OPINION ARTICLE

Revised World Health Organization (WHO)'s causality assessment of adverse events following immunization—a critique [version 1; referees: 2 approved with reservations]

Jacob Puliyel [1], Pathik Naik[2]

[1]St Stephen's Hospital, Delhi, 110054, India
[2]Pathik Children Hospital, Surat, 394219, India

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Abstract

The World Health Organisation (WHO) has recently revised how adverse events after immunization (AEFI) are classified. Only reactions that have previously been acknowledged in epidemiological studies to be caused by the vaccine, are classified as a vaccine-product–related-reaction. Deaths observed during post-marketing surveillance are not considered as "consistent with causal association with vaccine", if there was no statistically significant increase in deaths recorded during the small Phase 3 trials that preceded it. Of course, vaccines that caused deaths in the control-trials stage would not be licensed. After licensure, deaths and all new serious adverse reactions are labelled as 'coincidental deaths' or 'unclassifiable', and the association with vaccine is not acknowledged. The resulting paradox is evident.

The definition of causal association has also been changed. It is now used only if there is "no other factor intervening in the processes." Therefore, if a child with an underlying congenital heart disease (other factor), develops fever and cardiac decompensation after vaccination, the cardiac failure would not be considered causally related to the vaccine. The Global Advisory Committee on Vaccine Safety has documented many deaths in children with pre-existing heart disease after they were administered the Pentavalent vaccine. The WHO now advises precautions when vaccinating such children and this has reduced the risk of death. Using the new definition of causal association, this relationship would not be acknowledged and lives would be put at risk. In view of the above, it is necessary that the AEFI manual be revaluated and revised urgently. AEFI reporting is said to be for vaccine safety. Child safety (safety of children) rather than vaccine safety (safety for vaccines) needs to be the emphasis.

Keywords

Pentavalent vaccine; quinvaxim; pharmacovigilance; Hill criteria; macrophagicmyofasciitis; periodic safety update reports; Brighton classification; adverse drug reactions; sudden unexpected death; TOKEN study

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1 **Tom Jefferson**, University of Oxford, UK

2 **Peter Aaby**, Bandim Health Project, Guinea-Bissau

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Corresponding author: Jacob Puliyel (puliyel@gmail.com)

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Introduction

One of the earliest countries to introduce the pentavalent vaccine (combined diphtheria, tetanus, pertussis, Hib, and hepatitis B) was Sri Lanka[1]. A pentavalent vaccine Quinvaxim (Crucell) was introduced in Sri Lanka on January 1, 2008. On the 29th of April that year the vaccine was withdrawn by the government following five deaths. A World Health Organization (WHO) team of experts investigated the adverse events following immunization (AEFI) and reported the deaths were "unlikely" to be related to vaccination. The full report was not widely available before it was presented to the High Court in Delhi, India[2]. From the full report it became clear that there was no alternate explanation for three deaths and thus, they should have been classified as "probable/likely" related to immunization, using the WHO Brighton criteria for classification of AEFI (see Box 1). The experts deleted the categories "probable" and "possible" from the AEFI Classification they used for assessment and then reported that the deaths were "unlikely" related to vaccination. The way the Brighton Classification was altered to enable this misleading classification of the deaths in Sri Lanka was reported in the Indian Journal of Medical Research and the British Medical Journal[3,4]. On May 4, 2013 the Ministry of Health of Vietnam suspended the use of Quinvaxim (Crucell) after it had caused 12 deaths[5]. The WHO experts investigated the Vietnam deaths. This time they reported, "Quinvaxem was pre-qualified by WHO…, no fatal adverse event following immunisation (AEFI) has ever been associated with this vaccine[5]." This is the same brand of pentavalent vaccine that was used in Sri Lanka where WHO experts had previously documented AEFI deaths. It appears that after the Sri Lanka investigation and shortly preceding the Vietnam investigation, the methodology used for AEFI classification was revised. Using the revised AEFI causality assessment, AEFI reported from Sri Lanka could be classified as "Not a case of [AEFI]." From the WHO "Safety of Quinvaxem report,"[5] it is apparent that previously documented deaths following immunization were removed from the records after this new categorization started.

Historical background of causality assessment

The new mechanism that allows AEFI to be classified as "Not a case of [AEFI]" will be discussed.

The evolution of the logic of causality assessment is fascinating. Eminent philosophers, scientists, legal luminaries, and statisticians have grappled with the issue and a great deal has been written about it. It will be impossible to distil all of that for this write-up, except at the risk of oversimplification. As we are concerned primarily with assigning causality to alleged drug reactions, only some aspects of the debate are germane to this discussion.

Defining cause and effect (X is the cause of Y) has not been easy. According to Hume[6], the major features of causation are temporal precedence (X must precede Y), contiguity and regularity of the association of causes and their effects. Confounding, however, is possible by a third factor.

It is known that the consumption of ice cream is higher when there is a spike in the incidence of sunburns. One can conclude wrongly that eating ice cream can cause sunburns. The third factor in this case is hot weather conditions. Both eating ice cream and getting sun burnt are associated with sunny days. Hume avoided the confounding problem by stipulating that X can be considered as cause of Y only if X is sufficient for Y.

Box 1. WHO adverse events following immunization (AEFI): Causality assessment Brighton criteria

Causality Term	Assessment Criteria
Very likely/Certain	A clinical event with a plausible time relationship to vaccine administration and which cannot be explained by concurrent disease or other drugs or chemicals
Probable	A clinical event with a reasonable time relationship to vaccine administration; is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Possible	A clinical event with a reasonable time relationship to vaccine administration, but which could also be explained by concurrent disease or other drugs or chemicals.
Unlikely	A clinical event whose time relationship to vaccine administration makes a causal connection improbable, but which could be plausibly explained by underlying disease or other drugs or chemicals
Unrelated	A clinical event with an incompatible time relationship and which could be explained by underlying disease or other drugs or chemicals
Unclassifiable	A clinical event with insufficient information to permit assessment and identification of the cause

Reference

http://www.rho.org/files/rb3/AEFI_Causality_Assessment_WHO_2005.pdf

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That is however fallacious. Striking a match can light a fire only if there is oxygen. In itself, striking the match is not sufficient. The alternate position could be that X is cause of Y if, and only if, X is necessary for Y[7]. John Mackie suggested that in nature there could be multiple reasons (causes) for the same outcome[8]. Thus X may not be necessary for Y but at the same time, X may be sufficient for Y. A building may be set on fire by a spark from a short circuit in the electrical wiring (X) or as the result of an act of arson (Z). Thus neither (X) nor (Z) is necessary for Y, but both (X) and (Z) are sufficient causes for Y. The question then is whether Y would have occurred were it not for the factor X. This is known as the "but for" test. In jurisprudence, it has been acknowledged that where there are multiple causes working simultaneously the "but for" test is unworkable and the question of causality is whether the putative cause materially contributed to the result[9]. This has been argued in the case of Grahan Dickie V. Flexcon Glenrothes Limited [2009] ScotSC 143 (04 September 2009). Peter M. Willcock and James M. Lepp have discussed 'Causation in medical negligence cases' which elaborates on these issues.

In biology, there is further a probabilistic element to causation. If men of the same height and women of the same height were to have children, their children will not all be of the same height. For the same set of observed causal factors, there is probability distribution of possible heights[7].

Adverse drug reactions

Adverse drug reactions (ADRs) can follow after the use of any drug. Careful evaluation is required to distinguish the events that are causally related to the drug from coincidental events. Causality assessment is crucial because the events could be iatrogenic and avoidable. Usually only a few react adversely to drugs on the market, whereas others are unharmed. The attribution of causality for such occasional happenings is particularly complex. Investigations of ADRs put causative association on a probability scale. The causality-assessment system developed by the World Health Organization Collaborating Centre for International Drug Monitoring is called the Uppsala WHO Centre (WHO UMC) Scale. This is widely used as it offers a simple methodology (see Box 2). In consonance with Hume's postulates, the first step is to confirm temporal precedence and contiguity. The adverse event must appear after the suspected drug is administered and within a reasonable time-frame. Events where the time-to-drug-intake makes a relationship improbable are classified as "unlikely" to be related. Events within a reasonable time and for which there is no alternate explanation (which cannot be attributed to disease or other drugs) are classified as "probable/likely" related to the drug in question. Drug reaction is classified as "possible" where there is a reasonable time relationship, but for which there are also alternate explanations. In terms of John Mackie's aphorism, the drug is considered sufficient but not necessary for the effect.

Box 2. WHO–UMC causality categories

Causality Term	Assessment Criteria
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake, Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or Contradictory • Data cannot be supplemented or verified

Reference The Uppsala Monitoring Center. The use of the WHO-UMC system for standardised case causality assessment. Reproduced with permission of Uppsala monitoring centre. Available at https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf

To be classified as "very likely/certain" the reaction needs to be an objective and specific medical disorder or a recognized pharmacologic phenomenon, and there must be evidence of dose-related reaction or proof in terms of reappearance of symptoms on rechallenge. If death should occur as ADR, rechallenge is impossible. It is usually difficult to be certain about the causality of fatal ADR and the reaction is often classified as "probable/likely" or "possible."

The difference between certain and probable/likely is simply the acceptable standard of proof. For "certainly," a high-standard irrefutable proof is called for (falsification of the theory by a single irregular outcome). A single well-documented spontaneous rechallenge is strong evidence of regularity (even tough in just one patient). For "very likely," the standard of proof is proof beyond reasonable doubt.

"Balance of probability" is the level of proof needed to classify as "probable" or "possible" and this is the standard of proof, which is relevant to medicine and for pharmacovigilance. With this level of proof (prima facie true), the "Precautionary Principle" must be triggered. This is described later.

Adverse events following immunization

Vaccines are drugs used as a preventive measure, given to entire cohorts of healthy persons. As they are administered in the absence of any disease, there is a very high expectation that it produce few adverse effects, and there is low tolerance for serious adverse events and deaths. Adverse events following immunization (AEFI) must be monitored more carefully than other drugs. A credible immunization safety evaluation and monitoring system is essential for the success of immunization programmes. The WHO developed the "Adverse Events Following Immunization (AEFI): Causality Assessment" otherwise known as the Brighton Classification. It is very similar to the WHO UMC causality categories for ADR. Until recently, this was the touch-stone used by WHO experts when AEFI were reported (see Box 1).

One measure of the sensitivity and responsiveness of this system is the alacrity with which the rotavirus vaccine RotaShield was withdrawn in 1999 after 12 cases of vaccine-induced intussusceptions were reported. About 1 in 2000 children younger than 2 months of age, develop intussusception from other causes. Based on the results of the investigations, the Centre for Disease Control (CDC) estimated that one or two additional cases of intussusception would be caused among each 10,000 infants vaccinated with the RotaShield vaccine. After about 100,000 infants were immunized, the vaccine was withdrawn[10]. In 2013, the methodology of AEFI evaluation was, however, revised.

The Council for International Organizations of Medical Sciences (CIOMS)/WHO: Report on vaccine pharmcovigilance

In October 2010 after a series of meetings, 40 experts (of whom 19 were industry representatives with possible conflicts of interest) helped rewrite the classification criteria for AEFIs. The document entitled "Definitions and Application of Terms for Vaccine Pharmacovigilance" is reported to "provide tools for higher excellence of signal detection and investigation of adverse events following immunization."[11]

On page 170 of this 193-page document, under the heading "Notes for Guidelines," it is stated in small print: "If there is adequate evidence that an event does not meet a case definition, such an event should be rejected and should be reported as "Not a case of [AEFI]." Such evidence is considered adequate, if an exclusion criteria is met, or an investigation reveals a negative finding of a necessary criterion (necessary condition) for diagnosis. Such an event should be rejected and classified as "Not a case of [AEFI]."[11]

The CIOMS/WHO "tool for excellence in signal detection" works by turning a blind eye to AEFI—classifying AEFI as "Not a case of [AEFI]." Not only is the causative association of AEFI to immunization denied, but it is made to appear the AEFI never occurred. Signal detection is no longer possible once AEFIs are removed from the system after being designated as "Not a case of [AEFI]." The story in the *Introduction* above where the WHO asserted in May 2013 that no fatal AEFI has ever been associated with Pentavalent vaccine[5], suggests the Sri Lanka AEFI deaths[2] are now reclassified as "Not a case of [AEFI]" using the CIOMS/WHO tool.

