

Paola Bellavite (Verona University, Italy) has reviewed the WHO's causality classification of adverse events following immunization (AEFI) in an opinion piece. Using 3 case studies of AEFI deaths reported to the Italian Medicines Agency (Agenzia Italiana del Farmaco AIFA) he illustrates how application of the WHO algorithm is difficult and prone to error.

The glossary of the WHO manual (page vii) defines 'causal association' as a cause and effect relationship between causative factor and a disease with no other factor intervening in the process. Bellavite, quite rightly, feels that this is a wrong approach.

He lists (Table 1), a series of genetic disorders that have been associated with tendency to develop AEFI. Using the WHO definition, a causal association with vaccine would be denied because of the genetic factor intervening in the process. Bellavite has proposed that a 'consistent association of the adverse event with the vaccine' must only be excluded when the presumed 'other cause' independently (without interaction with the vaccine) causes the AEFI. This makes good sense.

At step 3 along the mandatory path of the algorithm, the question is: "Is there strong evidence against a causal association?" Bellavite correctly points out the impossibility of proving a negative. "Lack of evidence of association" may mistakenly be considered as "evidence of lack of association" or evidence against a causal association.

It is interesting that the WHO manual quotes an Institute of Medicine (IOM) report on a study looking at a possible relationship between SIDS and vaccines and which concluded that vaccines did not cause SIDS. Will this loose use of the generic term 'vaccines' mean that, hereinafter, no vaccine can have a causal association with SIDS or does this statement relate only to the vaccines examined by the IOM. The problem with proving a universal negative is that a single instance of a positive association can negate all the previous experiences and studies. Such a universal negative assertion is seldom made in scientific literature.

These are important issues that have been raised.

Till 2013 the WHO used the Brighton classification of AEFI (1) and causal association was classified as 'certain': 'probable': 'possible': 'unlikely' and 'unclassifiable'. The categories were revised in 2013 (2). F1000research published a critique of this classification by the reviewer (3). The Second Edition of Revised AEFI classification was published (with minor changes) in 2018 (4).

In a communication in the British Medical Journal, Chandler of the Brighton Collaboration has asserted (5) and I quote extensively (italicized):

"The WHO AEFI causality assessment was developed by the Vaccines Safety Group at the WHO with the support of the Global Advisory Committee on Vaccine Safety. The target user group for this classification system are persons working in countries in whom vaccines are administered via WHO sponsored public health programmes. Those persons are largely concerned with the detection of "signals" of changes in frequency of the more common, expected events which could suggest vaccine quality-related problems, immunisation errors, or multi-use vial contamination, etc. At the current time, most AEFI reports collected and assessed with the WHO AEFI Causality Classification remain within the databases of the public health programmes and are not forwarded into the databases of the national pharmacovigilance centres of most lower and middle income countries.

In contrast, more general guidance for causality assessment, such as the WHO-UMC causality criteria and the Naranjo algorithm, were developed by various groups working within the greater field of pharmacovigilance. The target user groups for these classification systems are those persons working within national pharmacovigilance centres, usually working within or collaboratively with national regulatory centres, and responsible for post-marketing safety surveillance of both drugs and vaccines used within their countries. Within such centres adverse event reports for drugs and vaccines are often maintained within a single database (one notable exception being the USA), and causality assessment is approached in a similar way for all products. Detection of "signals" within the database can be conducted qualitatively (on a "case-by-case" basis) and/or quantitatively (via statistical screening). Higher income countries which do not rely upon implementation of vaccine administration through WHO public health programmes will handle reports of AEFI through these national pharmacovigilance centres.

Furthermore, it is worth noting that most reports of AEFI contained within Vigibase, the database of individual case safety reports for the WHO Programme of International Drug Monitoring, are from countries who channel reports of AEFI through their national pharmacovigilance system, and therefore most reports within the global database have not been subject to WHO AEFI causality assessment.

Taking the specific example of narcolepsy, reports of this condition in association with Pandemrix, an H1N1 pandemic vaccine, were initially received into the national pharmacovigilance centres of Sweden and Finland, and therefore they were not subject to causality assessment by the WHO AEFI classification system. This signal was detected, in fact, because these clusters of reports in young children were "unexpected", by both the reporting physicians (based upon their clinical practice) and by the regulators (based upon the expected reporting patterns within their national databases of suspected adverse drug reactions).

