Assessment of causality of individual adverse events following immunization (AEFI): A WHO tool for global use

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ABSTRACT

Serious illnesses or even deaths may rarely occur after childhood vaccinations. Public health programs are faced with great challenges to establish if the events presenting after the administration of a vaccine are due to other conditions, and hence a coincidental presentation, rather than caused by the administered vaccines. Given its priority, the Global Advisory Committee for Vaccine Safety (GACVS) commissioned a group of experts to review the previously published World Health Organization (WHO) Adverse Event Following Immunization (AEFI) causality assessment methodology and aide-memoire, and to develop a standardized and user friendly tool to assist health care personnel in the processing and interpretation of data on individual events, and to assess the causality after AEFIs. We describe a tool developed for causality assessment of individual AEFIs that includes: (a) an eligibility component for the assessment that reviews the diagnosis associated with the event and identifies the administered vaccines; (b) a checklist that systematically guides users to gather available information to feed a decision algorithm; and (c) a decision support algorithm that assists the assessors to come to a classification of the individual AEFI. Final classification generated by the process includes four categories in which the event is either: (1) consistent; (2) inconsistent; or (3) indeterminate with respect of causal association; or (4) unclassifiable. Subcategories are identified to assist assessors in resulting public health decisions that can be used for action. This proposed tool should support the classification of AEFI cases in a standardized, transparent manner and to collect essential information during AEFI investigation. The algorithm should provide countries and health officials at the global level with an instrument to respond to vaccine safety alerts, and support the education, research and policy decisions on immunization safety.

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1. Background

Vaccines have saved millions of lives, contributing to an important reduction of infectious diseases worldwide, and promise to further improve the control of infectious diseases [1–4]. Like any other medication or biological product, vaccines may sometimes cause adverse reactions. When serious or unexpected adverse events occur, health care providers and public health officials should carefully and thoroughly assess the evidence reported during the investigation of the event, trying to define the possible causal relationship with one or more vaccines that may have been administered.

Most of the solid evidence regarding the association of specific adverse events with a particular vaccine comes from carefully designed epidemiological studies assessing absolute or relative risks [5]. However, when investigating an individual case of adverse event following immunization (AEFI), the probability, derived from these studies, that a causal association exists between a vaccine and an adverse event is not sufficient to draw definite conclusions, since other factors may intervene in the cause–effect relationship.

Although vaccines rarely cause serious adverse events (i.e. events resulting in death, life-threatening, requiring in-patient hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity, or being a congenital anomaly/birth defect) [5], some conditions coincidentally associated with vaccines have caused public concern, which resulted in

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Table 1
Definitions of AEFIs by cause according to CIOMS [9].

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 that is due to one or more quality defects the vaccine product including its administration device as provided by the manufacturer
Immunization error-related reaction	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and 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

AEFI, Adverse Events Following Immunization.
CIOMS, Council for International Organizations of Medical Sciences.

a decrease of vaccination coverage and in subsequent epidemics [6–8]. For these reasons, a systematic assessment of single episodes or of clusters of serious and unexpected AEFIs is crucial for achieving the highest safety in immunization programs, in order to inform public health actions and maintain public confidence in immunizations programs. Assessment of AEFIs should be part of routine pharmacovigilance practice, aimed at addressing concerns and identifying new associations, vaccine quality defects (any deviation of the vaccine product as manufactured from its set quality specifications) and immunization program errors.

An AEFI has been defined by the working group on vaccine pharmacovigilance of the Council for International Organizations of Medical Sciences (CIOMS) and by the World Health Organization (WHO) as "any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine" [9]. The adverse event may be any unfavorable or unintended sign, symptom, abnormal laboratory finding or disease. CIOMS also outlined AEFIs by their cause (Table 1).

Three questions are relevant to safety of vaccines in field practice: "Can a vaccine cause an adverse event in certain populations under certain circumstances?"; "Did the vaccine cause a specific adverse event?"; "Will the vaccine cause an adverse event in a specific individual?". Epidemiological studies including multiple observations base causal inference on well known criteria, including those proposed by Sir Bradford Hill [16] and those that underline the need for multiple components in the causality process proposed by Rothman [17]. The likelihood that an adverse event can occur after the administration of a vaccine in certain populations under certain circumstances provides an answer to the key causality question "Can it?". However, when assessing causality in a single AEFI, a different analysis of available case information is needed to estimate the likelihood that a certain vaccine caused a specific adverse event in a specific individual ("did it?"), and to estimate the probability (as attributable or relative risk) that a recipient of a certain vaccine will experience a certain adverse event ("will it?").