According to the CIOMS/WHO report (page 11), a case definition can be adopted from the standard literature or by the reviewers themselves; not necessarily "an existing case definition." The case definition helps draw on previous epidemiological research and facilitates further research to confirm a causal link. However, excluding causality in relation to an individual event cannot be dependent on that event conforming to a pre-existing case definition. It has been pointed out that the pejorative use of the term "rejected" (in the statement; 'Such an event should be rejected and classified as "Not a case of [AEFI]"'), suggests a defensive posture. Reports of AEFIs are to be assessed for causality and classified, they are not to be "rejected"[12].

The WHO revised AEFI manual

In March 2013, the revised WHO "User Manual for AEFI" was published with a new algorithm[13]. The manual acknowledges that it has adapted definitions and concepts from the CIOMS/WHO report. The new algorithm for AEFI is reproduced in Figure 1.

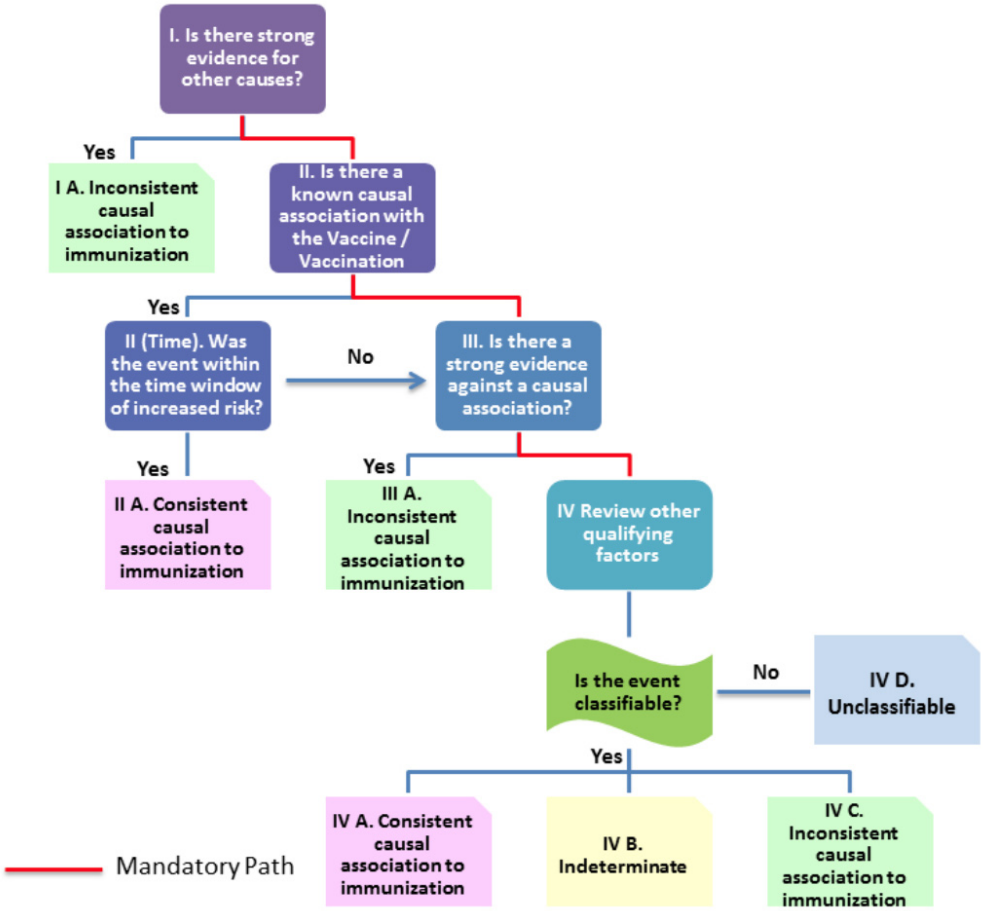

Figure 1. Flow chart demonstrating the revised AEFI classification new algorithm.

Revised AEFI classification: New categories of causality

Only events that occur after vaccine administration are eligible for AEFI causality assessment. This first step is reminiscent of Hume's dictum regarding precedence and contiguity. In the new scheme, causality is classified in four categories: "Consistent causal association to immunization," "Indeterminate," "Inconsistent causal association to immunization," and "Unclassifiable."

Consistent causal association to immunization

This is the highest level of causal association in this new classification. It is less definitive than "very likely/certain" in the old scheme. It does not call for irrefutable proof or even proof beyond reasonable doubt. Not even is the balance of probability assessed. In the new scheme, an adverse event can simultaneously be classified as "Consistent causal association with immunization" and "Inconsistent causal association with immunization." On page 36 of the revised manual for AEFI[13] is the example of acute flaccid paralysis in a child after oral polio vaccine, who had had a fever 1 month prior to onset of paralysis. The stool culture showed vaccine strain polio virus. It was classified as "Consistent causal association with immunization" as it is a known reaction and the paralysis happened within time window of increased risk. It was also classified as "Inconsistent causal association with immunization" because the fever, 1 month prior to paralysis had not been investigated completely. This ambiguity, which admits diametrically opposite conclusion simultaneously, is a hallmark of the new scheme.

It is suggested that before the question "Did the vaccine given to a particular individual cause the particular event reported?" (the question of 'Did it?') is answered, one has to answer the

question "Can the given vaccine cause a particular adverse event?" (Can it?). The inference is that only if there is evidence at the population level that the vaccine can cause the adverse event, is the reaction classified as "Consistent with causal association with immunization."

This inference is flawed on two grounds. On the one hand, it denies all new associations seen in Phase 4 trials. On the other, if it is a known adverse reaction, causal association is accepted even where the events could have happened by coincidence. Just because intussusceptions are acknowledged as an adverse event following rotavirus vaccination, it does not follow that all intussusceptions in the critical window of increased susceptibility are necessarily caused by it. The residual uncertainty at this highest level of causal association robs it of value in addressing the problem of AEFI caused by vaccines.

Inconsistent causal association to immunization

At the bottom of the new causality classification hierarchy is "Inconsistent causal association to immunization." This group can include reactions for which there is no alternate explanation (and which would have been classified in the "Probable" category previously). They would fall in the group "Inconsistent causal association with vaccination" merely because causal association with immunization has not been documented in prior epidemiological studies. Into the same group are placed reactions that would have been considered "Unlikely" to be associated, and those that would have been classified as "Unrelated." The use of the same category "Inconsistent causal association to immunization" for such a wide variety of clinical situations merely obfuscates the issues. In the revised scheme, this term is used to suggest that there is no relation between the AEFI and immunization. No matter how frequently the reaction categorized as "Inconsistent with causal association" occurs, it would not be investigated as a new signal of a causal association.

Indeterminate

Classification in the "Indeterminate" group is reserved for reactions that could have been caused by immunization, but for which causal association has not been documented previously. It is projected that information on AEFI that are classified as indeterminate will be pooled and analysed in order to understand if the AEFI represents a new signal of an unrecognized event. The scheme is however loaded such that literally no AEFI are categorized into this group. How this is accomplished is discussed later in this chapter.

Unclassifiable

Clinical events with insufficient information to permit assessment and identification of cause are put in the "Unclassifiable" group.

Revised AEFI classification: The new algorithm

Just as the final categories of causality association are vague, overlapping, and not clearly differentiated, the algorithm used to make a decision on causality[13] does not appear to be logical or well thought through.

The algorithm is shown in Figure 1.

Causality assessment algorithm

Four sets of questions need to be answered in sequence:

1. Is there strong evidence of other causes?

2. Is there known causal association with the vaccine or vaccination and if so, whether the event was within the time window of increased risk?

3. If there is no causal association known or if it is not within the time window of increased risk: Is there strong evidence against a causal association?

4. If there is no such strong evidence against causal association, the next step is to look at other qualifying factors for classification.

    a. Could it happen independently of vaccination (background rate)?

    b. Could the event be manifestation of another health condition?

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

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

    e. Was there acute illness prior to the event?

    f. Did the event occur in the past independently of vaccination?

    g. Was the patient taking any medication prior to vaccination?

    h. Is there biological plausibility?

Step 1

The first step in the revised algorithm is to look for strong evidence for other causes. If there is an alternate explanation, the AEFI is classified as "Inconsistent with causal association to immunization." John Mackie has noted that in nature there could be multiple reasons (causes) for the same outcome, and if two possible causes exist simultaneously either of them could be the causative factor[8]. It is to be noted that with the WHO UMC classification of ADR and the old WHO/Brighton Classification of AEFI, even if an alternate explanation is available, a causative association with drug or vaccine is still considered "Possible." Moreover, the two possible causes could be working synergistically. An example of this is where genetic and other individual susceptibility factors make one susceptible to developing an AEFI[14]. In the new algorithm, if there is an alternate explanation for the AEFI, or another factor is involved[15], causative association with vaccine is rejected[13].

Step 2

The COIMS/WHO Report on Pharmacovigilance is used at this level[11]. AEFI-specific case definitions for some reactions have been developed. In instances where specific case definitions and criteria are not available for a particular AEFI, it is permissible to improvise using case definitions adopted from "standard medical literature, or national guidelines or

they may be adopted locally by the reviewers" (page 11 CIOMS/WHO report). AEFI that meet case definitions and which occur within the time window of increased risk are classified as "consistent causal association to immunization."

The acceptable time window for each adverse event is different. For the macrophagic myofasciitis affected patients usually are middle-aged adults, presenting with diffuse arthromyalgias, chronic fatigue, and marked cognitive deficits, fatigue, or depression due to long-term persistence of aluminium hydroxide within macrophages at the site of previous immunization[16]. However, surveillance for Periodic Safety Update Reports (PSUR) do not extent for so long.

Step 3

Theoretically, reactions that are not known to have a causal association or those that are not in the time window of increased risk can move to Step 3. At this stage, an enquiry is made whether there is strong evidence against causal association. Proving of a negative is notoriously difficult as it is impossible to affirm that in every circumstance, an irregular outcome is impossible. The example provided in the manual relates to MMR and autism.

It is reported that the Global Advisory Committee on Vaccine Safety (GACVS) and Council for International Organizations of Medical Sciences (IOM committee) have concluded that no evidence exists of a causal association between MMR vaccine and autistic disorders. Such AEFI must be classified as "inconsistent with causal association to immunization" according to the new algorithm.

After publication of this AEFI user's manual, the conclusion about MMR and autism have become disputed again (see Box 3). This shifting evidence calls into question the usefulness of introducing this step in the algorithm of AEFI.

Step 4

Assuming that no such "strong evidence against a causal association" exists, reactions that are not known to have a causal association with the vaccine, can go to Step 4. The question at this point is whether it is "classifiable"— meaning whether all the tests needed, have been performed to allow it to be classified under the CIOMS/WHO definitions. This is the second time these definitions are invoked during the AEFI evaluation.

If some investigations are not done or not available, the AEFI is labelled as "Unclassifiable" (or classified as "Inconsistent with causal association to immunization" like how flaccid paralysis following OPV was classified, because investigations during an illness 1 month prior to paralysis, were not available— (see Appendix 3, page 36 of the AEFI manual[13] for this example).

If all the required investigations have been done and they did meet criteria, they would have been classified as "consistent causal association to immunization" at Step 2 and would not have come to Step 4.

The third possibility is that all the investigations had been done so it is classifiable but it did not meet case definitions. Bearing in mind the CIOMS/WHO definition, if there is adequate evidence that an event does not meet a case definition, such an event should be rejected and should be reported as "Not a case of [AEFI]." (See CIOMS/WHO Definitions and Application of Terms for Vaccine Pharmacovigilance, page 170[11]). It removes any chance that AEFI that has not been recognized as causatively associated with immunization in previous epidemiological studies will be included in the "Indeterminate" group and evaluated as a new signal.

