes" to any question in II, was the event within the time window of increased risk?</b>		
12. In this patient, did the event occur within a plausible time window after vaccine administration?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>III. Is there strong evidence against a causal association?</b>		
1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) against a causal association between the vaccine and the event?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>IV. Other qualifying factors for classification</b>		
1. In this patient, did such an event occur in the past after administration of a similar vaccine?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
2. In this patient did such an event occur in the past independent of vaccination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
3. Could the current event have occurred in this patient without vaccination (background rate)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
5. Was this patient taking any medication prior to the vaccination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?	<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 also important to find out if the event occurred within an plausible time window);
- evidence against a causal association;
- other qualifying factors for classification such as previous history of a similar event, the background rate of the event, pre-existing, present and past health conditions, potential risk factors, other medications, exposure to triggering factors etc.

The checklist and the questions are described in Table 1 with some suggestive examples. It is essential that all questions in the checklist be answered with any one of the options, “Yes”, “No”, “Unknown” or “Not applicable”. When there is a positive response to any question, (“Yes” response), it is essential to provide an explanation for the positive response in the corresponding row under remarks. It will be observed that sometimes explanations for other responses (“No”, “Unknown” or “Not applicable”) are also important to determine causality; therefore it is essential that the “Remarks” column is used to provide detailed explanation on 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.

#### ***I.1 In this patient, does the medical history, clinical examination and/ or investigations, confirm another cause for the event?***

A detailed history, clinical examination and investigations including laboratory tests in the patient 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.<sup>1</sup>
- About a quarter of patients with Guillain-Barré syndrome have had a recent *Campylobacter jejuni* infection.<sup>2</sup> 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.
- 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 suggested 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.<sup>3</sup>

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<sup>1</sup> See HPV vaccine in the clear at: <http://www.nhs.uk/news/2009/09September/Pages/Cervical-cancer-vaccine-QA.aspx> (accessed 2 January 2018).

<sup>2</sup> Hughes RAC et al. Guillain-Barré syndrome. *Lancet*, 2005, 366(9497):1653–1666. <https://www.ncbi.nlm.nih.gov/pubmed/16271648> (accessed 2 January 2018).

<sup>3</sup> *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 2 January 2018).

- In the United States, a review of the 2014 – 2015 Vaccine Adverse Events Reporting System (VAERS) data reveals that many of the death reports following MMR vaccine involved children with serious pre-existing medical conditions or were likely unrelated to vaccination (e.g., coincidental). A thorough review of medical records, autopsy reports and death certificates by US FDA and CDC physicians indicated no concerning patterns that would suggest a causal relationship with the MMR vaccine and death<sup>1</sup>.

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

To determine if there is a known causal association with the vaccine or vaccination, all relevant information including statements obtained from the patient, parent or guardian, treating physician and health care providers, supervisors, and community members during investigation are invaluable. In addition, hard evidence such as case records, laboratory records, immunization documents, photographs etc. collected by the investigator are very important. The vaccine package insert and the vaccine reaction rate information sheets<sup>2</sup> also provide supporting information. This will help the assessor to determine if the event is vaccine product related, quality defect related, immunization error or stress related or if the event was coincidental. It is important to be alert in order to detect new events with unknown causality (signals) particularly with new vaccines such as the Malaria vaccine, Dengue vaccine etc. that have been recently developed and approved for use in some countries.

### **Vaccine product(s)**

#### ***II.1 Is there evidence in published peer reviewed literature that this vaccine may cause such an event even if administered correctly?***

The purpose of a vaccine is to induce immunity by causing the recipient's immune system to react to the vaccine. The vaccine reactions rate information sheet of WHO and the package insert of the vaccines describe some of the common vaccine reactions that are expected to occur. Minor AEFI such as local site reactions such as redness and pain at injection site, systemic symptoms such as malaise and signs such as fever that result as part of the immune response are common. In addition, some of the vaccine's components (e.g. adjuvant) can lead to minor reactions. Minor AEFI brought to the notice of the health care system need to be reported but detailed AEFI investigation and causality assessment for such cases are not necessary unless a cluster is suspected.

It is rare for vaccines to produce serious adverse events due to the vaccine's inherent properties when administered correctly. For example:

- 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<sup>3</sup>.
- 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.<sup>4</sup>

<sup>1</sup> Elaine R. Miller et al. Deaths following vaccination: What does the evidence show? *Vaccine*. 2015 Jun 26 ; 33(29) : 3288–3292. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4599698/> (accessed 2 January 2018)

<sup>2</sup> [http://www.who.int/vaccine\\_safety/initiative/tools/vaccinfosheets/en/](http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/) (accessed 2 January 2018)

<sup>3</sup> WHO vaccine reaction rate information sheet – Polio  
[http://www.who.int/vaccine\\_safety/initiative/tools/polio\\_vaccine\\_rates\\_information\\_sheet.pdf?ua=1](http://www.who.int/vaccine_safety/initiative/tools/polio_vaccine_rates_information_sheet.pdf?ua=1)

<sup>4</sup> 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) <http://adc.bmj.com/content/84/3/227> (accessed 2 January 2018)

WHO has developed information sheets that provide details on expected adverse reaction rates of selected vaccines, including monovalent, multivalent and combined vaccines. They provide details of minor and severe adverse reactions (local and systemic) following immunization. Expected rates of vaccine reactions have been included if available in published literature. The information sheets are handy references for assessment. The same can be accessed at [http://www.who.int/vaccine\\_safety/initiative/tools/vaccinfosheets/en/](http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/)

### ***II.2 Is there a biological plausibility that this vaccine could cause such an 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.<sup>1</sup> 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.<sup>2</sup>
- 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.<sup>3</sup>

### ***II.3 In this patient, did a specific test demonstrate the causal role of the vaccine?***

- 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.<sup>4</sup>
- Mycobacterium bovis vaccine strain in BCG can be isolated in children who develop suppurative adenitis because of vaccination at non-recommended sites or with improper technique<sup>5</sup>.

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<sup>1</sup> 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 2 January 2018).

<sup>2</sup> 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](http://www.nap.edu/catalog.php?record_id=13164) (accessed 2 January 2018).

<sup>3</sup> 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 2 January 2018).

<sup>4</sup> 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 2 January 2018).

<sup>5</sup> Francesco d’Aleo, Roberta Bonanno, Antonella Lo Presti Costantino, Salvatore Arena, Angelina Midiri, Giuseppe Mancuso, Carmelo Biondo, and Concetta Beninati. *JMM Case Reports* (2015). A case of abscess after BCG vaccine in an immunocompetent child without other clinical signs <http://www.microbiologyresearch.org/docserver/fulltext/jmmcr/2/6/jmmcr000103.pdf?expires=1514904704&id=id&ccname=guest&checksum=40770A8F97BF8B4BA10F7FA8956CDE7D> (accessed 2 January 2018).

## Vaccine quality

### *II. 4 Could the vaccine given to this patient have a quality defect or is substandard or falsified?*

A vaccine quality defect-related reaction is an AEFI that is caused or precipitated by one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.

Investigations into an outbreak of suppurative lymphadenitis with a particular brand of BCG vaccine in Singapore showed that of the 283 cases of lymphadenitis identified, 76% were suppurative. A spike in suppurative lymphadenitis cases was seen in the 2011 vaccinated cohort, with an incidence rate of 3.16 per 1000 vaccinees, as compared to 0.71 to 0.85 per 1000 in the 2009, 2010 and 2012 cohorts. Detailed investigations identified the likely cause of the outbreak to be batch-related, arising from manufacturing issues encountered by the manufacturer, after ruling out vaccine administration-related and host-related factors<sup>1</sup>.

Death due to a vaccine quality defect has been only infrequently found through the course of history, primarily due to incomplete inactivation of a live vaccine<sup>2</sup>. Almost all such cases have occurred over 60 years ago. For example, in 1929 in the city of Lubeck, Germany, 72 of 252 infants vaccinated with BCG died because of contamination of the vaccine with a live human tuberculosis strain. In 1955, in the Cutter Incident in the United States incomplete activation of the oral polio vaccine resulted in 56 cases of paralytic polio and 5 deaths. This incident triggered the tightening of regulatory measures and strict monitoring of vaccine manufacturing all over the world<sup>3</sup>.