A previous aide memoire (a summary document to guide a systematic standardized causality assessment of AEFIs) developed by WHO, applied a generic scheme, developed for all pharmaceuticals, to assess the risk association between vaccines and adverse events. This scheme placed emphasis on temporal criteria and on the evidence of alternative etiological explanations (concurrent disease, drugs or chemicals) [10]. Since this guideline provided a 6-category classification (very likely/certain; probable; possible; unlikely; unrelated; unclassifiable), it was sometimes difficult to differentiate between "probable", "possible" and "unlikely" categories. Other methods have been elaborated to assess causality in pharmacovigilance at the individual level [11–15]. Nevertheless, these methods are not easily applicable to vaccines, and, therefore, not suitable to inform public health actions. In fact, some criteria such as increased drug dosage levels (cumulative or overdose), challenge, de-challenge and re-challenge, as used in drug pharmacovigilance, are not suitable to vaccines, as most immunizations are administered once or at stipulated dosages.

In order to improve the previous approach, the Global Advisory Committee for Vaccine Safety (GACVS) commissioned a group of experts from the Advisory Committee on Causality Assessment (ACCA, Canada), the Vaccine Adverse Event Surveillance & Communication of the European Union (EU/VAESCO), the Council for International Organizations of Medical Sciences (CIOMS) and a member of the Clinical Immunization Safety Assessment (CISA, USA) to review the previously published WHO AEFI causality assessment methodology [10] and develop a standardized and user friendly instrument to assist the assessors in collecting and interpreting data, and in assessing causality after single AEFIs.

Recently, an algorithmic approach for causality assessment of AEFIs was developed by the CISA project in the United States, indicating a systematic and guided analysis of a number of items which allow to classify AEFIs into 3 final categories [18]. This algorithm is suitable for settings in which clinical information from patients who experienced AEFIs is reasonably complete, but could be difficult to be applied in low resource settings.

In this paper we describe a new simple and flexible tool based on the revised WHO classification and the CISA project algorithm [19], which includes a process to support causality assessment of AEFIs. We also illustrate its application in single case reports as supplementary material.

2. Methods for developing the tool

2.1. Criteria considered in the development

The tool was developed as a simple and practical guide to support assessors in the interpretation of available information and in the definition of a possible causal association between an event and a vaccination. The tool is applied after obtaining information from thorough and careful data collection. Key attributes that were considered during the design phase were that the tool should be reproducible, explicit, transparent, complete, and should consider all the elements relevant to the causal model [20]. Additional requirements were the need to be simple, easily applicable by national immunization programs, and easily translatable into public health actions and educational activities on vaccine safety.

2.2. Steps in the development

A group of international experts reviewed the relevant literature in pharmacovigilance, identified key points and debated solutions for creating a practical application for causality assessment of AEFIs. Several prototypes were developed and tested by the group in an iterative fashion. They included serial and parallel algorithms, and a combination of causality elements. Benefits and flaws of each prototype were assessed and used to adapt the tool to the next stage of its development. The final revised WHO prototype was reviewed by the GACVS before being approved for distribution and field-testing. The prototype was piloted in a convenience sample of four middle-income countries in the South East Asia Region (India, Myanmar, Nepal and Sri Lanka). Subsequently, inconsistencies were corrected and its components improved.

The revised methodology was harmonized with the CISA project's newly developed algorithm [18]. The definitions and the concepts from the "Definition and Application of Terms for Vaccine Pharmacovigilance – Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance" have been largely adopted for the Revised WHO AEFI Causality Assessment scheme [9].

2.3. Review of the WHO process of causality assessment for an individual AEFI

The final tool was presented to the GACVS in June 2012, which considered that ". . . the new AEFI causality assessment system will provide a standardized and transparent method that allows stakeholders to understand the nature of the decision-making process, and pave the way for future evaluation of the guide to refine its effectiveness. GACVS has recommended that this new WHO AEFI causality assessment approach should be made public as soon as it is finalized, and that complementary materials and simple software be developed for use in countries to enable immunization staff to field-test the tool" [21].

In July 2012, a user manual was published online [19], the revised scheme was discussed by the vaccine safety authorities in several countries and incorporated in the WHO AEFI manual of the Western Pacific Region. An aide memoire has been developed, and an electronic tool to collect information and classify cases is being prepared.

3. Description of the tool

The different components of the tool are described in Table 2.