The exercise does not end there. Other qualifying factors are also enquired into at Step 4. It is recommended that alternate explanations in terms of background rate, other health conditions, exposure to a potential risk factor or toxin, acute illness, and other medication are again enquired into. Many of these "other qualifying factors," like prior illness and concurrent drug use would presumably have been eliminated at Step 1 when looking for evidence for other causes. This enquiry is repeated again at Step 4 quite unnecessarily. Box 4 illustrates how in spite of there being epidemiological

Box 3. MMR and autism risk in African American children.

In 2004 the CDC published research demonstrating that there was no link between the vaccinated children's risk of a subsequent diagnosis of autism and the age at which a child is vaccinated with MMR[a].It has now been revealed through the testimony of one of the authors Dr. W. W. Thompson who turned whistle blower, that that the risk of autism among African American children vaccinated before the age of two years was 340% that of those vaccinated later. However this data was deliberately removed from the analysis to arrive at the CDC's proclaimed conclusion. CNN published the story of the CDC whistle-blower[b], and Thomson has now been granted whistleblower immunity by the Obama administration[c].

References:

a. DeStefano F, Bhasin TK, Thompson WW, Yeargin-Allsopp M, Boyle C. Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta. Pediatrics. 2004;113:259–66. doi: 10.1542/peds.113.2.259

b. Goldschmidt D. Journal questions validity of autism and vaccine study [Internet]. CNN.com. 2014 Aug 28 [cited 2014 Sep 29]. Available from: http://edition.cnn.com/2014/08/27/health/irpt-cdc-autism-vaccine-study

c. http://dailycaller.com/2015/02/03/obama-admin-grants-immunity-to-cdc-scientist-that-fudged-vaccine-report-whistleblower-plans-to-testify-before-congress/

Box 4. Sudden unexpected deaths (SUD) after pentavalent vaccine and the TOKEN Study.

With regard to AEFI a cluster of cases is defined as two or more cases of the same adverse event related in time or place or to the vaccine administered[a]. Pentavalent vaccine has caused numerous deaths in Asia but it is yet to be considered a new signal[b–f].

After the AEFI algorithm was revised, the deaths are now classified as 'Not a case of [AEFI]' on the grounds that deaths have not been reported as AEFIs in epidemiological studies involving the vaccine. However, the TOKEN study contradicts this assertion[g].

The TOKEN study was done specifically to assess a possible causal relationship between vaccination and unexplained sudden unexpected death (SUD) of children between their 2nd and 24th month of life. vonKries had previously found a statistically significantly increased standardized mortality ratio (SMR) within two days after vaccination with one (Hexavac®) of the two licensed hexavalent vaccines and the TOKEN study was done to confirm or refute the association[g]. The study was sponsored and supported by the Paul-Ehrlich-Institute (PEI) and the Federal Ministry of Health (Bundesministeriumfür Gesundheit).

A self-controlled case series (SCCS) was examined to look for a temporal association of vaccination to SUD. Parents were invited to participate in the study if their child had died of SUD. 37.6% of the eligible parents participated. The researchers found that parents were twice as likely to participate if their child had died within one week of vaccination. They used an inverse probability weighted analysis to compensate for this bias. The authors note that this was helpful to overcome the selection bias for cases who died under 9 months, but even so, the results are still likely to overestimate the risk of SUD in older children.

The weighted SCCS analysis, relative risk of SUD after pentavalent vaccination(first and second year of life) looking at risk period 0-3 days after vaccination versus control period 4-28/183 days showed RR of 8.11 (p= 0.006, 95% CI=1.81-36.24; Table 41 in the TOKEN Report). The weighted SCCS analysis, relative risk of SUD after hexa- or pentavalent vaccination (1st and 2nd year of life) looking at risk period 0-3 days versus control period 4-28/183 days was RR.2.19 (p= 0.031, 95% CI=1.08-4.45; Table 36 in the TOKEN Report)

It is clear from the above that there is reasonable evidence in epidemiological studies that SUDS can occur as AEFI following use of the pentavalent vaccine and the deaths following the use of this vaccine should not be a priori classified as 'Not a case of [AEFI]'.

References

a. http://vaccine-safety-training.org/detection-and-reporting.html

b. Lone Z, Puliyel J. Introducing pentavalent vaccine in the EPI in India: A counsel for caution. Indian J Med Res 2010; 132,: pp 1-3

c. Puliyel J. AEFI and the pentavalent vaccine: looking for a composite picture. Indian J Med Ethics. 2013;10:142-6.

d. No authors listed. Global Advisory Committee on VaccineSafety,12–13 June2013. Wkly Epidemiol Rec. 2013;88:301-12. Available at http://www.who.int/vaccine_safety/committee/reports/Jun_2013/en/ Accessed on 1/11/15

e. Sreedhar S, Antony A, Poulose N. Study on the effectiveness and impact of pentavalent vaccination program in India and other south Asian countries. Hum Vaccin Immunother. 2014;10:2062-5.

f. Martin Schlaud M, Poethko-Müller C, Kuhnert R, Hecker H Robert Koch Institute. Study on deaths in young children (2nd to 24th month of life) (TOKEN Study) http://www.rki.de/DE/Content/Gesundheitsmonitoring/Studien/Weitere_Studien/TOKEN_Studie/Studyreport.pdf?__blob=publicationFile

g. vonKries R, Toschke AM, Strassburger K, Kundi M, Kalies H, Nennstiel U, Jorch G, Rosenbauer J, Giani G. Sudden and unexpected deaths after the administration of hexavalent vaccines (diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, Haemophiliusinfluenzae type b): is there a signal?. Eur J Pediatr. 2005;164:61-9.

evidence (the TOKEN Study) that pentavalent vaccine (as discussed in the introduction) can cause sudden unexpected death, the numerous deaths are not acknowledged as caused by the vaccine, and the WHO expert report denies that deaths were ever reported as AEFI. The causality assessment of 132 serious AEFI cases uploaded on the website of the Ministry of Health and Family Welfare in India illustrates the consequence of deploying this new classification. 54 of these babies died, whereas 78 survived. Not even one death was classified as vaccine-related, whereas the causality assessment found 50% of those who survived, had reactions to vaccination. Nearly all the deaths (96%) were simply classified as unclassifiable or coincidental[17]. Children admitted to hospital after vaccination with intractable convulsions, could be classified as having a vaccine-product related reaction, but if they died, the deaths would be classified as "coincidental deaths."

Other subtle changes in the definition of terms

"Causal association" redefined

The term causal association now means "a cause-and-effect relationship between causative factor and a disease with no factor intervening in the processes". This is a major step backward for patient safety. The old scheme recognized, for example, that an elderly person with chronic cardiac failure might develop symptoms of cardiac decompensation after influenza vaccination due to a vaccine-caused elevation in temperature or stress from a local reaction at the site of vaccination. The vaccine is therefore considered to have contributed to cardiac failure in this specific situation[18]. Under the new scheme, this outcome would not be considered as causally related to the vaccine. The question of whether the death would have occurred at that time, had it not been provoked by immunization, would not be acknowledged. Without this recognition, many elderly persons may be exposed to this risk of death unnecessarily when using this vaccine. If the vaccination of an infant was reported to have been followed by sudden death but the child was malnourished or otherwise unwell it does not mean that causality assessment should conclude no cause and effect relationship between the vaccine and the death. There is no scope in this definition to consider interacting causalities[12,14].

According to Collet and colleagues, it is possible that some individuals experience greater immunogenic response to vaccines compared to the general population, and therefore, understanding genetically determined predispositions to developing AEFIs is important[18]. However, these considerations will not be accounted for in the new CIOMS/WHO causality assessment scheme. The contribution of vaccine in precipitating encephalopathy in patients who are susceptible on account of genetic factors will also not be considered[14]. Berkovic has used genetic analyses to identify de novo mutations in the sodium channel gene SCNIA in patients with alleged vaccine-induced encephalopathy[15]. Unwisely, in all these cases the contribution of the vaccine in precipitating the encephalopathy will be ignored.

It is a pity that after all these years, the authors should fall for the Hume fallacy that causality can be claimed only if X is sufficient in itself for Y. The fact that the immunization could have 'materially contributed' to the adverse events, is ignored.

Box 5 describes how adverse events recorded in a randomized clinical trial (RCT) sent to the regulatory authority for vaccine approval and license are not made public. This goes against the European Court of Justice ruling that clinical study reports are made publically accessible.

Biological plausibility redefined

One of the qualifying factors considered at Step 4 is biological plausibility. The manual specifies that biological plausibility can only be invoked when laboratory findings or symptom or sign are similar or consistent with natural history and pathophysiology of the infection or antigen. Other biologically plausible explanations (demonstrating there is a mechanism and capacity to lead from the cause to the effect)[7], do not qualify. One would have presumed that symptom or sign similar or consistent with natural history and pathophysiology of the infection or antigen would be "AEFI with known causal association with vaccine" and would have been picked up in Step 2 and would not reach Step 4.

The four approaches to ascertaining causality described by Brady include detection of neo-Humean regularity, examining the counterfactual, experimental manipulation and examining mechanisms and capacities[7]. The new AEFI recognizes only the experimental approach to the exclusion of other valid approaches and as a result can fail to detect causality in number of cases and result in harm.

Chronic fatigue syndrome and the HPV vaccine trial

The above discussion has assumed that adverse events that are reported in a statistically significant proportion of the population given the trial drug in the original prelicensure randomised control trials would be classified as adverse events known to be associated with the vaccine.

Slate investigated of the randomised trials of human papillomavirus (HPV) vaccines and found that potential side effects were collected for only two weeks in the year long study. After the first 2 weeks, individual trial investigators decided on personal judgement whether to report medical problems as

Box 5. The prequalification of Rotavac without safety data

The revised AEFI Categories further enabled vaccine manufacturers to classify AEFI not previously known to be associated with the vaccine in randomized clinical trials or other epidemiological studies as 'Inconsistent with causal association to immunization.'

Vaccine trials and its reporting now seems designed not to report AEFI during the clinical trial.

Rotavirus trials in India

RotaSheilds that was withdrawn as it caused 1 excess case of intussusception per 10,000 children vaccine[10].

However a new rotavirus vaccine Rotavac (Bharat Biotec) was licenced in India after a trial in 3 centres where the vaccine was administered to a total of 4500 children (a sample size too small to show up a rare event that occurs 1 in 10,000). Even in spite of this small sample it appears intussusceptions were so common with this vaccine[a] in one of the centres (Vellore), it was significantly higher than controls. The trial doctors refused to provide this segregated data in spite of repeated requests for the same. The government promised to monitor safety in a post marketing surveillance. However the participants in this trial were not explained the risk seen in the RCT (as is mandatory for ethical clinical trials) and surveillance was for a limited window period of a few weeks after vaccination whereas the adverse events noticed in the RCT were outside that window period. In remote parts of this country where the vaccine is deployed, in the absence of paediatric surgeons and radiologists, deaths from intussusception are likely to be misclassified as deaths from dysentery.

Even before this data of this post marketing surveillance is available, the WHO recently prequalified the vaccine to be used internationally.

Other rotavirus vaccines that do not reduce incidence of diarrhoea or increase the incidence of diarrhoea[c] instead of decreasing it, have been published[b].

References

a. Bajaj J, Puliyel JM Intussusception risk with 116E rotavirus vaccine in Vellore, South India. Vaccine. 2016 Jan 20;34(4):403. doi: 10.1016/j.vaccine.2015.03.007. Epub 2015 Mar 21.

b. Kulkarni PS, Desai S, Tewari T, et al. https://www.ncbi.nlm.nih.gov/pubmed/28967523

c. Kaur J, Puliyel J. Heat-stable oral rotavirus vaccine. N Engl J Med 2017; 377:302

adverse events. Often they listed new problems as 'new medical history. Myalgic encephalomyelitis otherwise known as chronic fatigue syndrome (CFS) characterized by long-term fatigue that limits a person's ability to carry out ordinary daily activities. Participants in the trial reported to Slate that debilitating symptoms were not even registered as potential side effects.