Sometimes vaccines are falsified and are designed specifically to deceive patients, healthcare professionals and procurers into thinking that they are genuine. Others are substandard due to poor manufacturing practices or degradation of the product during distribution and storage. It is important that all steps are taken to ensure that all administered vaccines are authentic and procured from trusted and licensed outlets. Prior to vaccination, the responsible immunization staff should

- Examine the packaging for its condition, spelling mistakes or grammatical errors etc.
- Check registration number, manufacturing and expiry dates as shown on the label
- Ensure the product looks correct, is not discoloured, degraded etc.

Substandard (authorized vaccines that fail to meet either their quality standards or specifications) or falsified vaccines (vaccines that deliberately/fraudulently misrepresent their identity, composition or source) have been detected from all over the world. WHO has received reports of falsified vaccines for yellow fever<sup>4</sup>, meningitis<sup>5,6,7</sup> pentavalent and rabies vaccines<sup>8</sup>.

<sup>1</sup> Investigations into an outbreak of suppurative lymphadenitis with BCG vaccine SSI® in Singapore, Sally Bee Leng Soh et al Vaccine 32 (2014) 5809–5815 <https://www.ncbi.nlm.nih.gov/pubmed/25173482> (accessed 2 January 2018).

<sup>2</sup> An approach to death as an adverse event following immunization, Michael S. Gold Vaccine 34 (2016) 212–217 <https://www.ncbi.nlm.nih.gov/pubmed/26608326> (accessed 2 January 2018).

<sup>3</sup> Offit, Paul A, MD. The Cutter Incident, 50 Years Later. The New England Journal of Medicine; Boston 352.14 (Apr 7, 2005): 1411-2. <http://www.nejm.org/doi/full/10.1056/NEJMp048180> (accessed 2 January 2018).

<sup>4</sup> [http://www.who.int/medicines/publications/drugalerts/Alert2\\_2016\\_Fev\\_Falsified\\_AMARILyellow-fever-vaccine\\_searo\\_en.pdf?ua=1](http://www.who.int/medicines/publications/drugalerts/Alert2_2016_Fev_Falsified_AMARILyellow-fever-vaccine_searo_en.pdf?ua=1) (accessed 2 January 2018).

<sup>5</sup> [http://www.who.int/medicines/publications/drugalerts/AlertWHO2.2015MENCEVAX\\_EN.pdf?ua=1](http://www.who.int/medicines/publications/drugalerts/AlertWHO2.2015MENCEVAX_EN.pdf?ua=1) (accessed 2 January 2018).

<sup>6</sup> [http://www.who.int/medicines/publications/drugalerts/drug\\_alert1-2017/en/](http://www.who.int/medicines/publications/drugalerts/drug_alert1-2017/en/) (accessed 2 January 2018).

<sup>7</sup> [http://www.who.int/medicines/publications/drugalerts/VF\\_MenomuneAlertENversion.pdf?ua=1](http://www.who.int/medicines/publications/drugalerts/VF_MenomuneAlertENversion.pdf?ua=1) (accessed 2 January 2018).

<sup>8</sup> Reemerging Rabies and Lack of Systemic Surveillance in People's Republic of China. Emerg Infect Dis. 2009 Aug; 15(8): 1159–1164. Xianfu Wu et al, [https://wwwnc.cdc.gov/eid/article/15/8/08-1426\\_article](https://wwwnc.cdc.gov/eid/article/15/8/08-1426_article) (accessed 2 January 2018).

## **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 several serious AEFI are precipitated by immunization errors. 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.

### ***II.5 In this patient, 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.)?***

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, systemic and/or local reactions following administration of the product that was stored in non-recommended storage conditions;
- 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
- failure to screen and identify absolute contraindication which may have caused an expected AEFI

### ***II.6 In this patient, was the vaccine (or diluent) administered in an unsterile manner?***

Poor vaccination technique e.g. touching the hypodermic needle can cause abscess. Children immunized with contaminated vaccine (usually the bacterium *Staphylococcus aureus*) become unwell within a few hours. Injection site inflammation (redness, swelling and pain) high fever, rigors, vomiting, diarrhoea, rash and septic shock (toxic shock syndrome) may occur. Deaths have been reported due to septic shock. Bacterial culture of the vial contents, if still available, or of local tissue can confirm the source of the infection.<sup>1</sup>

### ***II.7 In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?***

Abnormal colour, turbidity or presence of visible contaminants may be the first indication that the vaccine contents are abnormal or unsterile and may have caused an AEFI such as injection site abscess.

### ***II.8 When this patient was vaccinated, was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?***

AEFI including deaths 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.<sup>2</sup> Vaccine failure can result if the entire content is not dissolved when freeze-dried vaccines are used or if the cold

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<sup>1</sup> 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 2 January 2018).

<sup>2</sup> 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 2 January 2018).

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.

***II.9 In this patient, was there an error in vaccine handling (e.g. a break in the 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).

***II.10 In this patient, 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 (Immunization Triggered Stress Response - ITSR)**

An “immunization anxiety related reaction” is the current terminology used to describe a range of signs and symptoms that describe an AEFI arising from anxiety about the immunization. However, this term does not capture all elements of such events and also some AEFIs that may not manifest with typical symptoms of anxiety<sup>1</sup>. WHO has proposed to refer to such events as “Immunization Triggered Stress Response (ITSR)<sup>2</sup>”. The terminology of ITSR are described as follows,

- The word **immunization** is used in this context to describe the process of administering the vaccine and to include the time period before, during and after vaccine administration. The immunization process is recognized to act as the **triggering** event.
- **Stress (response)** is used to include the array of symptoms and signs that may occur.
- **Response** recognizes that the manifestation of and reaction to stress. This is complex and involves a combination of biological factors occurring within an individual combined with his or her own psychological strengths and vulnerabilities within a particular social context (the biopsychosocial context).

***II.11 In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?***

The types of reactions caused by immunization stress responses include, but are not limited to, acute stress responses, vasovagal reactions and conversion disorders. For example:

- In September 1998, more than 800 young people in Jordan believed they had suffered from side-effects such as fever, feeling faint, headaches and dizziness, chest tightness and hypotension following administration 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

<sup>1</sup> Anxiety-related adverse events following immunization (AEFI):A systematic review of published clusters of illness. Anagha Loharikar et al, Vaccine 2017 <https://www.ncbi.nlm.nih.gov/pubmed/29198916> (accessed 2 January 2018).

<sup>2</sup> Weekly Epidemiological Record, 19 January 2018, vol. 93, 03 (pp. 17–32) <http://apps.who.int/iris/bitstream/10665/259874/1/WER9303.pdf?ua=1> (accessed on 2 February 2018)



review of the literature showed, however, that this mass reaction was similar in many ways to previous outbreaks, even though the underlying causes varied.<sup>1</sup>

- On 7 May 2007, 720 girls aged 12–17 years received 4vHPV at a girls school in metropolitan Melbourne. Within 2 hours of vaccination, 26 girls presented to the school's sick bay with symptoms including dizziness, syncope and neurological complaints. Four of them were hospitalized with a range of symptoms, including palpitations, dizziness, syncope or collapse, weakness and aphasia. Without evidence of an organic aetiology or similar reports of AEFI elsewhere after the initiation of population vaccination with 4vHPV using the same vaccine batch, it is highly likely that this cluster was the result of a psychogenic response to mass vaccination in a school setting<sup>2</sup>. Other studies on HPV vaccine administration in adolescents have similar findings<sup>3</sup>.

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).<sup>4</sup>

## **II (time). If “yes” to any question in II, was the event within the time window of increased risk?**

### **II. 12 In this patient, did the event occur within a plausible time window after vaccine administration?**

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

- The “plausible” 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.<sup>5</sup> 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.
- Syncope usually occurs very rapidly after immunization. In a large case series study conducted in the United States spanning over six years, of 697 cases of syncope evaluated, 63% occurred 5 minutes or less, 89% occurred 15 minutes or less, and 98% occurred 30 minutes or less after vaccination<sup>6</sup>

## **III. Is there strong evidence against a causal association?**

### **III.1 Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) against a causal association between the vaccine and the event?**

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:

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<sup>1</sup> 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 2 January 2018).