3.1. Eligibility criteria for tool application (Fig. 1)

The tool can be applied to any AEFI with a diagnosis that can be validated against a standard definition, such as those provided by the Brighton collaboration [22] or other standard epidemiological or clinical definitions in use. In order to apply the tool, the AEFI investigation must be reasonably complete. All available information deriving from the case investigation, including laboratory, clinical or autopsy findings should be made available before applying the tool. The assessment can be revisited if additional relevant information becomes available later on.

3.2. Data review (Table 3)

Data collected during the AEFI investigation are reviewed through the causality assessment checklist, which includes specific items relevant to the process: availability of a confirmatory evidence for a specific cause other than a vaccine; assessment of all possible causes of the AEFI (vaccine product, immunization error or anxiety, proof of an alternative cause), as appropriate to the given context; evidence against a causal vaccine-event association. Other factors included in the checklist are the background rate of the
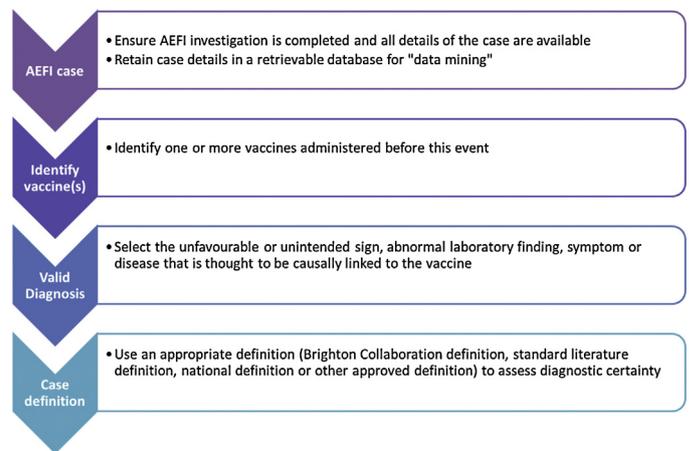
Table 2
Components of the causality assessment tool.

Item	Scope
Eligibility	To determine if information collected in AEFI case investigation is sufficient for conducting causality assessment
Data review	To support the review of specific and essential information to assess causality
Algorithm	To guide the assessor in the interpretation of available data and review their consistency
Classification	To classify the AEFI in one of four final categories that can facilitate appropriate actions

Fig. 1. Eligibility criteria for tool application. Brighton collaboration [22].

event in the general population and the potential impact of the individual's health status and past medical history on the event, including other exposures that could have caused it. Regarding the published evidence that a vaccine may cause the reported event, WHO has prepared and constantly updates information sheets on evidence and rates of adverse events for several vaccines. This information is publicly available [23].

3.3. Algorithm (Fig. 2)

Summarized information from each of the 4 domains of the checklist (evidence for other causes; known causal association with vaccine or vaccination; strong evidence against causal association; other qualifying factors for classification) is then used to feed the algorithm, and the reviewers are guided to applying deductive logic to the interpretation of all available data. The assessor must go through all steps, from I to IV, to categorize information collected in each domain of the checklist. It should be noted that this process may yield answers that are both consistent and inconsistent with a causal association to immunization. Yet, all information should be included in the final consideration of causality and the final classification should be based on the personal judgment of the assessor (Fig. 3).

3.4. Classification of AEFI (Fig. 3)

The final classification of the event is based on previously described principles for vaccine pharmacovigilance [19]. The three final categories (consistent causal association with immunization, inconsistent/coincidental or indeterminate) include subcategories useful for guiding public health actions.

If the occurrence of the AEFI is consistent with a causal relationship with the immunization, the tool allows subcategorizing the event as follows: associated with the vaccine product; associated with a vaccine quality defect; due to an immunization error; due to anxiety. This will enable stakeholders to take appropriate actions based on most likely cause(s).

An event may also be classified as having an indeterminate association with immunization. Should this be the case, events can be sub-classified as follows: events with a consistent temporal relationship but with insufficient evidence for the vaccine as a cause, according to well designed epidemiologic studies (in this case, further studies are encouraged if other similar events are identified); events with conflicting evidence of causal association with immunization. The latter case may lead to further assess the safety of repeated immunizations as appropriate to the given situation.

Table 3
The causality assessment checklist.

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

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

Finally, events are categorized as "unclassifiable" when information is insufficient and additional details are required to perform causality assessment.

3.5. Actions to be taken after assessment

Although the tool does not include a precise guide for implementing public health actions, determining causality is not an end in itself. The lessons learned from the assessment should provide insights for immunization programs and administrative managers on different steps, including individual case management, training, research, modifying systems, refining strategies, in order to avoid and/or minimize recurrences, guide appropriate communication strategies, and maintain confidence in immunization programs.