Given that CFS was not recorded as an adverse event, it allowed the manufacturers to claim that CFS is not a 'known adverse event with the vaccine' and so to discount every case that was reported subsequently. Box 5 describes how trial data in a Rotavirus trial in India was concealed and the WHO approved the vaccine.

Other problems with recording and reporting AEFI

Box 6 describes how the Periodic Safety Update Reports (PSUR) 15 and 16 of Infanrix Hexa was opened to public scrutiny by an Italian court. Box 7 PSUR 19 was obtained under the Freedom of Information rules and shows how deaths reported in PSUR 16 were deleted from PSUR 19 when it was evident that the reported deaths exceeded the deaths expected by chance[19]. Box 8 describe the changes that prevent patients from holding manufacturers to account for adverse events caused by their products. Box 9 shows how AEFI data is no longer available easily. While on the one hand, the new classification discounts AEFI as 'Not a case of [AEFI]', safety data is being manipulated and made inaccessible.

Revised AEFI classification and the precautionary principles

It is evident from the discussion earlier that the revised AEFI evaluation scheme produced by the CIOMS/WHO is designed to deny the possibility that any newly observed adverse event may be causally related to the immunization. The AEFI manual states "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…"[19,20].

Box 6. Periodic safety update reports : Unfit for public consumption?

Justice Nicola Di Leo in Italy made public the 'confidential' 15th and 16th Periodic Safety Update Report (PSUR) on Infanrix hexa (GlaxoSmithKline Biological) and this is now available on the internet[a]

Pages 246-249 document an analysis of the number of 'sudden deaths' after receiving the vaccine, to examine if it exceeds the number of deaths one could expect from the natural background incidence of sudden death. The background incidence was calculated as 0.454/1000 in the first year and 0.062/1000 live births in the second year. No allowance is made for the notoriously poor AEFI reporting rate. The number of sudden deaths expected to occur by chance between day 1 and 20, is tabulated in Table 36 on page 24. The denominator used to examine deaths following vaccination is the number of doses of the vaccine distributed not the number of children vaccinated. This denominator would dilute any potential signal because many more vaccine doses are distributed than are actually administered!

Further, the number of doses actually administered may be appropriate for milder reactions that can recur with each dose, but it is not appropriate for deaths which can happen only once. Appendix 5A shows that 13 fatal cases were reported. There were more deaths after the first dose than after the second dose and third doses and the deaths after the second was more than after the third dose. This pattern is commonly seen with AEFIs that are causatively related. The appropriate denominator in all these cases is the number of babies vaccinated.

There were 42 deaths in the first three days after vaccination where there were only 16 deaths in the next 3 days. The fact makes it apparent that many of the deaths are related to the vaccination episode.

Patient safety data should not be considered as trade secrets by any stretch of imagination. The practice of keeping safety reports confidential permits such data manipulation in a cozy relationship with the regulators, away from public scrutiny. Such practice ought to be reformed.

Reference

a http://autismoevaccini.files.wordpress.com/2012/12/vaccin-dc3a9cc3a8s.pdf Accessed 12/11/15

Box 7. EMA and Failure of Regulatory Oversight: Absence of critical appraisal of PSUR

GlaxoSmithKline (GSK), 19th confidential periodic safety update reports[a] (PSUR 19 (deaths up to October 22, 2014)) on Infanrix hexa makes interesting reading. Infanrix hexa has all the components of the Pentavalent vaccine except that it has replaced the whole cell pertussis with an acellular pertussis component and in addition has injectable polio vaccine. The cumulative number of deaths after vaccination reported in the 19th report is less than that reported in the 16th PSUR. It can be seen that deaths in children older than 1 year was significantly higher than the deaths expected by coincidence, if the deaths deleted from the 16th PSUR were restored.

It appears that the EMA accepts PSUR reports filed by manufacturers, without reviewing them critically. Regulatory authorities internationally, rely on due diligence by the EMA in such circumstances. This may need to be reappraised.

Reference

a. http://ijme.in/wp-content/uploads/2017/09/infanrix-pusr.pdf

Box 8. Product liability: Protecting patients not patents.

Hexavalent vaccine(DTaP-IPV-HepB/Hib) - Hexavac was withdrawn by the manufacturers without giving reasons after 5 cases of SIDS within 48 hours of receiving the vaccine were reported by Zinka[a]. vonKries found that in the 2nd year of life, the standardized mortality rate (SMRs) for sudden unexplained deaths (SUD) cases within 1 day of vaccination with the vaccine were 31.3 (95% CI 3.8–113.1); and within 2 days after vaccination it was 23.5 (95% CI 4.8–68,6)[b].

Similarly it will be noted that RotaSheild was voluntarily removed from the market after 12 cases of intussusceptions were reported. The background rate of intussusceptions at this age was 5 times the risk of intussusceptions from the vaccine. There was no biologically plausible explanation to link the intussusceptions to the immunization. Yet the vaccine was withdrawn[c].

The manufacturers withdrew the vaccines voluntarily without indicating the reasons. Whether the prospect of product liability suits influenced manufacturer caution is not clear.

Two significant changes have taken place after 1980. The threat of vaccine manufacturers being held responsible for marketing a defective product has diminished greatly as a consequence of these changes.

1. A no-fault compensatory mechanism has been put in many countries in the 1980s and 1990s[d] and this means that vaccine injured children need not provide clear evidence of negligence as cause of the harm, before they qualify for compensation. However, it also means that manufacturers do not have to admit to faults. The risk of product liability has now greatly decreased with no fault compensation being provided by Governments. As a result, manufacturers may be emboldened to be more reckless on vaccine safety issues.
2. The second significant change was in 2013, when the methodology for assessment of AEFI was completely overhauled. It is no longer sufficient to show temporal association of the AEFI happening repeatedly. The flow diagram below depicts all conditions that need to be satisfied before an AEFI is labelled 'Consistent causal association to immunization.' This too could embolden manufacturers to be more reckless with regard adverse reactions.

References

a. Zinka B, Rauch E, Buettner A, Ruëff F, Penning R. Unexplained cases of sudden infant death shortly after hexavalent vaccination. *Vaccine*. 2006;24:5779-80.

b. vonKries R, Toschke AM, Strassburger K, Kundi M, Kalies H, Nennstiel U, Jorch G, Rosenbauer J, Giani G. Sudden and unexpecteddeathsafter the administration of hexavalentvaccines (diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, Haemophiliusinfluenzae type b): is there a signal?*Eur J Pediatr*. 2005;164:61-9.

c. Center for Disease Control and Prevention.Rotavirus Vaccine (RotaShield) and Intussusception.http://www.cdc.gov/vaccines/vpd-vac/rotavirus/vac-rotashield-historical.htm

d. Looker C, Kelly H. No-fault compensation following adverse events attributed to vaccination: a review of international programmes. Bulletin of the World Health Organization 2011;89:371-378. Available at http://www.who.int/bulletin/volumes/89/5/10-081901/en/ Accessed on 23/10/15

Box 9. Difficulties in accessing AEFI data

In 1986 President Ronal Reagan signed the National Childhood Vaccine Injury Act (NCVIA) (42 U.S.C. §§ 300aa-1 to 300aa-34 created a no-fault system to compensate vaccine related injuries. This made it difficult to sue vaccine manufactures. It also set up Vaccine Adverse Event Reporting System (VAERS) mandating the reporting of adverse events.

1. **Polio and Acute Flaccid Paralysis in India**

   As awareness of adverse events is increasing among the public it is becoming more difficult to access data on these adverse events. The National Polio surveillance provided monthly data on acute flaccid paralysis in India. An analysis of the data showed that in 2011, there an additional 47,500 children were newly paralysed in the year, over and above the standard 2/100,000 non-polio AFP that is generally accepted as the norm. The non-polio AFP rate during the year best correlates to the cumulative doses received in the previous three years[a].

   The analysis was repeated after 2 years when the number of doses administered to children under 5 was reduced and it showed the AFP rate had begun to decline[b].

   However, the data is no longer provided on the National Polio Surveillance Project/WHO website.

2. **Data Analysis Prints on Vaccines**

   Medicines and healthcare products regulatory agency of the government of UK (MHRA) provides easily accessible Drug Analysis Prints and interactive Drug Analysis Profiles (iDAPs)[c] from 'Yellow Card' notifications of adverse events but this is not provided for vaccines. One is required to request this MHRA Pharmacovigilance for this.

Reference

a. Vashisht N, Puliyel J. Polio programme: let us declare victory and move on. Indian J Med Ethics. 2012 Apr-Jun;9(2):114-7.

b. Vashisht N, Puliyel J, Sreenivas V. Trends in nonpolio acute flaccid paralysis incidence in India 2000 to 2013. Pediatrics. 2015 Feb;135 Suppl 1:S16-7. doi: 10.1542/peds.2014-3330DD. PMID: 26005734

Figure 2 shows how all cases AEFI are classified as not causally related except those that are known adverse effects of vaccine.

The AEFI-denialism is a clear violation of the 'precautionary principle' (European Union law), which mandates that "when an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically'. Society and Government is urged that until the full scientific evidence is available, where there is evidence of risk, it must take precautionary measures". This new AEFI classification scheme that allows for an outright denial of any new causative association with vaccination could also fall foul of the Article 2 European Convention on Human Rights (Art 2 ECHR), which mandates governments to establish a framework of laws, precautions, and means of enforcement which will, to the greatest extendreasonably practicable, protect life.

Paradoxically the AEFI algorithm is said to be for vaccine safety. Perhaps we need a scheme for public safety rather than vaccine safety.

The story of Pentavalent vaccine was introduced at the beginning of this paper and is summarised in Box 10. It is primarily a vaccine used in developing countries where AEFI surveillance is poor, the press is less vigilant to report adverse events and where drug regulation is less strict. (The richer countries in West; Europe and the USA do not use the whole cell pertussis vaccine so this vaccine is not marketed in those countries). Isolated cases of unexplained deaths continued to be reported in the press. With the new AEFI classification, in the absence of 'epidemiological evidence' linking deaths to the vaccine, these deaths have been passed off as 'coincidental' SIDS deaths. Epidemiological evidence is now available linking the deaths to vaccine.