The current system referred to as "robust" within this analysis therefore refers to practice of vaccine pharmacovigilance by national pharmacovigilance/regulatory centres, not that of national immunisation centres routinely utilising the WHO-AEFI causality classification system."

It seems from this that the WHO causality assessment is meant for poor and developing countries and most reports within the global database for pharmacovigilance have not been subject to WHO AEFI causality assessment. It is interesting that the cases cited by Bellavite, the AEFI deaths reported to the Italian Medicines Agency were subjected to the WHO AEFI assessment.

The point that Bellavite makes is that compensation may be denied to families who die after vaccination, utilizing this classification. It will be intriguing to know if this classification is used in Italy to deny compensation but, as a 'developed country', it uses a second system for pharmacovigilance.

The 2018 revised manual says it was 'scientifically evaluated' looking for inter-rater reliability between teams from India and Zimbabwe. It was not examined against any gold standard. If two populations consistently perceive the world is flat, it does little to validate the 'scientific' reliability of that perception.

The paper by Bellavite is an important addition to the literature. However, it can be improved by extensive revision. The language can be improved and corrected in many places. This reviewer has often had to resort to such help, for his scientific communications.

1. Introduction: The author writes that AEFI harms a few “unlucky” individuals. The term related to luck put within quotation marks is best deleted in a scientific communication.

2. Page 4 Innate immune response. It is not clear what the author wants to convey about the risk of fever after MMR. He says this is more in children under 35 months compared to children older than 4 years of age.

I am not able to understand what this has to do with the AEFI classification and why this is brought up here.

3. Page 5 The author suggests that some autoimmune disorders may be associated with immunization but it is not specified what changes in the AEFI classification will help to identify the role that vaccines play.

4. The list of genetic disorders listed in Table 1 is useful as a ready-reckoner, but for that, it must be as exhaustive as possible. I am not an expert in this area but the association of AEFI with mitochondrial disorders is one that I recognize is missing from the list (Poling PMID 16566887)

5. Page 7 The text says “It is important to point out vaccines may safely be administered in children with Di George syndrome.”

Why is it important to state this? There are a whole host of genetic disorders where vaccines can be administered with impunity. Why has Di Gorge been singled out to be declared as safe

6. Microbiome - The relevance of the paragraph on the microbiome is also not clear in the context of AEFI classification.

7. Page 8 The first two paragraphs: It is not clear what the author wants to convey and how it relates to the WHO AEFI classification method

8. Page 9 Top paragraph not clear

9. So also Note 3 The Literature (Delete ‘Note 3’ from the paragraph heading)

The content of this paragraph is not clear

10. Page 10 Second last paragraph

The author writes

“The most obvious case of a possible overlap between autism spectrum symptoms and another disease, surely caused by vaccine adjuvants, is the macrophagic myofasciitis.”

A little more elaboration would be helpful because macrophagic myofasciitis is a relatively new syndrome associated with vaccine aluminium adjuvants and its association with cognitive disorders is known even less.

- **Is the topic of the opinion article discussed accurately in the context of the current literature?**

Partly

- **Are all factual statements correct and adequately supported by citations?**

Partly

- **Are arguments sufficiently supported by evidence from the published literature?**

Partly

- **Are the conclusions drawn balanced and justified on the basis of the presented arguments?**

Partly

References

1. WHO: Adverse Events Following Immunization(AEFI): Causality Assessment. 2005. [Reference Source](#)
 2. WHO: Causality assessment of an adverse event following immunization (AEFI). 2018. [Reference Source](#)
 3. Puliye J, Naik P: Revised World Health Organization (WHO)'s causality assessment of adverse events following immunization-a critique. *F1000Res*. 2018; 7: 243 [PubMed Abstract](#) | [Publisher Full Text](#)
 4. Chandler R: Modernising vaccine surveillance systems to improve detection of rare or poorly defined adverse events. *BMJ*. 2019. [Publisher Full Text](#)
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Competing Interests

No competing interests were disclosed.

Reviewer Expertise

Pediatrics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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