4. Discussion

The causality assessment tool described above is intended for reviewing evidence retrieved during the investigation of an AEFI, and to help countries assess the potential causal relationship between serious or unexpected adverse events and immunizations. This tool is simple, suitable for use around the globe, operational with modest available information, and including only 4 classification categories. Moreover, the format of the tool allows the implementation of the method with traditional pen and paper, or on a web interface which can extend its flexibility. The tool also represents a paradigm improvement compared with the previous WHO approach [10], as it helps to better address the reasons why

a case may be "unclassifiable"/"indeterminate", when the investigation is incomplete and case information is limited. It is also more transparent as the entire assessment is easy to track. Moreover, it allows to take into account conflicting evidence for causality emerging during AEFI investigations. Finally, instead of assigning a final category through an automatic classification process, the final outcome of the case investigation depends on the personal judgment of the assessor. This is particularly important when collected information has conflicting relevance with respect to causality.

Due to its flexibility, the tool helps to collect essential information and enables assessors to revisit the causality process when additional information becomes available. Moreover, cases are classified according to the standard CIOMS/WHO definitions, using standard terms for vaccine pharmacovigilance [9]. The tool is built upon a logic which is similar to that of the recently published CISA project algorithm [18]. Like the CISA project algorithm, our tool assesses causality through multiple criteria such as known causal association with the vaccine, other qualifying factors, and laboratory evidence for a causal role of an infectious agent or of the vaccine. However, our approach may use less information than that required by the CISA project algorithm, and does not include a hierarchical order of the assessed criteria. Instead of assigning predetermined weights to collected information to reach a final classification, this tool rather prompts the reviewers to collect and review all information available as a whole and to make deductions based on their interpretation before applying the algorithmic logic for classification. Another advantage of the proposed method is that it prompts the collection of additional information when cases are
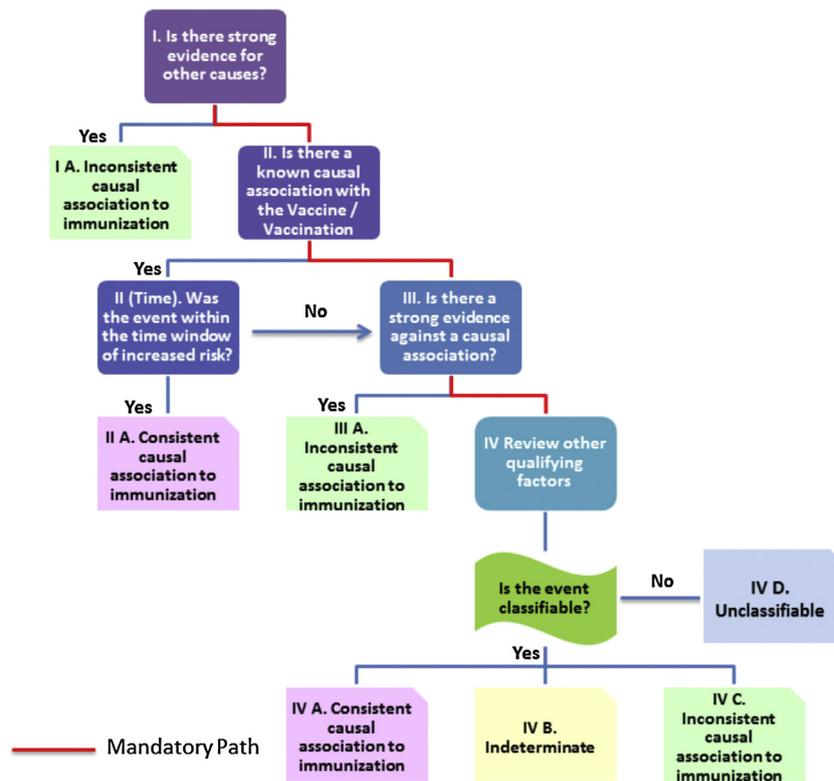
Fig. 2. Algorithm. The assessment should be performed going through each step indicated by the red path to 10 categorize information collected in each domain of the checklist in Table 3.

classified as "indeterminate". Moreover, it facilitates future analyses of aggregated data derived from individual assessments.