To examine if deaths following Pentavalent vaccine were merely coincidental SIDS deaths, a study of 45 million infants given DPT vaccination and 25 million who received PV was undertaken. The study assumed that all the deaths associated (self-reported to the Government surveillance system with 72 hours of vaccination) with DPT could be coincidental SIDS deaths but any increase in the deaths rate after PV may be assumed to have been caused by PV. The odds of death after Pentavalent vaccine was doubled (OR 1.98 (95% CI 1.65 to 2.38)) compared to DPT. There were 4.7 additional deaths (95% CI: 3.5-5.9), per million vaccinated with Pentavalent vaccine instead of DPT ($p<0.0001$). By the time this evidence

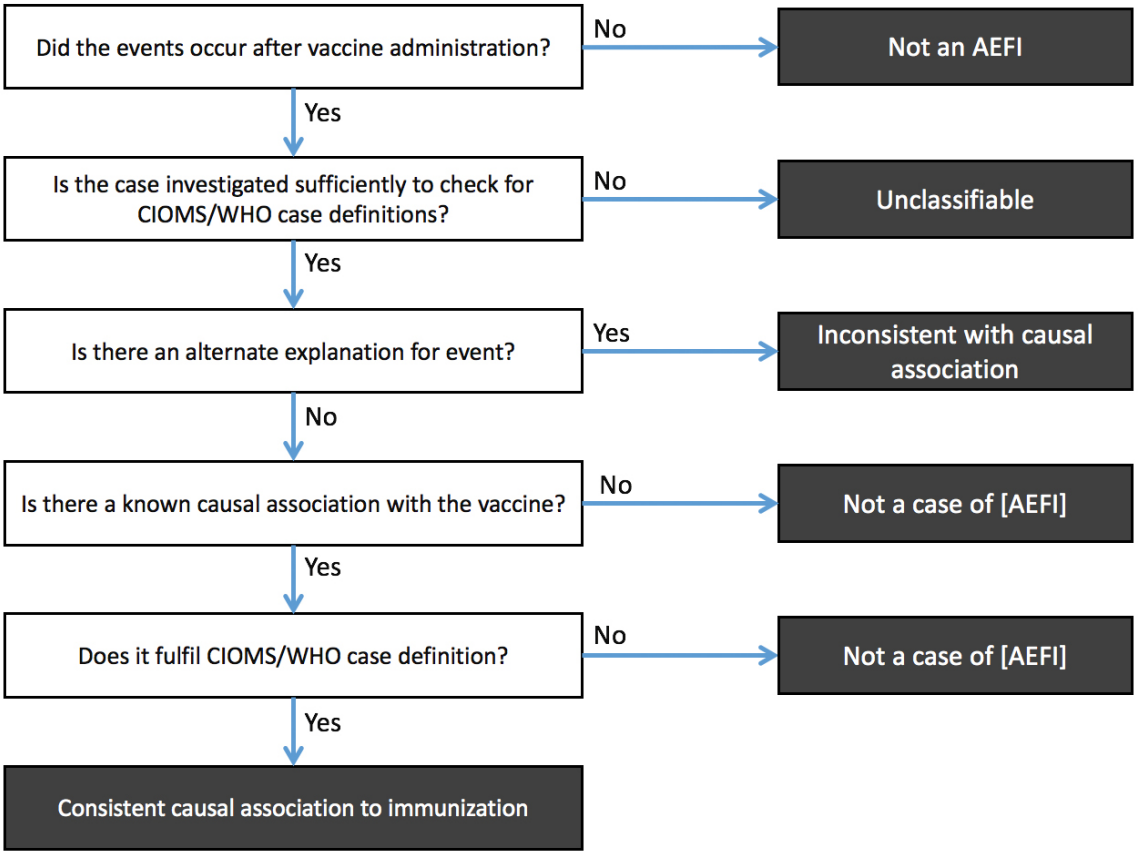

Figure 2. Pathway to achieving 'consistent causal association to immunizatio' status.

Box 10. The vaccine that changed the definition of AEFI

The story of Pentavalent vaccine

In 1949 the DTP vaccine was introduced[a] against diphtheria tetanus and pertussis. The first two were frequently fatal diseases. However, DPT was responsible for neurological adverse effects; seizures, encephalopathy, and hypotensive episodes (HHE)[b]. An acellular DTaP was developed and this has replaced DPT in the West.

In 1981 Hepatitis B was introduced[a] against this a viral infection that could lead to chronic liver disease and hepatocellular carcinoma (HCC) especially if acquired at birth. Vaccine uptake was poor in developing countries. One reason was that, although hepatitis B was common in the potentially large vaccine uptake countries like India, the incidence of HCC was very low[c]. It is now thought that newborn babies in India may be protected in the early years (where the chance of becoming a chronic carrier is worst) by passive immunity from mother to babies. This may be lost once vaccine use becomes widespread and there could be a paradoxical increase in HCC[d].

In 1987 Protein-conjugated Haemophilus influenza type b vaccine was introduced. The incidence of invasive disease in Asia is low[e] perhaps due to cross protection other bacteria have cross-reactive antigens to the Hib capsular polysaccharide[f]. Hib vaccine uptake was poor in Asia.

It is said that the Pentavalent vaccine was introduced to improve the uptake of Hib and Hepatitis B, by combining new underused vaccines with a prior UIP vaccine like DTP as a way for the new vaccines to get a piggyback ride into the UIP[g]. The Pentavalent vaccine was used only in developing countries which had not switched to DTaP.

Pentavalent vaccine has been associated with deaths. In the investigation of deaths in Sri Lanka rather than reporting that the vaccine was probably related to the vaccine the WHO experts deleted the categories 'probable' and 'possible' from the Brighton classification. This ad-hoc improvisation was reported in medical journals. The AEFI classification was then formally revised so that reactions (deaths in this case) noticed for the first time in the Phase 4 trials (post marketing trials) could all be classified as "Inconsistent with causal association to immunization" and passed off as 'coincidental SIDS deaths'.

A new study involving 45 million infants given DPT vaccination and 25 million who received Pentavalent vaccine now provides epidemiological evidence that the odds of death after Pentavalent was doubled (OR 1.98 (95% CI 1.65 to 2.38)) compared to DPT. There were 122 additional deaths (95% CI: 101-145) within 72 hours, reported to the Government surveillance system, due to the switch from DPT to Pentavalent vaccine. A large number of these deaths could have been avoided had the AEFI manual not been revised and the AEFI were evaluated earlier. Protection against these disease could have been had even if the vaccines were administered separately. In fact combined DTP-Hepatitis B-Hib vaccine causes more there were more local reactions and it is less effective than when they were administered separately[h].

References

a. http://www.immunize.org/timeline/

b. https://www.sciencedirect.com/science/article/pii/0264410X9190283C

c. https://www.ncbi.nlm.nih.gov/pubmed/?term=Hepatitis+B+in+India%3A+Systematic+review+%26+report+of+the+_IMA+sub-committee+on+immunization

d. https://www.ncbi.nlm.nih.gov/pubmed/29318526

e. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2557750/

f. https://www.ncbi.nlm.nih.gov/pubmed/?term=Natural+immunity+to+Haemophilus+influenza+b+in+infancy+in+Indian+children

g. https://www.researchgate.net/publication/238069905_New_combination_vaccines_Backdoor_entry_into_India%27s_universal_immunization_programme

h. https://www.ncbi.nlm.nih.gov/pubmed/19588375

was put together 122 excess deaths (95% CI: 101-145) had been reported to the Government, due to the switch from DPT to Pentavalent vaccine. The contribution of the new AEFI classification in this delay in recognizing the problem is stark[21].

Conclusions

That vaccines do more good than harm is taken as an article of faith – a dogma or tenet. The purpose of this exercise in AEFI-denialism is to prevent the undermining confidence in vaccines. However, the scheme does not seem to be working. Indeed, public scepticism seems to be increasing rather than diminishing with these efforts at reassurance that vaccines are safe[22,23]. Epidemics of vaccine preventable disease have resulted[24].

The response in some States in the United States has been to make vaccination mandatory for admission to public schools. Personal and religious belief exemptions for vaccination are not be allowed in California, effective July 1, 2016. If the debates among US Republican Presidential aspirants are anything to go by, it is clear that there is a lack of widespread support for this measure. The Department of Health and Human Services Office for Civil Rights has now set up the Conscience and Religious Freedom Division to which individuals could complain if their conscience or religious freedom has been

abridged. How these forces will interact is anyone's guess, but the present scenario augur badly for public trust in vaccines and voluntary vaccination.

Competing interests

No competing interests were disclosed.

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References

1. WHO: **Global Vaccine Safety. Pentavalent vaccine in Asian countries.** (accessed 20 February 2018).
Reference Source
2. WHO Experts Report: **High Court of Delhi at New Delhi WP (C) 13698 of 2009 Dr KB Saxena and others (petitioners) versus Union of India and others (respondents).** Submission of respondents dated 03/04/2010. [accessed 19.10.15].
3. Puliyel J, Mathew JL, Priya R: **Incomplete reporting of research in press releases: et tu, WHO?** *Indian J Med Res.* 2010; **131**: 588–9.
PubMed Abstract
4. Saxena KB, Banerji D, Qadeer I, *et al.*: **"Antivaccine lobby" replies to the *BMJ*.** *BMJ.* 2010; **341**: c4001.
PubMed Abstract | Publisher Full Text
5. WHO: **Safety of Quinvaxem (DTwP-HepB-Hib) pentavalent vaccine.** [accessed 15.10.15]. May 10, 2013.
Reference Source
6. Hume DA: In: Selby-Bigge LA, Nidditch PH, editors. **Treatise of Human Nature.** Oxford: Clarndon; 1739.
Reference Source
7. Brady HE: **Causality and explanation in social research.** In *The Oxford Handbook of Political Methodology.* ed Janet M. Box-Steffensmeier, Henry E. Brady, and David Collier. Oxford University Press Oxford.
Publisher Full Text
8. Mackie JL: **Causes and conditions.** *American Philosophical Quarterly.* 1965; **2**: 245–64.
Reference Source
9. **Athey v. Leonati (1996), 140 D.L.R. (4th) 235 at para. 32, [1996] 3 S.C.R. 458, [1997] 1 W.W.R. 97 quoted in David H, McCague WP, Yaniszewski PF *The Advocates' Quarterly*.** 2005; **30**: 216–238.
Reference Source
10. Center for Disease Control and Prevention: **Rotavirus Vaccine (RotaShield) and Intussusception.**
Reference Source
11. Definitions and Application of Terms for Vaccine Pharmacovigilance CIOMS/WHO: **Definitions and Application of Terms for Vaccine Pharmacovigilance Report of CIOMS/ WHO Working Group on Vaccine Pharmacovigilance.**
Reference Source
12. Legge D, Puliyel J: **Enhancing community confidence in vaccines safety.** *BMJ.* 2017; **357**: j2449.
Reference Source
13. WHO: **The Causality assessment of an adverse event following immunization (AEFI): User manual for the revised WHO classification.** WHO/HIS/EMP/QSS. March 2013.
Reference Source
14. Soriano A, Nesher G, Shoenfeld Y: **Predicting post-vaccination autoimmunity: Who might be at risk?** *Pharmacol Res.* 2015; **92**: 18–22.
PubMed Abstract | Publisher Full Text
15. Berkovic SF, Harkin L, McMahon JM, *et al.*: **De-novo mutations of the sodium channel gene *SCN1A* in alleged vaccine encephalopathy: a retrospective study.** *Lancet Neurol.* 2006; **5**(6): 488–92.
PubMed Abstract | Publisher Full Text
16. Rigolet M, Aouizerate J, Couette M, *et al.*: **Clinical features in patients with long-lasting macrophagic myofasciitis.** *Front Neurol.* 2014; **5**: 230.
PubMed Abstract | Publisher Full Text | Free Full Text
17. Puliyel J, Phadke A: **Deaths following pentavalent vaccine and the revised AEFI classification.** *Ind J Med Ethics.* 2017; **2**(4): 300–301.
PubMed Abstract | Publisher Full Text
18. Collet JP, MacDonald N, Cashman N, *et al.*: **Monitoring signals for vaccine safety: the assessment of individual adverse event reports by an expert advisory committee. Advisory Committee on Causality Assessment.** *Bull World Health Organ.* 2000; **78**(2): 178–85.
PubMed Abstract | Free Full Text
19. Puliyel J, Sathyamala C: **Infanrix hexa and sudden death: a review of the periodic safety update reports submitted to the European Medicines Agency.** *Indian J Med Ethics.* 2018; **1**(1): 43–47.
PubMed Abstract | Publisher Full Text
20. **Global Advisory Committee on Vaccine Safety,12–13 June 2013.** *Wkly Epidemiol Rec.* 2013; **88**: 301–12.
PubMed Abstract
21. Puliyel J, Kaur J, Puliyel A, *et al.*: **Deaths reported after Pentavalent vaccine compared with death reported after diphtheria-tetanus-pertussis vaccine – an exploratory analysis.** *Med J DY Patil Univ.* In print.
22. MacDonald NE; SAGE Working Group on Vaccine Hesitancy: **Vaccine hesitancy: Definition, scope and determinants.** *Vaccine.* **33**(34): 4161–4164.
PubMed Abstract | Publisher Full Text
23. Sci Dev Net: **Parental doubt drives drop in vaccination.**
Reference Source
24. Clemmons NS, Gastanaduy PA, Fiebelkorn AP, *et al.*: **Measles - United States, January 4-April 2, 2015.** *MMWR Morb Mortal Wkly Rep.* 2015; **64**(14): 373–376.
PubMed Abstract

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? **Peter Aaby**
Bandim Health Project, Bissau, Guinea-Bissau

The authors are to be complimented for having conducted this study. Proper handling of AEFIs is very important if we are to maintain trust between public health vaccinology and the community. However, I am missing the authors' specific suggestions for how to improve the situation. As discussed below there are also details of presentation which could be improved.

