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Part VI

dct0015

Level and Adequacy of Regulatory Oversight and Current Research Methods

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c0023 Chapter 23

Revised World Health Organization (WHO)'s Causality Assessment of Adverse Events Following Immunization—A Critique

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s9010 INTRODUCTION

p9400 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 On the 29th of April that year the vaccine was withdrawn by the government following five deaths.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 23.1). 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 prequalified by WHO. . .no fatal adverse event following immunisation (AEFI) has ever been associated with this vaccine.[6]" This is the same brand of pentavalent vaccine which 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 could be classified as "Not a case of [AEFI]." From the WHO "Safety of Quinvaxem report," it is apparent that previously documented deaths following immunization were removed from the records after this new categorization started.

s0010 HISTORICAL BACKGROUND OF CAUSALITY ASSESSMENT

p0400 In this chapter I will discuss the new mechanism which allows adverse events following immunization (AEFI) to be classified as "Not a case of [AEFI]."

p0405 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 distill all of that for this chapter 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.

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b0010

BOX 23.1 World Health Organization-Uppsala Monitoring Center (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 recognized 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 standardized case causality assessment. Available at http://who-umc.org/Graphics/24734.pdf.

AU:1

p0410 Defining cause and effect (X is the cause of Y) has not been easy. According to Hume,[7] 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.

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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 sunburnt 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. 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.[8] John Mackie suggested that in nature there could be multiple reasons (causes) for the same outcome.[9] 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.[10]

p0415 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.[8]

s0015 ADVERSE DRUG REACTIONS

p0420 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 the 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 simple methodology (see Box 23.1). 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)

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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.

p0425 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."

p0430 The difference between certainly/very likely/probably 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.

p0435 "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. According to European Union law, the Precautionary Principle 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 the government are urged that, until the full scientific evidence is available, where there is evidence of risk, precautionary measures must be implemented and such drugs must be proscribed till there is evidence the drug is safe.[11]

s0020 ADVERSE EVENTS FOLLOWING IMMUNIZATION

p0440 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 touchstone used by WHO experts when AEFI were reported (see Box 23.2).

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b0015 **BOX 23.2 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.

p0445 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.[12] In 2013, the methodology of AEFI evaluation was however revised.

s0025 THE COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS)/WHO REPORT ON VACCINE PHARMCOVIGILANCE

p0450 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

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"provide tools for higher excellence of *signal detection* and *investigation of adverse events following immunization*."[13]

p0455 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]."

p0460 This is at odds with the advice on page 11 of the manual which is that a case definition can be adopted from the standard literature or by the reviewers themselves; not necessarily "an existing case definition." The purpose of the case definition is to draw on previous epidemiological research or undertake further research in order to confirm or exclude a causal link. Excluding causality in relation to an individual event is not dependent on that event conforming to a perexisting case definition. One also notes the pejorative use of the term "rejected" which suggests a somewhat defensive posture. Reports of AEFIs are not to be "rejected"; they are to be assessed for causality and classified accordingly.[18]

p9660 The CIOMS/WHO "tool for excellence in signal detection" works by turning 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 this vaccine, suggests the Sri Lanka AEFI deaths are now reclassified as "Not a case of [AEFI]" using the CIOMS/WHO tool.[6]

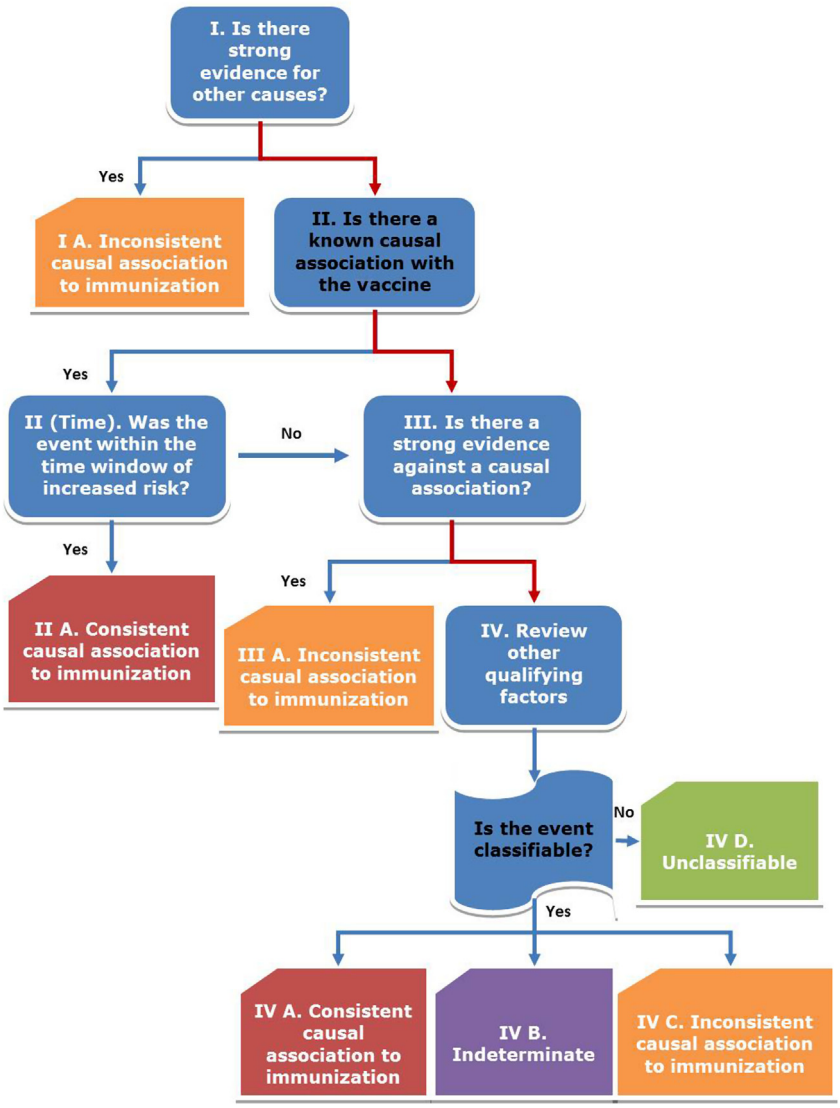
s0030 THE WHO REVISED AEFI MANUAL

p0465 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 Fig. 23.1.