<sup>2</sup> Jim P Buttery et al. Mass psychogenic response to human papillomavirus vaccination, *The Medical Journal of Australia* Volume 189 Number 5 1 September 2008 <https://www.mja.com.au/journal/2008/189/5/mass-psychogenic-response-human-papillomavirus-vaccination> (accessed 2 January 2018).

<sup>3</sup> Diana M Bernard et al. The domino effect: adolescent girls' response to human papillomavirus vaccination *Med J Aust* 2011; 194 (6): 297-300. <https://www.ncbi.nlm.nih.gov/pubmed/21426284> (accessed 2 January 2018).

<sup>4</sup> 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 2 January 2018).

<sup>5</sup> *Case definition: poliomyelitis*. Pan American Health Organization. See: <http://www.paho.org/english/ad/fch/im/PolioCaseDefinition.htm> (accessed 2 January 2018).

<sup>6</sup> Syncope after immunization. Braun MM et al *Arch Pediatr Adolesc Med*. 1997 Mar;151(3):255-9. <https://www.ncbi.nlm.nih.gov/pubmed/9080932> (accessed 2 January 2018).

- 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.<sup>1 2</sup>
- A 2003 Institute of Medicine (IOM) report “Immunization Safety Review: Vaccination and Sudden Unexpected Death in Infancy.” The committee reviewed scientific evidence focusing on sudden unexpected death in infancy and looked for possible relationships between SIDS and vaccines. Based on all the research findings they reviewed, the committee concluded that vaccines did not cause SIDS<sup>3</sup>.

#### ***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.

##### ***IV. 1 In this patient, did such an event occur in the past after administration 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.<sup>4</sup>
- 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.<sup>5</sup>

##### ***IV. 2 In this patient did such an event occur in the past independent 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:

<sup>1</sup> *MMR and autism*. World Health Organization. See: [http://www.who.int/vaccine\\_safety/topics/mmr/mmr\\_autism/en/](http://www.who.int/vaccine_safety/topics/mmr/mmr_autism/en/) (accessed 2 January 2018).

<sup>2</sup> *Adverse effects of vaccines: evidence and causality*. United States Institute of Medicine. See: <https://www.nap.edu/catalog/13164/adverse-effects-of-vaccines-evidence-and-causality> (accessed 2 January 2018).

<sup>3</sup> Immunization Safety Review: Vaccinations and Sudden Unexpected Death in Infancy <http://www.nationalacademies.org/hmd/Reports/2003/Immunization-Safety-Review-Vaccinations-and-Sudden-Unexpected-Death-in-Infancy.aspx> (accessed 2 January 2018).

<sup>4</sup> 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 2 January 2018).

<sup>5</sup> 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 2 January 2018).

- Atopic dermatitis is a chronic inflammatory skin disease, affecting 10-20% of children. Measles vaccination has been reported to have contradictory effects on incidence of Atopic dermatitis in children. A study to determine the influence of measles vaccination on the progression of atopic dermatitis in infants showed that measles vaccination not only does not aggravate Atopic dermatitis, but may also improve some of the immunological parameters of this allergic disease. Thus for example if a 24-month-old child receives MMR immunization and two days later presents with a diagnosis of atopic dermatitis, a careful clinical history, may reveal that the child may have developed atopic dermatitis previously and had experienced frequent flares in the past.<sup>1</sup>

#### ***IV. 3 Could the current event have occurred in this patient without vaccination (background rate)?***

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:

- A nationwide population based cohort study determining the background rates of disease in a population in Denmark to assess vaccine safety in childhood and mass immunisation showed that the incidence of outcome diagnoses spanned from 0.32 per 100 000 patient years for autoimmune thrombocytopenia to 189.82 per 100 000 patient years for seizure. Seasonal differences were most pronounced for anaphylactic shock, seizure, and multiple sclerosis. Even for rare outcomes, numerous events were predicted in the hypothetical vaccine cohort, for example 20 cases of type 1 diabetes mellitus, 19 of juvenile or rheumatoid arthritis, eight of facial nerve palsy, and five of multiple sclerosis per 1 000 000 children would occur within 42 days after vaccination<sup>2</sup>.
- 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).<sup>3</sup>

#### ***IV. 4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event ?***

During an AEFI investigation, by obtaining a detailed history, clinical examination and laboratory investigation in a patient may unravel other intrinsic pre-existing illness, health conditions or risk factors that may have precipitated the AEFI. For example:

- Severe Myoclonic Epilepsy in infancy (SMEI, or Dravet syndrome) is a drug-resistant epilepsy that occurs in the first year of life of previously healthy children. The main clinical features are prolonged and repeated febrile and afebrile generalized or unilateral

<sup>1</sup> 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 2 January 2018).

<sup>2</sup> Use of population based background rates of disease to assess vaccine safety in childhood and mass immunisation in Denmark: nationwide population based cohort study. Thomas A Rasmussen et al *BMJ*. 2012; 345: e5823. Published online 2012 Sep 17. doi: 10.1136/bmj.e5823 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3444137/> (accessed 2 January 2018).

<sup>3</sup> 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 2 January 2018).

convulsive seizures. In the course of the epilepsy, cognitive deterioration becomes evident, and interictal myoclonus, clumsiness and ataxia appear. One third of the children with SMEI show de novo mutations of the SCN1A gene, and additional familial genes probably contribute to the phenotype<sup>1</sup>. Vaccination might trigger earlier onset of Dravet syndrome in children who, because of an SCN1A mutation, are destined to develop the disease. However, vaccination should not be withheld from children with SCN1A mutations because it was found that there was no evidence that vaccinations before or after disease onset affect outcome<sup>2</sup>.

- It has been observed that the risk of disseminated BCG disease is increased several hundred fold in HIV-infected infants compared to the documented risk in HIV-uninfected infants. Recent evidence shows that children who were HIV-infected when vaccinated with BCG at birth, and who later developed AIDS, were at increased risk of developing disseminated BCG disease. Since risks outweigh benefits for BCG vaccination for infants who are known to be HIV infected with or without signs or reported symptoms of HIV infection. WHO recommends that these infants should not be immunized with BCG vaccine<sup>3</sup>.

#### ***IV. 5 Was this patient taking any medication prior to the vaccination?***

Medications are known to cause adverse reactions and, when given concurrently with vaccine(s), must be considered as possible coincidental 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).

#### ***IV.6 Was this patient exposed to a potential risk factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc)?***

Prior exposure to extrinsic 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<sup>4</sup>.

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<sup>1</sup> Markus Wolff, Catherine Cass'e-Perrot and Charlotte Drave; *Epilepsia*, 47(Suppl. 2):45 - 48, 2006 Blackwell Publishing, Inc. International League Against Epilepsy Severe Myoclonic Epilepsy of Infants (Dravet Syndrome): Natural History and Neuropsychological Findings <https://www.ncbi.nlm.nih.gov/pubmed/17105460> (accessed 2 January 2018).

<sup>2</sup> Anne M McIntosh et al, *The Lancet* Volume 9, No. 6, p592–598, June 2010; Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study <https://www.ncbi.nlm.nih.gov/pubmed/20447868> (accessed 2 January 2018).

<sup>3</sup> *Weekly Epidemiological Record*, NO. 21, 25 MAY 2007 <http://www.who.int/wer/2007/wer8221.pdf> (accessed 2 January 2018).