There is a rather detailed description of the changes in the definition of causality in relation to the current concept of AEFI. However, I am missing some presentation of where is the AEFIs concept coming from historically and what is the underlying theoretical biological model of why AEFI might occur and how does that affect how AEFI are observed, reported and used. Furthermore, what are the regulators requirements? Apparently the dominant thinking is that vaccines only induce disease specific memory. Presumably genetic variability may in rare cases affect how this biological process takes place and this could cause specific AEFIs. What else are the causes of other AEFIs: co-incidental infections or chronic disease, co-administration of drugs or other vaccinations? Most of such events can presumably be rejected as not "caused" directly by the vaccine.

However, the concept of vaccines may be changing. WHO experts have recognized that vaccines may have non-specific effects (NSEs) with consequences for child survival [1]. Apparently, through epigenetic and metabolic changes, vaccines can reprogram the immune system and upregulate or downregulate both the innate and the adaptive immune system [2-5]. If that is the case there is room for both beneficial and deleterious unexpected events following immunization (UEFI). Proper monitoring systems should also be able to detect beneficial UEFIs; for example, we have found that BCG reduces the risk of neonatal sepsis in low-birth weight children [6]. On the other hand, DTP consistently increases female relative to male mortality, also in societies that have no sex-differential treatment [7]. This is "unnatural" since there was no excess female mortality in the pre-vaccination era in West Africa [8]. This being the case there should be room not only for the short-term AEFI as in the current system (14 days?) but also for much more protracted biological processes being classified as AEFI/UEFI. This would require new standards for how UEFI/AEFI are observed and registered.

Parallel with the description of the changes in the definition of AEFI, there is a series of examples where the authors apparently think there are real differences in mortality/safety issues between different vaccination groups. I have noted at least: Pentavalent vaccine and congenital heart disease; MMR and autism in African American children; Hexavac; Rotavac; HPV and chronic fatigue syndrome; Pentavalent vaccine vs DTP for SIDS. Sometimes these safety issues are mentioned in passing as examples in the

discussion of the processes related to AEFI assessment. I found it sometimes unclear whether these example were presented in their own right as safety issues or whether they were only meant to illustrate problems in the assessment of AEFI, e.g. safety reports not forthcoming, etc. Sometimes the presentation was too short or unclear to be really convincing; for example, I had problems with the ROTAVAC story (box 5). It is unclear why it is said in Box 5: “Other rotavirus vaccines that do not reduce incidence of diarrhoea or increase the incidence of diarrhoea instead of decreasing it, have been published (b)”. The paper which is referenced apparently reported a 40% reduction in rota-diarrhoea. If the problem is that overall diarrhea was not reduced I think this can be present more clearly.

I think the paper would be stronger/more convincing if the safety-issues that the authors believe have been documented as safety concerns were presented as safety-case stories in specific boxes; the effect of Pentavalent vaccine on SIDS is apparently such a concern. Then the text on the changes in the assessment of AEFI could refer to this or that AEFI problem which was illustrated in the safety-case stories. On the other hand if the story is about mismanagement of the assessment of AEFI, then the cases should be presented as such without implying a causal link between vaccination and AEFI; for example box 3 is an example of poor public communication but it has hardly been documented that MMR causes autism.

Abstract:
It should not be assumed that ”Of course, vaccines that caused deaths in the control-trials stage would not be licensed.” RTS,S malaria vaccine was recently approved by EMA but the trial data indicate that RTS,S compared with control vaccines was associated with 2-fold higher mortality for girls [9,10]. Neither the authors nor EMA apparently analysed the mortality data, overall or by sex.

The example with cardiac failure in children is not presented in the paper and should therefore not appear in the abstract unless it is fully described in the paper. The case might well warrant further presentation in the paper itself.

Introduction
Being presented with the Sri Lanka and Vietnam cases in the first paragraphs, the reader is left wondering what was the implications of the WHO experts’ classifications. Was the pentavalent vaccine (Penta) reintroduced in the countries and how did that decision come about?

Causality assessment
In the long description of changes in the manual for AEFI assessment, it would be good to have an explanation of WHO’s own justification for these changes.

Sometimes the text appears to have been written some years back but have been maintained unchanged in in the current 2018-version. For example in Box 3 it is said that “Thomson has now been granted whistleblower status by the Obama administration”. By now this sentence should probably be: “Thomson was granted whistleblower status by the Obama administration”. Similar in the conclusion it is said that if the debates among Republican presidential aspirants “are anything to go by”. By now it can no longer be “are”.

Box 10: this sentence has problems: “In fact combined DTP-Hepatitis B-Hib vaccine causes more there were more local reactions and it is less effective than when they were administered separately.”

Page 10: Biological plausibility.
There appears to be an increasing trend to dismiss “unexpected observations”/unpleasant observations

with the argument that there is no “biological plausibility”. This was one of the arguments used by WHO experts to dismiss that high-titre measles vaccine (HTMV) could be associated with excess female mortality [11]. There can obviously not be biological plausibility for a pattern just detected, that no one has ever thought about. The only relevant question is whether a pattern is repeatable – arguments about biological plausibility should not be allowed to dismiss observations of potential AEFIs. The excess female mortality was repeated in subsequent studies and WHO eventually withdrew the HTMV (1992).

I found this sentence strange: “Slate investigated of the randomised trials of human papillomavirus (HPV) vaccines and found that potential side effects were collected for only two weeks in the year long study.”

Page 13: “PV” has not been defined as the abbreviation for pentavalent vaccine.

The comparison of DTP and pentavalent vaccine is frightening. Please indicate whether it is SIDS death or all-cause deaths when it is said for example: “The odds of death after pentavalent vaccine was doubled”. Since it is your study I would have indicated that to the readers: “To examine if deaths following Pentavalent vaccine (PV) were merely coincidental SIDS deaths, we undertook a study of 45 million infants given DPT vaccination and 25 million who received PV”. Given the scary character of this report a bit more information on methods in data collection and analysis would be appropriate. Any hypothesis of why there would be a two-fold difference in SIDS (?) mortality? Did the patterns differ for boys and girls? We have found that DTP and Penta are both associated with much higher female-than-male all-cause mortality rates [7,12].

Conclusion

I do not think the conclusion is really a conclusion to the content of the paper.

How do we proceed from here? How can we built a better system that finds even the AEFIs we do not want to see and had not expected – and at the same do not create mistrust in the vaccines (BCG, measles vaccines, OPV) which are associated with major reductions in child mortality in low-income countries. What time-frame should be used? AEFI should always be presented by sex. If there are sex-differential patterns of AEFI it might enhance the credibility of this patterns as a true AEFI since we have found sex-differential effects on mortality of most of common vaccines.

Biological plausibility should not be used to dismiss any new and unexpected pattern. There is now evidence that vaccines may reprogram both the innate and the adaptive immune system epigenetically with effect on general susceptibility to non-targeted infections [2,5]. Hence, the starting point should be that ***unlikely effects are likely*** because we have never examined the possibility.

It is standard practice in small safety study with deaths to dismiss them because we cannot see a connection. However, deaths following vaccinations should always be classified as potential-even-though-unlikely AEFIs. Otherwise we cannot accumulate the data and detect patterns we had not imagined. For example, when DTaP was tested in an RCT in Sweden there were 4 deaths among 2847 vaccinated children but none among 954 controls [13]. Though the authors recognized that 4 deaths was too high and would have been significant if the whole Swedish population of eligible children had been used as controls, the study could find no link between the vaccine and the deaths. All properly conducted studies from low-income countries have found DTwP to be associated with increased child mortality [14-16].

References

1. Higgins JP, Soares-Weiser K, López-López JA, Kakourou A, Chaplin K, Christensen H, Martin NK,

Sterne JA, Reingold AL: Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review.*BMJ*. 2016; **355**: i5170 PubMed Abstract
2. Benn CS, Netea MG, Selin LK, Aaby P: A small jab - a big effect: nonspecific immunomodulation by vaccines.*Trends Immunol*. 2013; **34** (9): 431-9 PubMed Abstract | Publisher Full Text
3. Kleinnijenhuis J, Quintin J, Preijers F, Joosten LA, Ifrim DC, Saeed S, Jacobs C, van Loenhout J, de Jong D, Stunnenberg HG, Xavier RJ, van der Meer JW, van Crevel R, Netea MG: Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes.*Proc Natl Acad Sci U S A*. 2012; **109** (43): 17537-42 PubMed Abstract | Publisher Full Text
4. Kleinnijenhuis J, Quintin J, Preijers F, Benn CS, Joosten LA, Jacobs C, van Loenhout J, Xavier RJ, Aaby P, van der Meer JW, van Crevel R, Netea MG: Long-lasting effects of BCG vaccination on both heterologous Th1/Th17 responses and innate trained immunity.*J Innate Immun*. 2014; **6** (2): 152-8 PubMed Abstract | Publisher Full Text
5. Arts RJW, Moorlag SJCFM, Novakovic B, Li Y, Wang SY, Oosting M, Kumar V, Xavier RJ, Wijmenga C, Joosten LAB, Reusken CBEM, Benn CS, Aaby P, Koopmans MP, Stunnenberg HG, van Crevel R, Netea MG: BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity.*Cell Host Microbe*. 2018; **23** (1): 89-100.e5 PubMed Abstract | Publisher Full Text
6. Biering-Sørensen S, Aaby P, Lund N, Monteiro I, Jensen KJ, Eriksen HB, Schaltz-Buchholzer F, Jørgensen ASP, Rodrigues A, Fisker AB, Benn CS: Early BCG-Denmark and Neonatal Mortality Among Infants Weighing <2500 g: A Randomized Controlled Trial.*Clin Infect Dis*. 2017; **65** (7): 1183-1190 PubMed Abstract | Publisher Full Text
7. Aaby P, Ravn H, Fisker AB, Rodrigues A, Benn CS: Is diphtheria-tetanus-pertussis (DTP) associated with increased female mortality? A meta-analysis testing the hypotheses of sex-differential non-specific effects of DTP vaccine.*Trans R Soc Trop Med Hyg*. 2016; **110** (10): 570-581 PubMed Abstract | Publisher Full Text
8. Aaby P, Martins CL, Garly ML, Rodrigues A, Benn CS, Whittle H: The optimal age of measles immunisation in low-income countries: a secondary analysis of the assumptions underlying the current policy.*BMJ Open*. 2012; **2** (4). PubMed Abstract | Publisher Full Text
9. Klein S, Shann F, Moss W, Benn C, Aaby P: RTS,S Malaria Vaccine and Increased Mortality in Girls. *mBio*. 2016; **7** (2): e00514-16 Publisher Full Text
10. Aaby P, Rodrigues A, Kofoed P, Benn C: RTS,S/AS01 malaria vaccine and child mortality. *The Lancet* . 2015; **386** (10005): 1735-1736 Publisher Full Text
11. Aaby P, Jensen H, Samb B, Cisse B, Sodemann M, Jakobsen M, Poulsen A, Rodrigues A, Lisse IM, Simondon F, Whittle H: Differences in female-male mortality after high-titre measles vaccine and association with subsequent vaccination with diphtheria-tetanus-pertussis and inactivated poliovirus: reanalysis of West African studies.*Lancet*. 2003; **361** (9376): 2183-8 PubMed Abstract | Publisher Full Text
12. Fisker A, Biering-Sørensen S, Lund N, Djana Q, Rodrigues A, Martins C, Benn C: Contrasting female-male mortality ratios after routine vaccinations with pentavalent vaccine versus measles and yellow fever vaccine. A cohort study from urban Guinea-Bissau. *Vaccine*. 2016; **34** (38): 4551-4557 Publisher Full Text
13. Storsaeter J, Olin P, Renemar B, Lagergård T, Norberg R, Romanus V, Tiru M: Mortality and morbidity from invasive bacterial infections during a clinical trial of acellular pertussis vaccines in Sweden.*Pediatr Infect Dis J*. 1988; **7** (9): 637-45 PubMed Abstract
14. Aaby P, Ravn H, Benn CS: The WHO Review of the Possible Nonspecific Effects of Diphtheria-Tetanus-Pertussis Vaccine.*Pediatr Infect Dis J*. 2016; **35** (11): 1247-1257 PubMed Abstract | Publisher Full Text
15. Mogensen SW, Andersen A, Rodrigues A, Benn CS, Aaby P: The Introduction of Diphtheria-Tetanus-Pertussis and Oral Polio Vaccine Among Young Infants in an Urban African

Community: A Natural Experiment.*EBioMedicine*. 2017; **17**: 192-198 PubMed Abstract | Publisher Full Text
16. Aaby P, Mogensen S, Rodrigues A, Benn C: Evidence of Increase in Mortality After the Introduction of Diphtheria–Tetanus–Pertussis Vaccine to Children Aged 6–35Months in Guinea-Bissau: A Time for Reflection?. *Frontiers in Public Health*. 2018; **6**. Publisher Full Text

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

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?
Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I 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.