Most importantly, the tool provides national immunization program managers and regulatory authorities with information for action. While interventions regarding AEFIs which are related to immunization errors and immunization anxiety could be safely addressed at the local level, AEFIs related to vaccine products and quality defects might have wider implications for vaccine use, both at the national and regional levels, and for the manufacturers. Coincidental AEFIs, the most common form of AEFI, should prompt appropriate communication to provide reassurance to the parents and the public. On the other hand, information on AEFIs that are

classified as indeterminate should be pooled and analyzed by time and place, in order to understand if the AEFI represents a new signal of an unrecognized event. Should this be the case, a more comprehensive epidemiological investigation should be performed. When the algorithm groups collected information into conflicting categories, both consistent and inconsistent with vaccine causality, actions focused on the management of future immunizations would be appropriate. Since the reasons for "unclassifiable" AEFIs are listed in the tool, the relevant information to be gathered can be easily identified.

The use of this tool may help addressing public concerns in a more timely and transparent fashion, thereby avoiding program
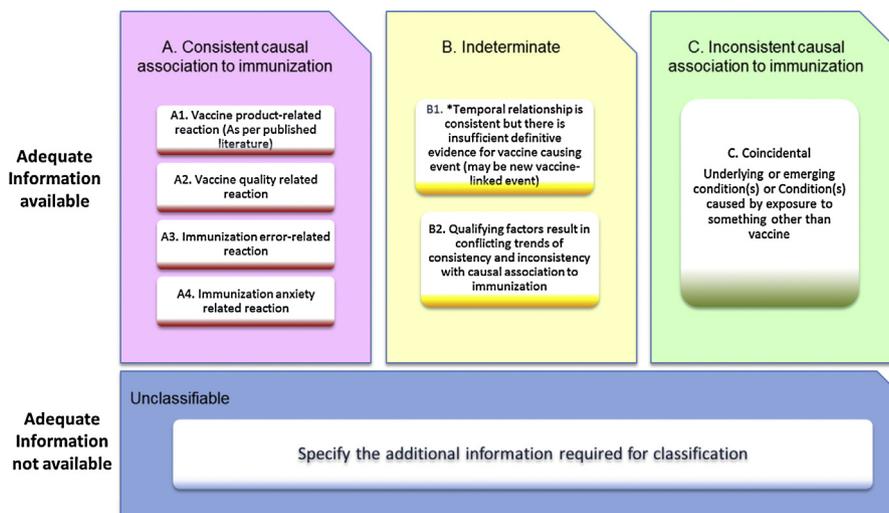
*B1 : Potential signal and maybe considered for investigation

Fig. 3. AEFI causality assessment classification of a single case.

disruptions or decreases in coverage that may lead to serious outbreaks of vaccine preventable diseases. Such a tool can also help to identify new suspected associations that had not been previously recognized, even as rare as they appear.

The tool could also become useful for training and teaching purposes, as each step and their logic are available upfront for recognition and discussion. Computer logic can be applied to the tool except for the final classification step, which requires the experience and the local expertise of the assessor in addition to the available evidence.

We did not conduct a field trial yet to evaluate the present tool's reliability, reproducibility, and consistency with other approaches. Studies comparing this approach with other methods (e.g. CISA, Australia, Brighton Collaboration definitions, etc.) have been planned and may provide future evidence to adjust and refine its performance in the field.

Currently, in vaccine clinical trials, the causality assessment is based on expert judgment only. The present tool may provide in such a context an additional source of comparison that may be useful in pharmacovigilance. Moreover, the standardized approach here described may help establishing common dataset structures that may favor AEFI database linkage to address new research questions through appropriate study designs, including case control, cohort, and active case finding.

The development of the tool was followed by a probing with different clinical scenarios yielding a satisfactory performance (see Supplementary material). Moreover, the feedback received from health care workers during piloting underlined that the tool is usable and the causality assessment process is transparent (data not shown). Further feedbacks following application of the tool by different countries will be necessary to precisely evaluate its applicability in the field and its potential for misclassification.

There are several limitations of the current approaches to causality assessment for vaccines, and this tool is not a full solution, as the GACVS acknowledged. Any causality assessment tool may be affected by the following factors: scarcity of information on the host's responses to vaccination (genetics, vulnerability and exposure); lack of quality data; adverse event diagnoses not meeting standard case definitions. Moreover, the expertise and experience of the public health professionals continues to be crucial for AEFI classification.

In conclusion, the application of a tool which standardizes causality assessment has the practical implication to guide and educate assessors to considering every relevant information and to reviewing the pertinent epidemiological evidence before reaching a final classification.

We believe that the systematic AEFI review through a standardized process of causality assessment will provide additional substrate to guide new epidemiological studies that enhance the confidence in vaccines as an invaluable public health tool.

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.08.087.

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