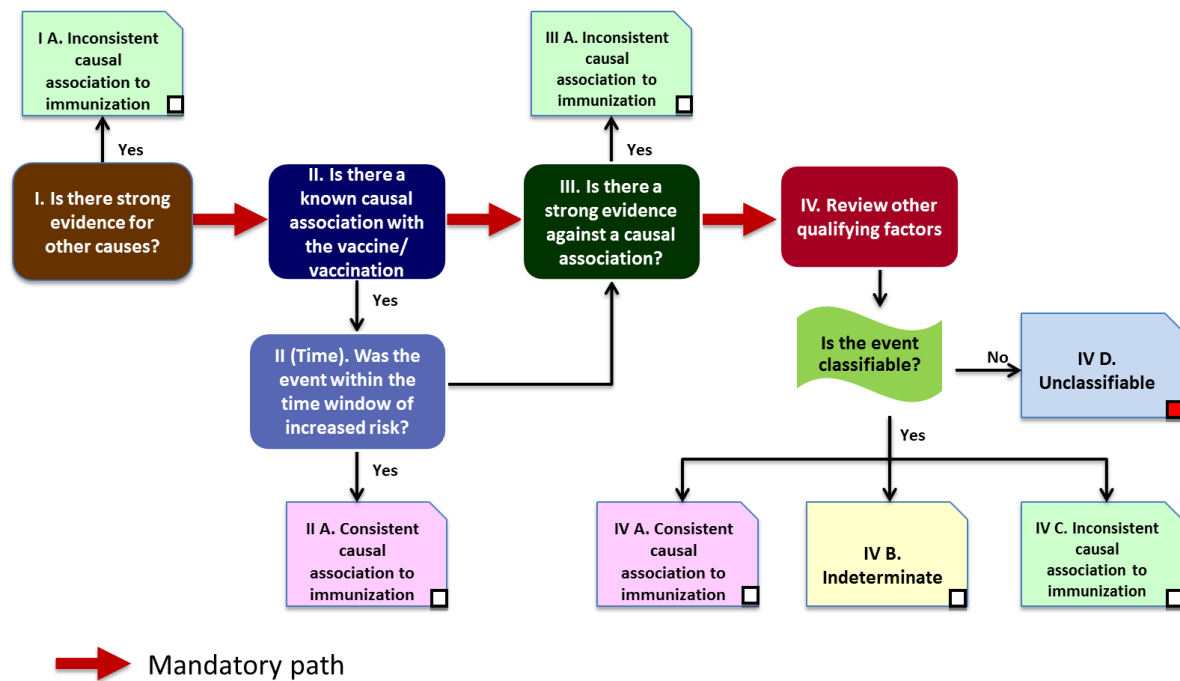
<sup>4</sup> Wise RP et al, Hair loss after routine immunizations. *JAMA*. 1997 Oct 8;278(14):1176-8. <https://www.ncbi.nlm.nih.gov/pubmed/9326478> (accessed 2 January 2018).

- 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.<sup>1</sup>

### Step 3: Algorithm

After the checklist is completed, data related to the association under investigation 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).

**Fig. 3. Causality assessment algorithm**



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 (red arrow) 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.

During the initial stages of the assessment when considering the eligibility (step 1), the reviewer may consider the available information to be sufficient for initiating the causality assessment process. However after completing the checklist (step 2), it may be discovered that the information is insufficient to arrive at a definite conclusion. At this stage of the review, the

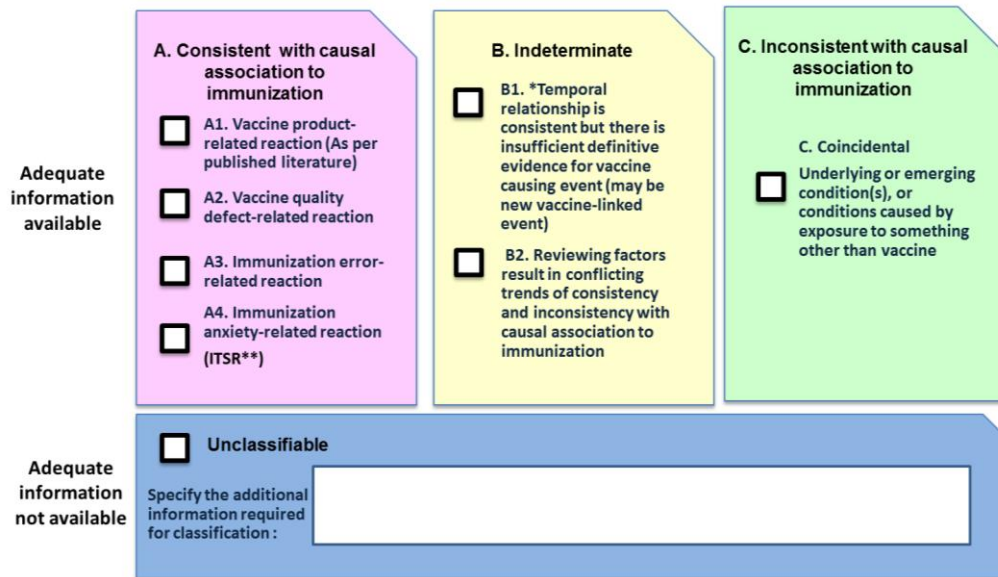
<sup>1</sup> Robertson WC Jr. Carbamazepine toxicity after influenza vaccination. *Pediatric Neurology*, 2002, 26(1):61–63. See: <http://www.sciencedirect.com/science/article/pii/S0887899401003320> (accessed 2 January 2018).

reviewer may decide to categorize the case as “Unclassifiable” (check-box marked in red in Fig 3) and specify the missing information that prevents the classification of the case. 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. 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 and document 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*.<sup>1</sup> 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



\*B1: This is a potential signal and maybe considered for investigation  
\*\* Immunization Triggered Stress Response

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

<sup>1</sup> *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.  
[http://www.who.int/vaccine\\_safety/initiative/tools/CIOMS\\_report\\_WG\\_vaccine.pdf](http://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf) (accessed 2 January 2018)

- 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***

As mentioned above, such cases are 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.

## VI. Summarizing the logic of AEFI causality assessment

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 a case that is initially evaluated as eligible for classification when assessed is found to have inadequate information, causality assessment is not possible and the case is categorised as unclassifiable. Even with adequate information, the precision of causality is largely determined by the expertise, experience and skill of the assessors (Fig. 5).

It must be remembered that 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. 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. The final decision on prioritizing the choices logically needs to be made after discussion and arriving at a consensus.

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*<sup>1</sup> and are described in the next chapter. With available evidence, several cases would still 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.

**Fig. 5. Summary of classification logic**

<p><b>Summarize the classification logic in the order of priority:</b> With available evidence, we could conclude that the most likely classification is _____ because:</p> <ol style="list-style-type: none"><li>1.</li><li>2.</li></ol> <p>With available evidence, we could NOT classify the case because _____</p>
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Causality can change when additional information becomes available either about the same case or about similar cases. For example, a case of narcolepsy after H1N1 influenza vaccine may currently be classified as a likely vaccine product related AEFI, while the same case would have been classified as coincidental or indeterminate prior to establishing the association between narcolepsy and influenza vaccine in 2010 by scientific evidence<sup>2</sup>. 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.

<sup>1</sup> *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.  
[http://www.who.int/vaccine\\_safety/initiative/tools/CIOMS\\_report\\_WG\\_vaccine.pdf](http://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf) (accessed 2 January 2018)

<sup>2</sup> Markku Partinen et al. Increased Incidence and Clinical Picture of Childhood Narcolepsy following the 2009 H1N1 Pandemic Vaccination Campaign in Finland. *Plos One* Published: March 28, 2012  
<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0033723> (accessed 2 January 2018)



## VII. Underlying mechanisms for the classification of AEFI

### 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 an inactivated intranasal influenza vaccine<sup>1</sup> 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-DTaP vaccination<sup>2</sup>,
      - 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

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<sup>1</sup> Margot Mutsch et al, Use of the Inactivated Intranasal Influenza Vaccine and the Risk of Bell's Palsy in Switzerland. N Engl J Med 2004; 350:896-903 February 26, 2004 <https://www.ncbi.nlm.nih.gov/pubmed/14985487> (accessed 2 January 2018)

<sup>2</sup> Margaret B. Rennels et al, Extensive Swelling After Booster Doses of Acellular Pertussis–Tetanus–Diphtheria Vaccines Pediatrics January 2000, Volume 105 / Issue 1 <https://www.ncbi.nlm.nih.gov/pubmed/10617749> (accessed 2 January 2018)

- 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.