Author Response 04 May 2018

Jacob Puliyel, St Stephens Hospital, India

Reviewer 2

Reviewer Professor Peter Aaby

Reviewer Comment
Authors' response

The authors are to be complimented for having conducted this study. Proper handling of AEFIs is very important if we are to maintain trust between public health vaccinology and the community. I am missing the authors' specific suggestions for how to improve the situation.
We thank the reviewer for his detailed review and this compliment.

We attempt only to critique the revised AEFI classification. Before one makes an effort to improve it, there has to be an acknowledgement of the flaws in the present system.

We make no claim to have developed an alternate system of classification. An appropriate body of experts will need to draft it, if there is a consensus on what is flawed with the present system.

We have now introduced a new paragraph entitled: "Where do we go from here". We have suggested that the WHO-UMC causality categories for drug reactions has stood the test of

time (and the older Brighton system was adapted from it) may be used till a better system evolves.

There is a rather detailed description of the changes in the definition of causality in relation to the current concept of AEFI. However, I am missing some presentation of where is the AEFIs concept coming from historically and what is the underlying theoretical biological model of why AEFI might occur and how does that affect how AEFI are observed, reported and used. Furthermore, what are the regulators requirements? Apparently the dominant thinking is that vaccines only induce disease specific memory. Presumably genetic variability may in rare cases affect how this biological process takes place and this could cause specific AEFIs. What else are the causes of other AEFIs: co-incidental infections or chronic disease, co-administration of drugs or other vaccinations? Most of such events can presumably be rejected as not “caused” directly by the vaccine.

We have dealt very briefly with the historic and theoretical background – but within the 8000 word-limit, we could not deal with this in greater detail.
Regarding: ‘AEFIs concept coming from historically’
The other reviewer Prof. Tom Jefferson (TJ) has suggested we introduce the contributions made by the AB Hill and we have made reference to that.

We refer to genetic predisposition to AEFI in our article and also how underlying disease like congenital heart lesions can precipitate an AEFI. This paragraph has been added in the main body on the text.

In the new version we make reference to non-specific effects of vaccine and we thank the reviewer for his suggestion.

However, the concept of vaccines may be changing. WHO experts have recognized that vaccines may have non-specific effects (NSEs) with consequences for child survival [1]. Apparently, through epigenetic and metabolic changes, vaccines can reprogram the immune system and upregulate or downregulate both the innate and the adaptive immune system [2-5]. If that is the case there is room for both beneficial and deleterious unexpected events following immunization (UEFI). Proper monitoring systems should also be able to detect beneficial UEFIs; for example, we have found that BCG reduces the risk of neonatal sepsis in low-birth weight children [6]. On the other hand, DTP consistently increases female relative to male mortality, also in societies that have no sex-differential treatment [7]. This is “unnatural” since there was no excess female mortality in the pre-vaccination era in West Africa [8]. This being the case there should be room not only for the short-term AEFI as in the current system (14 days?) but also for much more protracted biological processes being classified as AEFI/UEFI. This would require new standards for how UEFI/AEFI are observed and registered.

We thank the reviewer for the references. In our new submission we refer briefly to these NSEs and the benefits and harms than can result.

Parallel with the description of the changes in the definition of AEFI, there is a series of examples where the authors apparently think there are real differences in mortality/safety issues between

different vaccination groups. I have noted at least: Pentavalent vaccine and congenital heart disease; MMR and autism in African American children; Hexavac; Rotavac; HPV and chronic fatigue syndrome; Pentavalent vaccine vs DTP for SIDS. Sometimes these safety issues are mentioned in passing as examples in the discussion of the processes related to AEFI assessment. I found it sometimes unclear whether these example were presented in their own right as safety issues or whether they were only meant to illustrate problems in the assessment of AEFI, e.g. safety reports not forthcoming, etc. Sometimes the presentation was too short or unclear to be really convincing; for example, I had problems with the ROTAVAC story (box 5). It is unclear why it is said in Box 5: “Other rotavirus vaccines that do not reduce incidence of diarrhoea or increase the incidence of diarrhoea instead of decreasing it, have been published (b)”. The paper which is referenced apparently reported a 40% reduction in rota-diarrhoea. If the problem is that overall diarrhea was not reduced I think this can be present more clearly.

I think the paper would be stronger/more convincing if the safety-issues that the authors believe have been documented as safety concerns were presented as safety-case stories in specific boxes; the effect of Pentavalent vaccine on SIDS is apparently such a concern. Then the text on the changes in the assessment of AEFI could refer to this or that AEFI problem which was illustrated in the safety-case stories. On the other hand if the story is about mismanagement of the assessment of AEFI, then the cases should be presented as such without implying a causal link between vaccination and AEFI; for example box 3 is an example of poor public communication but it has hardly been documented that MMR causes autism.

They are presented as potential safety problems that seem to get glossed over, by the Revised AEFI assessment methodology. (Please also see next point in row below).

Regarding Rotavac the problem is that overall diarrhea is not decreased and this is clarified in the revised text

Safety-case stories with Pentavac and Hexavac have been identified as such in the revised manuscript

The MMR story Box 3 was about increased autism seen in African American boys vaccinated prior to age of 2 years (compared to those vaccinated after 2 years).

Post-hoc, data of many African American children were excluded on the grounds that they did not possess a valid birth certificate –and reanalysis of this truncated data was published to suggest that MMR was not related autism in any group.

This suggests a possible link between Autism and MMR (albeit in one specific ethnic and age group).

In summary, all the examples noted by the reviewer in the article (Pentavalent vaccine and congenital heart disease; MMR and autism in African American children; Hexavac; Rotavac; HPV and chronic fatigue syndrome; Pentavalent vaccine vs DTP for SIDS) are AEFI that are ‘probably’ related causatively with vaccination which are not acknowledged.

In the case of MMR and Hexavac the new revised classification cannot be blamed as the data itself was falsified (Many African American boys excluded from MMR study and deaths deleted from PSUR 19).

Abstract
It should not be assumed that "Of course, vaccines that caused deaths in the control-trials stage would not be licensed." RTS,S malaria vaccine was recently approved by EMA but the trial data indicate that RTS,S compared with control vaccines was associated with 2-fold higher mortality for girls [9,10]. Neither the authors nor EMA apparently analysed the mortality data, overall or by sex.

The example with cardiac failure in children is not presented in the paper and should therefore not appear in the abstract unless it is fully described in the paper. The case might well warrant further presentation in the paper itself.

This sentence has been corrected in abstract

The case of heart failure in children is now included in the paper as suggested by the reviewer.

Introduction
Being presented with the Sri Lanka and Vietnam cases in the first paragraphs, the reader is left wondering what was the implications of the WHO experts' classifications. Was the pentavalent vaccine (Penta) reintroduced in the countries and how did that decision come about?

The vaccines were reintroduced after the 'WHO experts' report, and this is mentioned now in the revised manuscript.
The inevitable follow-up question then is: Were there deaths after it was reintroduced? We know from the data from India that using the Revised AEFI manual, each death is certified as 'inconsistent with causal association' on the grounds that death has so far never been acknowledged as having occurred in epidemiological studies with the vaccine. This is explained in the paper with reference from literature.

Causality assessment
1. In the long description of changes in the manual for AEFI assessment, it would be good to have an explanation of WHO's own justification for these changes.

2. Sometimes the text appears to have been written some years back but have been maintained unchanged in the current 2018-version. For example in Box 3 it is said that "Thomson has now been granted whistleblower status by the Obama administration". By now this sentence should probably be: "Thomson was granted whistleblower status by the Obama administration". Similar in the conclusion it is said that if the debates among Republican presidential aspirants "are anything to go by". By now it can no longer be "are".

Box 10: this sentence has problems: "In fact combined DTP-Hepatitis B-Hib vaccine causes more there were more local reactions and it is less effective than when they were administered separately."

3. Page 10: Biological plausibility.
There appears to be an increasing trend to dismiss “unexpected observations”/unpleasant observations with the argument that there is no “biological plausibility”. This was one of the arguments used by WHO experts to dismiss that high-titre measles vaccine (HTMV) could be associated with excess female mortality [11]. There can obviously not be biological plausibility for a pattern just detected, that no one has ever thought about. The only relevant question is whether a pattern is repeatable – arguments about biological plausibility should not be allowed to dismiss observations of potential AEFIs. The excess female mortality was repeated in subsequent studies and WHO eventually withdrew the HTMV (1992).

4. I found this sentence strange: “Slate investigated of the randomised trials of human papillomavirus (HPV) vaccines and found that potential side effects were collected for only two weeks in the year long study.”

5. Page 13: “PV” has not been defined as the abbreviation for pentavalent vaccine.

6. The comparison of DTP and pentavalent vaccine is frightening. Please indicate whether it is SIDS death or all-cause deaths when it is said for example: “The odds of death after pentavalent vaccine was doubled”. Since it is your study I would have indicated that to the readers: “To examine if deaths following Pentavalent vaccine (PV) were merely coincidental SIDS deaths, we undertook a study of 45 million infants given DPT vaccination and 25 million who received PV”. Given the scary character of this report a bit more information on methods in data collection and analysis would be appropriate. Any hypothesis of why there would be a two-fold difference in SIDS (?) mortality? Did the patterns differ for boys and girls? We have found that DTP and Penta are both associated with much higher female-than-male all-cause mortality rates [7,12].

1. This has not been justified as far as we know. The rationale for revising the Brighton classification has also not been stated explicitly.

Reviewer TJ suggested that WHO must be given an opportunity to defend the changes.

David Legge and I had written to WHO, before we published the short critique in BMJ referenced in the paper (Reference 14). This is copied in the response to TJ. There was no response from WHO.

This present paper was also sent to WHO after it appeared in F1000 to seek their comments. There has not been any response so far.

2. The reviewer is correct that the article has been written in parts and the tense needs to be corrected for consistency. This has now been done.

3. We thank the reviewer for this example that has been included in the text.

4. The Slate story: that was the point of the Slate report – that adverse events were not recorded properly.

5. Abbreviation PV has been removed

6. The DPT Pentavalent story is about deaths within 72 hours of vaccination. As babies taken for vaccination are usually not unwell, these must be considered as SIDS deaths in 'well children' and comparisons can only be made with the acceptable death rate for 'well children' and it must NOT be compared to the 'all cause death rate' which includes in the cohort well and unwell children. This is sometimes referred to as the 'healthy vaccinee effect'

When we report "The odds of death after pentavalent vaccine was doubled" we DO NOT have to make any extra allowance for the 'healthy vaccinee effect' as both DPT and Pentavalent vaccine are given to healthy children. The deaths among children getting pentavalent vaccine was twice as high as those getting DPT

There is no hypothesis for the deaths - except as explained in the Boatman case - that the use of multiple vaccines release more inflammatory cytokines (than when single vaccines given) which can act as neuro-modulators and can cause depression of the serotonergic 5-hydroxytryptophan (5-HT) system in the infant medulla and blunt the normal chemo-sensitive response to excess carbon dioxide and this can result in the death of vulnerable infants during sleep.

The method of data collection is described in great detail in the reference (which would be too long to reproduce in this paper). It may suffice to say that both DPT and Pentavalent deaths were captured in the same 'improved' government surveillance system and the data has been made freely available on-line for rechecking by stake holders, and more studies by future researchers.

The records did not specify sex of child.

Conclusion

1. I do not think the conclusion is really a conclusion to the content of the paper.

   How do we proceed from here? How can we built a better system that finds even the AEFIs we do not want to see and had not expected – and at the same do not create mistrust in the vaccines (BCG, measles vaccines, OPV) which are associated with major reductions in child mortality in low-income countries. What time-frame should be used? AEFI should always be presented by sex. If there are sex-differential patterns of AEFI it might enhance the credibility of this patterns as a true AEFI since we have found sex-differential effects on mortality of most of common vaccines.

   Biological plausibility should not be used to dismiss any new and unexpected pattern. There is now evidence that vaccines may reprogram both the innate and the adaptive immune system epigenetically with effect on general susceptibility to non-targeted infections [2,5]. Hence, the starting point should be that ***unlikely effects are likely*** because we have never examined the possibility.

   It is standard practice in small safety study with deaths to dismiss them because we cannot see a connection. However, deaths following vaccinations should always be classified as potential-even-though-unlikely AEFIs. Otherwise we cannot accumulate the data and detect patterns we had not imagined. For example, when DTaP was tested in an RCT in Sweden

there were 4 deaths among 2847 vaccinated children but none among 954 controls [13]. Though the authors recognized that 4 deaths was too high and would have been significant if the whole Swedish population of eligible children had been used as controls, the study could find no link between the vaccine and the deaths. All properly conducted studies from low-income countries have found DTwP to be associated with increased child mortality [14-16].

1. **The conclusion has been revised as suggested**
2. **We have included a paragraph on "Where do we go from here".**

Competing Interests: None

Referee Report 14 March 2018

doi:10.5256/f1000research.14875.r31301

Tom Jefferson
Centre for Evidence Based Medicine, University of Oxford, Oxford, UK

Thank you for asking my views on this paper.

This is a very long and detailed examination of the philosophical, historical rationale and principles of causality assessment of possible vaccine harms, chiefly death. This is mixed with the narrative of the changes made by WHO to their own assessment rules.

The authors use several important examples to make their points.

I regard this topic as extremely interesting and important and the authors should be congratulated for attempting to pull the main strands together, from David Hume to the Brighton Collaboration.

Despite my interest I found the manuscript extremely heavy going with a difficult-to-follow thread.
It soon became apparent that the authors think there has been something akin to an international conspiracy to bury the dead by changing the definitions of probable and likely causality. That may be so, but I could not find any convincing evidence in the paper.

Here and there inaccuracies and typos add to the distractions. For example in box 10, DTP becomes DPT or the suggestions that Rotashield was withdrawn in 1999 as a consequence of the Brighton criteria. As far as I remember in 1999 we were setting up and had not produced the criteria or any other output yet.

I would also check the data of Rotashield withdrawal from the market.

What follows are a few suggestions to improve the manuscript (ms).

First I would split the ms into 2 parts. One discussing the philosophical-historical basis for causality assessment perhaps as far as Brighton and the second one looking at the more recent changes.

Here I have two further suggestions to offer.

Bradford Hill's criteria should be cited, even though they are not a perfect solution as Hill himself recognised. They should be cited because they have had an enormous influence on modern epidemiology (see Geoffrey Rose's variant for example) and because the formulation of some of them (temporality, strength, gradient) is very apt for vaccine exposure. Take temporality for example. The term AEFI which is so extensively cited concedes temporality when in fact temporality is only as good as the vaccination records. Often "AEFI" is used when we are not sure that exposure has taken place at all or that it preceded the clinical event/possible harm. So a balanced discussion of temporality (one of the absolute conditions for determining causality) must include absolute certainty or high probability that exposure preceded the event and that it had taken place at all.

Second I would offer the connection of probabilism and Fisherian theory with Hume's problem of induction. I see Fisher's work as the patch that allows us to go on with at least a partially clear conscience, as I do not think there is a solution to Hume's problem as nature is not (and never will be) universally uniform.

I would tone down the plot theory rhetoric and would seek a written explanation from WHO for their actions. WHO do not have a good track record of answering researchers but the effort must be made and reported. Ditto for any other point which was unclear to the authors. I am not a great believer in plots, blunders fit the picture and my experience better, but the authors must try and get to the bottom of the rationale for the changes and, while at it, they might just want to ask WHO, CIOMS etc. to check the authors' facts and dates (but not their opinions of course).

Last but not least please ask Brighton whether they were aware of WHO's actions (they must be) and what their views are.

I hope these suggestions are useful to the authors.

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

Competing Interests: TJ was a recipient of a UK National Institute for Health Research grant for a Cochrane review of neuraminidase inhibitors for influenza. In addition, TJ receives royalties from his books published by Il Pensiero Scientifico Editore, Rome and Blackwells. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products. In 2011-13, TJ acted as an

expert witness in litigation related to the antiviral oseltamivir, in two litigation cases on potential vaccine-related damage and in a labour case on influenza vaccines in healthcare workers in Canada. He has acted as a consultant for Roche (1997-99), GSK (2001-2), Sanofi-Synthelabo (2003), and IMS Health (2013).In 2014 he was retained as a scientific adviser to a legal team acting on oseltamivir. TJ has a potential financial conflict of interest in the drug oseltamivir. In 2014-16, TJ was a member of three advisory boards for Boerhinger Ingelheim. TJ was holder of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine. Between 1994 and 2013, TJ was the coordinator of the Cochrane Vaccines Field. TJ was a co-signatory of the Nordic Cochrane Centre Complaint to the European Medicines Agency (EMA) over maladministration at the EMA in relation to the investigation of alleged harms of HPV vaccines and consequent complaints to the European Ombudsman. TJ is co-holder of a John and Laura Arnold Foundation grant for development of a RIAT support centre (2017-2020) and Jean Monnet Network Grant, 2017-2020 for The Jean Monnet Health Law and Policy Network. TJ is an unpaid collaborator to the project Beyond Transparency in Pharmaceutical Research and Regulation led by Dalhousie University and funded by the Canadian Institutes of Health Research (2018-2022).

Referee Expertise: Tom Jefferson, Clinical epidemiologist

I have read this submission. I 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.

Author Response 04 May 2018

Jacob Puliyel, St Stephens Hospital, India

Reviewer 1

Referee Prof Tom Jefferson
Reviewer Comment
Authors' response

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Thanks

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conspiracy to bury the dead by changing the definitions of probable and likely causality. That may be so, but I could not find any convincing evidence in the paper.

'Conspiracy theory' according to Barkun is a closed and unfalsifiable system and it is merely a matter of faith with no proof.
We hope we have critiqued various provisions in the revised manual for AEFI and shown how it can lead to harm – how it can result in delays in the acknowledgment of the problems that can result from vaccines. We hope this is a critique of the revised manual 'not unfalsifiable conspiracy theory'.

According to the revised AEFI classification reactions must be 'known to be associated with the vaccine' before it is acknowledged as caused by the vaccine. We have shown how new signals can be (and are being) ignored on account of this proviso.

We merely suggest there is potential for harm inherent in the revised system.

Regarding the observation
"international conspiracy to bury the dead by changing the definitions of probable and likely causality. That may be so, but I could not find any convincing evidence in the paper."

The WHO experts in Sri Lanka removed these categories ('probable' and 'possible') before they reported the deaths were 'unlikely' to be caused by vaccine. This is a verifiable fact. Had the categories not been removed, they would have had to report that 3 death (for with there was no alternate explanation) were 'probably' related to vaccination.

Chronologically at least, the new 'Revised AEFI' categories were developed after the Sri Lanka report was criticized in the BMJ etc.

After the AEFI classification was revised, experts no longer have the mortification of having to report they have deleted 'Probable' and 'possible'. The revised AEFI have eliminated the categories 'probable/likely' and 'possible'.

In fact the Sri Lanka experts were very keen to absolve the vaccine. They write they felt reluctant to even classify the deaths as 'unlikely' to be related to vaccine. I quote from the Sri Lanka report:
"Unlikely: In defining this category, the panel took note of the fact that the WHO category 'unlikely' is often interpreted to mean that there is (conversely) some likelihood of a causal association between the adverse event and the vaccine(s) administered…." (The full report is uploaded here for easy access http://www.jacob.puliyel.com/download.php?id=213)

I have no doubt that the experts are motivated by a laudable desire to reduce vaccine hesitancy and the attendant risk of vaccine preventable disease.

The reasoning for the revised AEFI categories must be similar to that of the experts of the Sri Lanka report.

We have added a new paragraph explaining that we feel the motivation for the change was a laudable desire to reduce vaccine hesitancy.

Here and there inaccuracies and typos add to the distractions. For example in box 10, DTP becomes DPT or the suggestions that Rotashield was withdrawn in 1999 as a consequence of the Brighton criteria. As far as I remember in 1999 we were setting up and had not produced the criteria or any other output yet.

I would also check the data of Rotashield withdrawal from the market.

The errors have been corrected in the revised manuscript.

The point made by the reviewer about Rotashield is correct. It has been revised. As pointed out by the reviewer, RotaShield was marketed before Brighton was developed. The WHO/UMC system was in place at that time.
Corrections have been made in the revised version.

Bradford Hill's criteria should be cited, even though they are not a perfect solution as Hill himself recognised. They should be cited because they have had an enormous influence on modern epidemiology (see Geoffrey Rose's variant for example) and because the formulation of some of them (temporality, strength, gradient) is very apt for vaccine exposure. Take temporality for example. The term AEFI which is so extensively cited concedes temporality when in fact temporality is only as good as the vaccination records. Often "AEFI" is used when we are not sure that exposure has taken place at all or that it preceded the clinical event/possible harm. So a balanced discussion of temporality (one of the absolute conditions for determining causality) must include absolute certainty or high probability that exposure preceded the event and that it had taken place at all.

Bradford Hill's criteria have been cited. Thanks.

Second I would offer the connection of probabilism and Fisherian theory with Hume's problem of induction. I see Fisher's work as the patch that allows us to go on with at least a partially clear conscience, as I do not think there is a solution to Hume's problem as nature is not (and never will be) universally uniform.

We did not take the reviewers suggestion to introduce Fisherian theory - to avoid making the write-up even more complicated. As the reviewer stated: the manuscript is already "extremely heavy going"

I would tone down the plot theory rhetoric and would seek a written explanation from WHO for their actions. WHO do not have a good track record of answering researchers but the effort must be made and reported. Ditto for any other point which was unclear to the authors. I am not a great believer in plots, blunders fit the picture and my experience better, but the authors must try and get to the bottom of the rationale for the changes and, while at it, they might just want to ask WHO,

CIOMS etc. to check the authors' facts and dates (but not their opinions of course).

The revised manuscript states explicitly that the motivation for the changes is probably to reduce vaccine hesitancy.

The WHO was contacted a year prior to publishing this article in the BMJ but there was no response (*BMJ* 2017;357:j2449, published 19 May 2017). They were again contacted after the first version of this manuscript was published on F1000Research, so they could respond in the comments section. There is no response so far (as of 12/4/18).

Last but not least please ask Brighton whether they were aware of WHO's actions (they must be) and what their views are.

Apparently the present Brighton team approves of these changes. They are now tasked with the responsibility to develop 'case definition' for 'known AEFI' (See CIOMS/WHO report)

Competing Interests: None. I am one of the authors of the article.