### ***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 cause adequate immune response 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 cause adequate immune response 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 and other bodily injuries 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 (Immunization Triggered Stress Response - ITSR)***

Stress responses to immunization can be triggered and may manifest just prior to, during, or after immunization. It is called Immunization Triggered Stress Response (ITSR). ITSR can be broadly classified as

- Peri-immunization stress responses **where** symptoms may manifest immediately before, during, or after immunization. Unlike other classifications of AEFIs that always present post-immunization, **peri-immunization ITSR may even** occur prior to immunization in anticipation of the procedure. Peri-immunization stress responses are usually immediate, transient and resolve spontaneously.
- Post-immunization stress responses may or may not be preceded by a peri-**immunization** ITSR. The symptoms and signs may take many hours to days to develop. Longer-lasting

responses may involve increased sensitivity of the Hypothalamic Pituitary Adrenocortical axis.

- Other disorders or syndromes that can occur post-immunization **where the delayed and ongoing symptoms are reported post-immunization and the symptoms and signs are unexplained after appropriate medical investigations and the causal association with immunization is unclear.**

## **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.

## VIII. Initiating action after AEFI causality assessment

Determining causality is not an end in itself. The lessons learned from the assessment should provide insights and guidance for the technical, immunization programme and administrative managers on the causes and the logical next steps – 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.
- 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.
- Substandard and/or falsified vaccines when detected should be reported to the local Ministry of Public Health / National Medicines Regulatory Authorities/ National Pharmacovigilance Centre and the WHO Global Surveillance and Monitoring System for Substandard and Falsified medical products at [rapidalert@who.int](mailto:rapidalert@who.int). Further information is available at [www.who.int/medicines/regulation/ssffc/en/](http://www.who.int/medicines/regulation/ssffc/en/).

#### A3. Immunization error-related reaction

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

#### A4. Immunization anxiety-related reaction (Immunization Triggered Stress Response - ITSr)

- Depending on the solitary or cluster nature of the ITSr, there are separate approaches for prevention, diagnosis and management including communications, training and capacity-building to avoid recurrences of such reactions.

### 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.

## **D. Ineligible cases and Unclassifiable cases**

Cases ineligible for causality assessment are those where the amount of information available to the assessor is limited such that a causality question cannot be created. For example, the reviewer does not have information on the type of vaccines administered to the patient or the clinical details are insufficient to formulate a causality question. Cases may also be considered ineligible prior to the assessment if the investigation is incomplete and the essential information is not available.

Unclassifiable cases occur in instances where the reviewer is able to formulate a causality question, but during the process of assessment discovers that some important elements are missing to enable a logical classification.

For both ineligible and unclassifiable cases, it is important to specify the missing elements and make attempts to obtain the information so that causality assessment could be attempted again. It is essential that the available details of such cases are placed in a central repository that the investigators can revert back to when additional information that would help with the causality assessment is available.

## IX. 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 eligibility are achieved, 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. WHO has developed an electronic software that can assist with the AEFI causality assessment process using the method described in this manual. The same can be accessed online at <http://gvsj-aeji-tools.org/>.

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.<sup>1</sup>

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<sup>1</sup> 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 2 January 2018)

# Annex 1: Worksheet for AEFI causality assessment

Patient ID/ Name :

DoB/ Age:

Sex: Male/ Female

## Step 1 (Eligibility)

Name one of the 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 for review in step 2 - valid diagnosis)

**Is this case eligible for causality assessment? Yes/ No; If, "Yes", proceed to step 2**

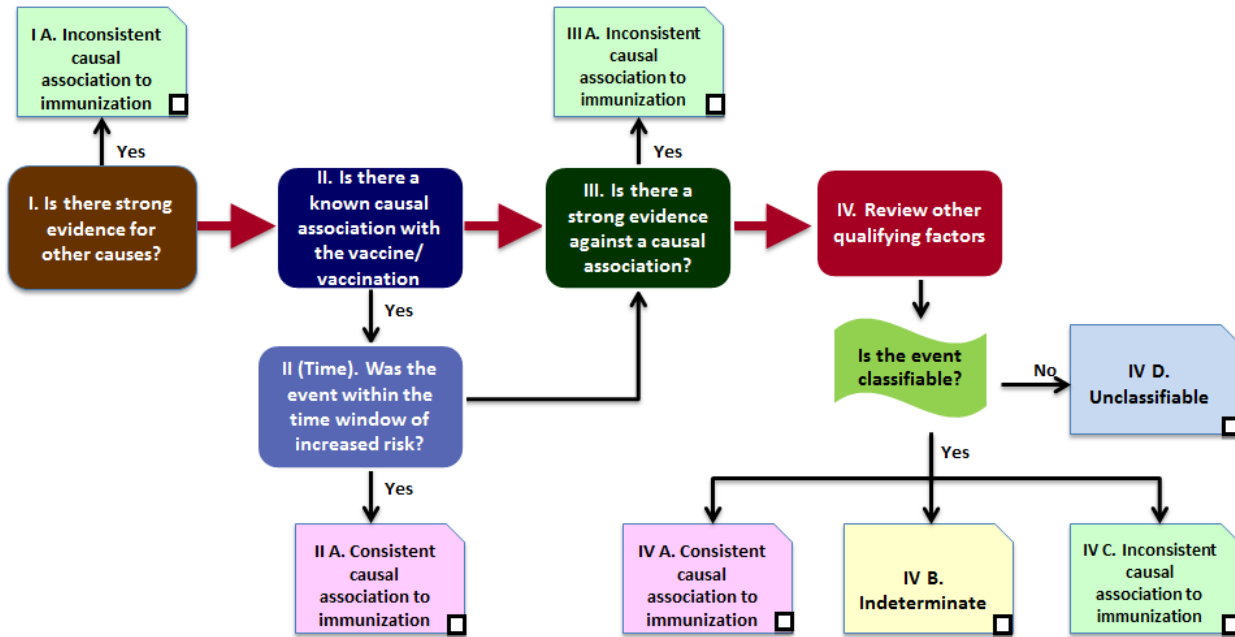
## Step 2 (Event Checklist) ✓ (check) all boxes that apply

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
1. In this patient, does the medical history, clinical examination and/ or investigations, confirm another cause for the event?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>II. Is there a known causal association with the vaccine or vaccination?</b>		
<b>Vaccine product</b>		
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
2. Is there a biological plausibility that this vaccine could cause such an event?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
3. In this patient, did a specific test demonstrate the causal role of the vaccine ?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>Vaccine quality</b>		
4. Could the vaccine given to this patient have a quality defect or is substandard or falsified?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>Immunization error</b>		
5. In this patient, 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"/>	
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
8. When this patient was vaccinated, 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"/>	
9. In this patient, 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"/>	
10. In this patient, 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"/>	
<b>Immunization anxiety (Immunization Triggered Stress Response - ITSR)</b>		
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>II (time). If "yes" to any question in II, was the event within the time window of increased risk?</b>		
12. In this patient, did the event occur within a plausible time window after vaccine administration?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>III. Is there strong evidence against a causal association?</b>		
1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) <b>against</b> a causal association between the vaccine and the event?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>IV. Other qualifying factors for classification</b>		
1. In this patient, did such an event occur in the past after administration of a similar vaccine?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
2. In this patient did such an event occur in the past independent of vaccination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
3. Could the current event have occurred in this patient without vaccination (background rate)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
5. Was this patient taking any medication prior to the vaccination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	

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



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



**→** Mandatory path

**Notes for Step 3:**

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

<b>Adequate information available</b>	<p><b>A. Consistent with causal association to immunization</b></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 (ITSR**)</p>	<p><b>B. Indeterminate</b></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><b>C. Inconsistent with causal association to immunization</b></p> <p><input type="checkbox"/> C. Coincidental Underlying or emerging condition(s), or conditions caused by exposure to something other than vaccine</p>
<b>Adequate information not available</b>	<p><input type="checkbox"/> <b>Unclassifiable</b></p> <p>Specify the additional information required for classification: <input style="width: 100%;" type="text"/></p>		

\*B1: This is a potential signal and maybe considered for investigation  
 \*\* Immunization Triggered Stress Response

**Summarize the classification logic in the order of priority:**  
 With available evidence, we could conclude that the classification is \_\_\_\_\_ because:

With available evidence, we could **NOT** classify the case 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 quality, application of correct procedures and technique 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)

Patient ID/ Name : PQ

DoB/ Age: 5 Months

Sex:  Male/ Female

Name one of the vaccines administered before this event	What is the Valid Diagnosis?	Does the diagnosis meet a case definition?
Menjugate (Meningococcal Gr C conjugate vaccine)	Meningoencephalitis	Yes (level 2 of Brighton Collaboration)

**Create your question on causality here**

Has the Menjugate vaccine / vaccination caused \_\_\_\_\_ Meningoencephalitis \_\_\_\_\_ (The event for review in step 2)

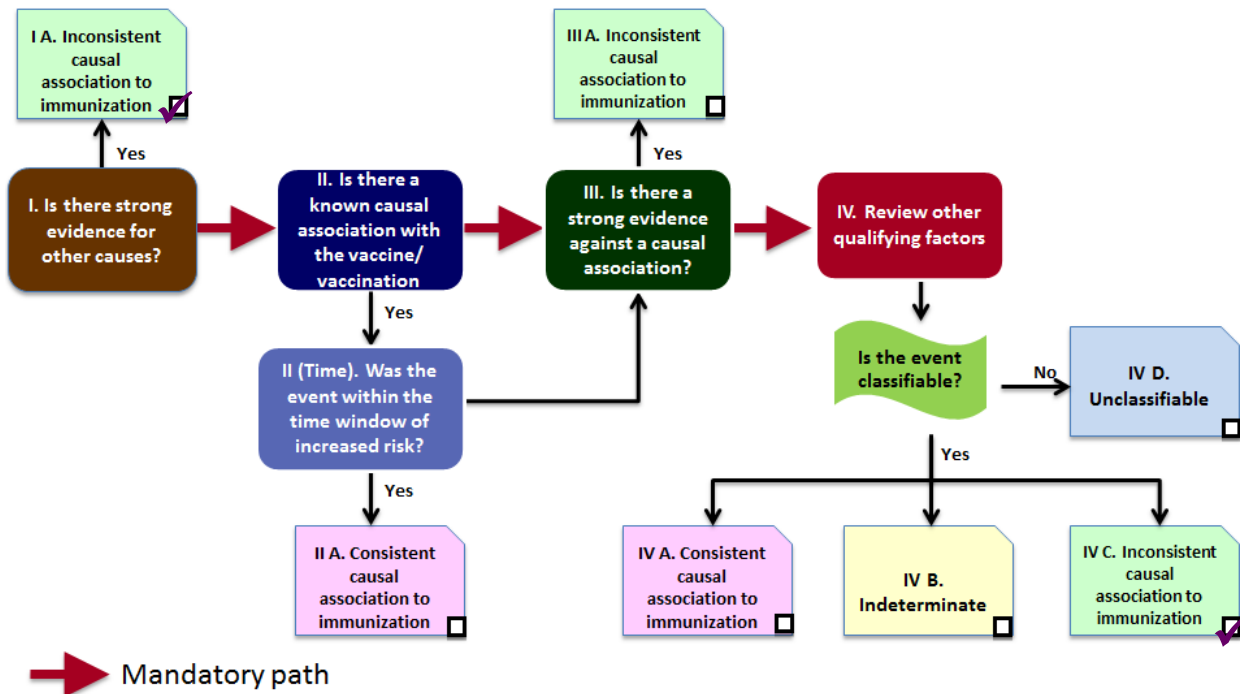
Is this case eligible for causality assessment?  Yes/ No; If, "Yes", proceed to step 2

## Step 2 (Event Checklist) (check) all boxes that apply

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
1. In this patient, does the medical history, clinical examination and/ or investigations, confirm another cause for the event?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Yes – CSF PCR positive for herpes simplex virus
<b>II. Is there a known causal association with the vaccine or vaccination?</b>		
<b>Vaccine product</b>		
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Unknown – not reported so far in literature
2. Is there a biological plausibility that this vaccine could cause such an event?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	Contains inactivated extracts of <i>Neisseria meningitidis</i> group C bacteria
3. In this patient, did a specific test demonstrate the causal role of the vaccine?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	No – CSF PCR positive for herpes simplex virus
<b>Vaccine quality</b>		
4. Could the vaccine given to this patient have a quality defect or is substandard or falsified?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	As per investigation report
<b>Immunization error</b>		
5. In this patient, 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"/>	As per investigation report
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	As per investigation report
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	As per investigation report
8. When this patient was vaccinated, 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"/>	As per investigation report
9. In this patient, 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"/>	As per investigation report
10. In this patient, 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"/>	As per investigation report
<b>Immunization anxiety (Immunization Triggered Stress Response - ITSR)</b>		
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Anxiety cannot cause Meningoencephalitis
<b>II (time). If "yes" to any question in II, was the event within the time window of increased risk?</b>		
12. In this patient, did the event occur within a plausible time window after vaccine administration?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/>	Because there are no, "Yes" responses in II.
<b>III. Is there strong evidence against a causal association?</b>		
1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) against a causal association between the vaccine and the event?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	Unknown – hasn't been studied
<b>IV. Other qualifying factors for classification</b>		
1. In this patient, did such an event occur in the past after administration of a similar vaccine?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Child fine after first dose
2. In this patient did such an event occur in the past independent of vaccination?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Was in good health previously
3. Could the current event have occurred in this patient without vaccination (background rate)?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Several causes for infant meningoencephalitis
4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
5. Was this patient taking any medication prior to the vaccination?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	"No" is also ok here
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	

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

### Step 3 (Algorithm) review all steps and ✓ 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) ✓ all boxes that apply

Adequate information available	<b>A. Consistent with causal association to immunization</b> <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 (ITSR**)	<b>B. Indeterminate</b> <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	<b>C. Inconsistent with causal association to immunization</b> <input checked="" type="checkbox"/> C. Coincidental Underlying or emerging condition(s), or conditions caused by exposure to something other than vaccine
	<input type="checkbox"/> <b>Unclassifiable</b> Specify the additional information required for classification:		

Summarize the classification logic in the order of priority:  
*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 (SIA). The last OPV before paralysis onset (and stool sample collection) was administered on 7 June 2009 as a part of SIA.

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.

Patient ID/ Name :MA

DoB/ Age: 29.12.2006

Sex:  Male/ Female

**Step 1 (Eligibility)**

Name one of the vaccines administered before this event	What is the Valid Diagnosis?	Does the diagnosis meet a case definition?
OPV	AFP	Yes*

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

Is this case eligible for causality assessment?  Yes/ No; If, "Yes", proceed to step 2

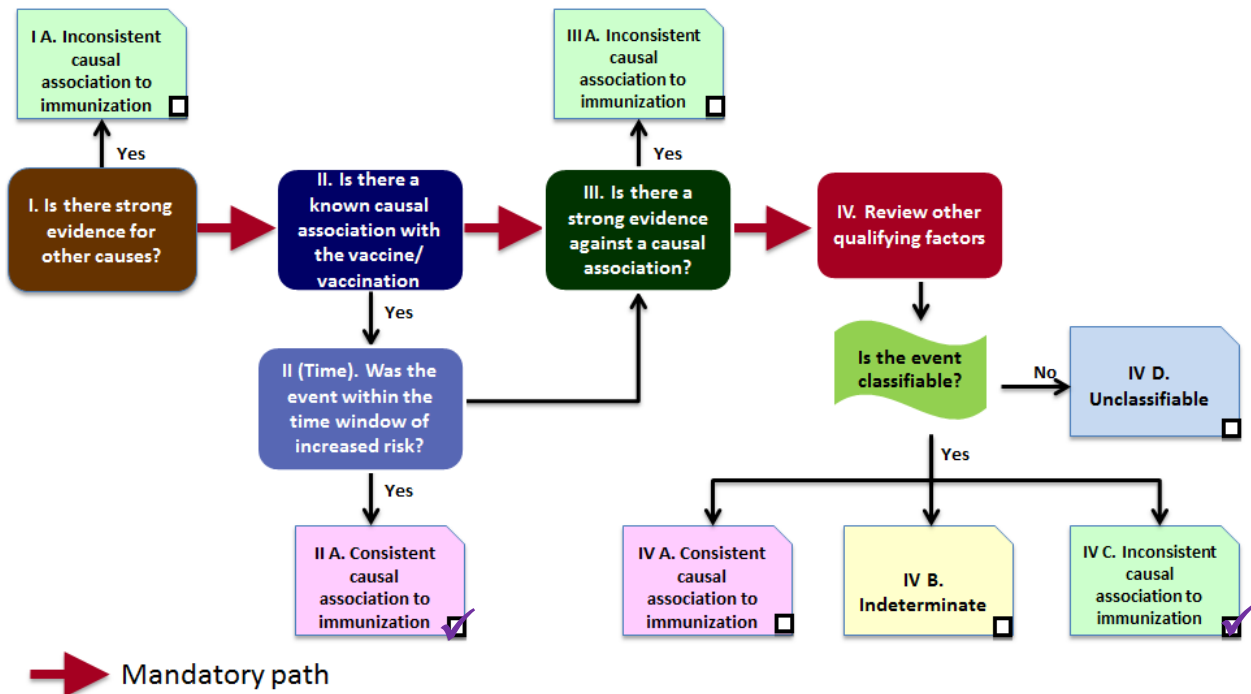
**Step 2 (Event Checklist)**  (check) all boxes that apply

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
1. In this patient, does the medical history, clinical examination and/ or investigations, confirm another cause for the event?	<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>
<b>II. Is there a known causal association with the vaccine or vaccination?</b>		
<b>Vaccine product</b>		
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>VAPP is a recognized event</i>
2. Is there a biological plausibility that this vaccine could cause such an event?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Sabin OPV can cause AFP</i>
3. In this patient, did a specific test demonstrate the causal role of the vaccine ?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Sabin 1 and 2 isolated from stool</i>
<b>Vaccine quality</b>		
4. Could the vaccine given to this patient have a quality defect or is substandard or falsified?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Very unlikely in OPV SIA</i>
<b>Immunization error</b>		
5. In this patient, 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"/>	<i>Details unavailable</i>
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	<i>Details unavailable</i>
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	<i>Details unavailable</i>
8. When this patient was vaccinated, 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"/>	<i>OPV is not reconstituted</i>
9. In this patient, 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"/>	<i>Details unavailable</i>
10. In this patient, 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>Details unavailable</i>
<b>Immunization anxiety (Immunization Triggered Stress Response - ITSR)</b>		
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>II (time). If "yes" to any question in II, was the event within the time window of increased risk?</b>		
12. In this patient, did the event occur within a plausible time window after vaccine administration?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Yes, 24 days after OPV</i>
<b>III. Is there strong evidence against a causal association?</b>		
1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) <b>against</b> a causal association between the vaccine and the event?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>IV. Other qualifying factors for classification</b>		
1. In this patient, did such an event occur in the past after administration of a similar vaccine?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
2. In this patient did such an event occur in the past independent of vaccination?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
3. Could the current event have occurred in this patient without vaccination (background rate)?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>There are many causes for AFP</i>
4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Unknown illness &lt; 30 days</i>
5. Was this patient taking any medication prior to the vaccination?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Unknown injection &lt; 30 days previously</i>
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>IM injections 30 days prior: A risk factor for VAPP</i>

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

\*[http://www.who.int/immunization\\_monitoring/diseases/poliomyelitis](http://www.who.int/immunization_monitoring/diseases/poliomyelitis)

### Step 3 (Algorithm) review all steps and ✓ 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 AFP 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) ✓ all boxes that apply

Adequate information available	<b>A. Consistent with causal association to immunization</b> <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 (ITSR**)	<b>B. Indeterminate</b> <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	<b>C. Inconsistent with causal association to immunization</b> <input checked="" type="checkbox"/> C. Coincidental Underlying or emerging condition(s), or conditions caused by exposure to something other than vaccine
	<input type="checkbox"/> <b>Unclassifiable</b> Specify the additional information required for classification:		
	Adequate information not available		

**Summarize the classification logic in the order of priority:**  
*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 25nm 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.



**Step 1 (Eligibility)**

**Option 1 – MMR vaccine and thrombocytopenia**

Patient ID/ Name : XX

DoB/ Age: 01.12.2010

Sex: Male/  Female

Name one of the vaccines administered before this event	What is the Valid Diagnosis?	Does the diagnosis meet a case definition?
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MMR	Thrombocytopenia	Yes, Brighton level 2
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**Create your question on causality here**

Has the MMR vaccine / vaccination caused Thrombocytopenia (The event for review in step 2)

Is this case eligible for causality assessment?  Yes/ No; If, "Yes", proceed to step 2

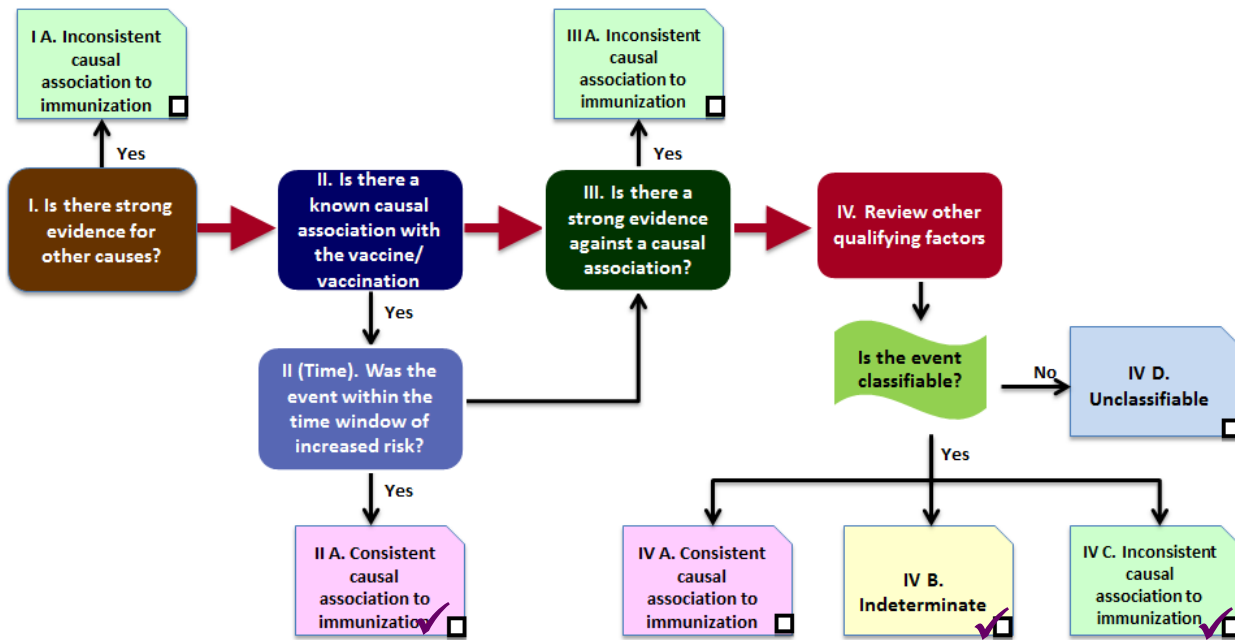
**Step 2 (Event Checklist)**  (check) all boxes that apply

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
1. In this patient, does the medical history, clinical examination and/ or investigations, confirm another cause for the event?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	With platelet count ↓, Liver enlarged, TWBC ↓ the tests may support dengue as a dx but unable to confirm it
<b>II. Is there a known causal association with the vaccine or vaccination?</b>		
<b>Vaccine product</b>		
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Measles vaccine can cause thrombocytopenia
2. Is there a biological plausibility that this vaccine could cause such an event?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Many viral infections cause thrombocytopenia
3. In this patient, did a specific test demonstrate the causal role of the vaccine ?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>Vaccine quality</b>		
4. Could the vaccine given to this patient have a quality defect or is substandard or falsified?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	As per investigation report
<b>Immunization error</b>		
5. In this patient, 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"/>	As per investigation report
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	As per investigation report
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
8. When this patient was vaccinated, 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"/>	As per investigation report
9. In this patient, 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"/>	As per investigation report
10. In this patient, 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"/>	As per investigation report
<b>Immunization anxiety (Immunization Triggered Stress Response - ITSR)</b>		
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>II (time). If "yes" to any question in II, was the event within the time window of increased risk?</b>		
12. In this patient, did the event occur within a plausible time window after vaccine administration?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	< 6 weeks - see Ref <sup>1</sup> below
<b>III. Is there strong evidence against a causal association?</b>		
1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) <b>against</b> a causal association between the vaccine and the event?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>IV. Other qualifying factors for classification</b>		
1. In this patient, did such an event occur in the past after administration of a similar vaccine?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/>	
2. In this patient did such an event occur in the past independent of vaccination?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	She had an attack of fever one week prior
3. Could the current event have occurred in this patient without vaccination (background rate)?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Dengue endemic country
4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event?	<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 cough and vomiting, diarrhoea)
5. Was this patient taking any medication prior to the vaccination?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	

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

<sup>1</sup> Idiopathic thrombocytopenic purpura and MMR vaccine; E. Miller et al <http://adc.bmj.com/content/84/3/22>

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



➔ Mandatory path

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

### Step 4 (Classification) ✓ all boxes that apply

Adequate information available	<b>A. Consistent with causal association to immunization</b> <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 (ITSR**)	<b>B. Indeterminate</b> <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	<b>C. Inconsistent with causal association to immunization</b> <input checked="" type="checkbox"/> C. Coincidental Underlying or emerging condition(s), or conditions caused by exposure to something other than vaccine
	<input type="checkbox"/> <b>Unclassifiable</b> Specify the additional information required for classification:		

**Summarize the classification logic in the order of priority:**  
 With available evidence, we could conclude that the classification could be indeterminate / inconsistent because: 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. Death could have occurred by fluid overload.

**Option 2 – MMR vaccine and sepsis**

**Step 1 (Eligibility)**

Patient ID/ Name : XX

DoB/ Age: 01.12.2010

Sex: Male/  Female

Name one of the vaccines administered before this event	What is the Valid Diagnosis?	Does the diagnosis meet a case definition?
MMR	Sepsis	<i>Yes weblink: <a href="http://www.bmj.com/content/335/7625/879">http://www.bmj.com/content/335/7625/879</a></i>

**Create your question on causality here**

Has the MMR vaccine / vaccination caused Sepsis (The event for review in step 2)

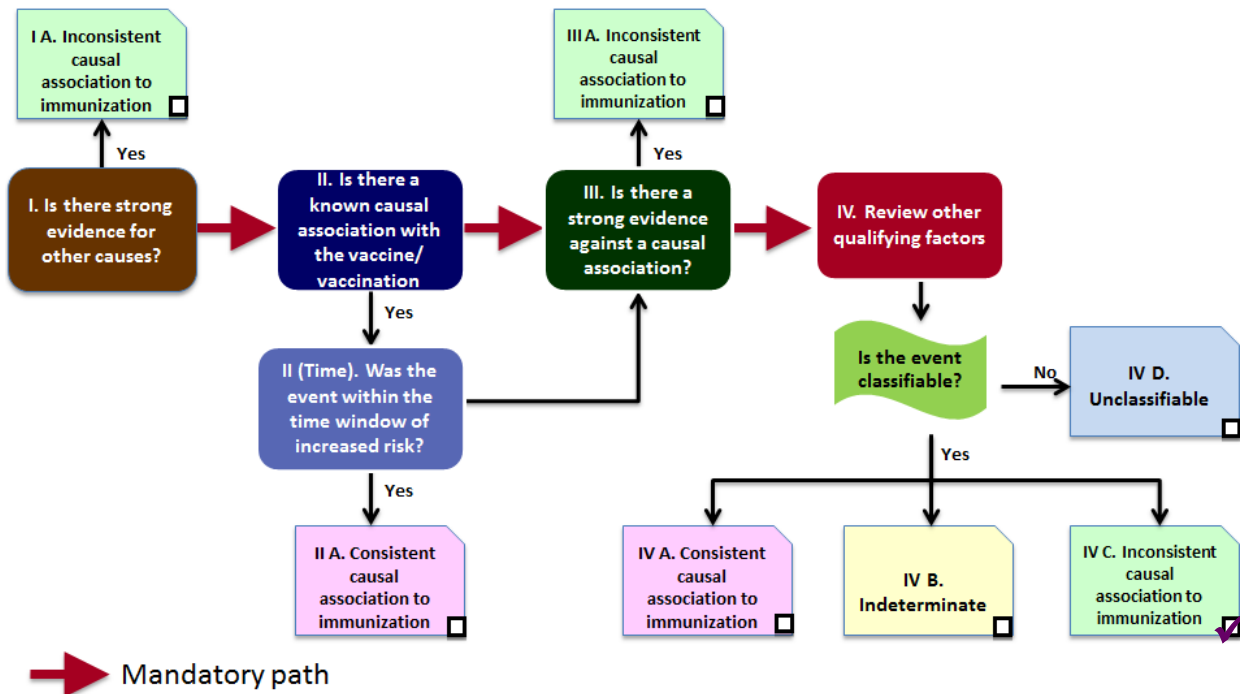
**Is this case eligible for causality assessment? Yes/ No; If, "Yes", proceed to step 2**

**Step 2 (Event Checklist)  (check) all boxes that apply**

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
1. In this patient, does the medical history, clinical examination and/ or investigations, <b>confirm</b> another cause for the event?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	<i>Dengue is suspected but not confirmed. (Platelets ↓, TWBC ↓, liver ++). But X ray, Culture, IgM and virus isolation not done</i>
<b>II. Is there a known causal association with the vaccine or vaccination?</b>		
<b>Vaccine product</b>		
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
2. Is there a biological plausibility that this vaccine could cause such an event?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
3. In this patient, did a specific test demonstrate the causal role of the vaccine ?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>Vaccine quality</b>		
4. Could the vaccine given to this patient have a quality defect or is substandard or falsified?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>As per investigation report</i>
<b>Immunization error</b>		
5. In this patient, 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>As per investigation report</i>
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>As per investigation report</i>
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
8. When this patient was vaccinated, 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"/>	<i>As per investigation report</i>
9. In this patient, 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>As per investigation report</i>
10. In this patient, 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>As per investigation report</i>
<b>Immunization anxiety (Immunization Triggered Stress Response - ITSR)</b>		
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>II (time). If "yes" to any question in II, was the event within the time window of increased risk?</b>		
12. In this patient, did the event occur within a plausible time window after vaccine administration?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/>	<i>Because there are no, "Yes" responses to questions in II</i>
<b>III. Is there strong evidence against a causal association?</b>		
1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) <b>against</b> a causal association between the vaccine and the event?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>IV. Other qualifying factors for classification</b>		
1. In this patient, did such an event occur in the past after administration of a similar vaccine?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/>	
2. In this patient did such an event occur in the past independent of vaccination?	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
3. Could the current event have occurred in this patient without 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>
4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Fever one week prior to immunization</i>
5. Was this patient taking any medication prior to the vaccination?	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?	<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<i>Other infections, (unconfirmed)</i>

**Y: Yes N: No UK: Unknown NA: Not applicable or Not available**

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



**Notes for Step 3: IV C:** *In this situation, it is possible that sepsis that may have caused the death is a complication of the respiratory tract infection. Other infections, probably dengue (unconfirmed) need to be considered as the fever one week prior to immunization is suggestive that she was probably unwell at the time of vaccination.*

### Step 4 (Classification) ✓ all boxes that apply

Adequate information available	<b>A. Consistent with causal association to immunization</b> <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 (ITSR**)	<b>B. Indeterminate</b> <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	<b>C. Inconsistent with causal association to immunization</b> <input checked="" type="checkbox"/> C. Coincidental Underlying or emerging condition(s), or conditions caused by exposure to something other than vaccine
	<input type="checkbox"/> <b>Unclassifiable</b> Specify the additional information required for classification:		

**Summarize the classification logic in the order of priority:**

*With available evidence, we could conclude that the classification is coincidental / inconsistent because: 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. MMR is not the cause of death*

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/](http://www.who.int/immunization_safety/en/).

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