s0035 REVISED AEFI CLASSIFICATION: NEW CATEGORIES OF CAUSALITY

p0470 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."

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f0010 **FIGURE 23.1** The revised AEFI causality assessment algorithm.

s0040 Consistent Causal Association to Immunization

p0475 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

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simultaneously be classified as "Consistent causal association with immunization" and "Inconsistent causal association with immunization." On page 36 of the revised manual for AEFI is the example of acute flaccid paralysis in a child after OPV, 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.

p0480 It is suggests that before 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."

p0485 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 use of rotavirus vaccine, 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.

s0045 Inconsistent Causal Association to Immunization

p0490 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, which 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.

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s0050 ## Indeterminate

p0495 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 analyzed 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.

s0055 ## Unclassifiable

p0500 Clinical events with insufficient information to permit assessment and identification of cause are put in the "Unclassifiable" group.

s0060 # REVISED AEFI CLASSIFICATION: THE NEW ALGORITHM

p0505 Just as the final categories of causality association are vague, overlapping, and not clearly differentiated, the algorithm used to make a decision on causality does not appear to be logical or well thought through.

p0510 The algorithm is shown in Fig. 23.1. Four sets of questions need to be answered in sequence:

o0020 **1.** Is there strong evidence of other causes?

o0025 **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?

o0030 **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?

o0035 **4.** If there is no such strong evidence against causal association, the next step is to look at other qualifying factors for classification.

o0040 **a.** Could it happen independently of vaccination (background rate)?

o0045 **b.** Could the event be manifestation of another health condition?

o0050 **c.** Did a comparable event occur after a previous dose of a similar vaccine?

o0055 **d.** Was there exposure to a potential risk factor or toxin prior to the event?

o0060 **e.** Was there acute illness prior to the event?

o0065 **f.** Did the event occur in the past independently of vaccination?

o0070 **g.** Was the patient taking any medication prior to vaccination?

o0075 **h.** Is there biological plausibility?

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s0065 ## Step 1

p0575 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.[9] 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 which 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, causative association with vaccine is rejected.[15]

s0070 ## Step 2

p0580 The COIMS/WHO Report on Pharmacovigilance is used at this level. 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 may also be adopted locally by the reviewers" (page 11 AEFI manual). AEFI that meet case definitions and which occur within the time window of increased risk are classified as "consistent causal association to immunization."

p0590 The acceptable time window for each adverse event is different. For the macrophagicmyofasciitis 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 aluminum hydroxide within macrophages at the site of previous immunization.[16] However, surveillance for Periodic Safety Update Reports (PSUR) do not extent for so long.

s0075 ## Step 3

p0595 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.

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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.

p0600 After publication of this AEFI user's manual, the conclusion about MMR and autism have become disputed again (see Box 23.3). This shifting evidence calls into question the usefulness of introducing this step in the algorithm of AEFI.

s0080 Step 4

p0605 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.

o0080 **a.** If some investigations are not done or not available, the AEFI is labeled as "Unclassifiable" (or classified as "Inconsistent with causal association to immunization" like how flaccid paralysis following OPV was

b0020 **BOX 23.3 MMR and Autism Risk in African American Children**

p0125 In 2004 the Center for Disease Control published research denying a relationship between MMR and autism.[a] Ten years later one of the authors of that study, William Thompson, admitted that he and his coauthors omitted statistically significant information that African American males who received MMR before the age of 36 months were at increased risk of autism.[b] The authors deleted data of children without Georgia birth certificates[c] and so disqualified a disproportionate number of black children and presented their data that there was no increased risk.

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.
b. Morgan FM. Statement of William W Thompson PhD, regarding the 2004 article examining the possibility of a relationship between MMR and autism dated August 27, 2015. Available from: https://leftbrainrightbrain.co.uk/2014/08/28/statement-of-william-wthompson-ph-d-regarding-the-2004-articleexamining-the-possibility-of-a-relationship-between-mmr-vaccine-and-autism/ [accessed 03.08.17] .
c. CDC. CDC Statement Regarding 2004 Pediatrics Article, Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta. Available from: https://www.cdc.gov/vaccinesafety/concerns/autism/cdc2004pediatrics.html [accessed 02.08.17].

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classified, because investigations during an illness 1 month prior to paralysis, were not available—(see Appendix 3 page 36 of the AEFI manual for this example).

o0085 **b.** 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.

o0090 **c.** The third possibility is that all the investigations had been done so it is classifiable but it did not meet case definitions. 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). 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.

p0625 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 23.4 illustrates how in spite of there being epidemiological evidence (the TOKEN Study) that pentavalent vaccine (as discussed in the introduction) can cause sudden unexpected death (SUD), 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 consequences of using the new classification are illustrated starkly in the causality assessment of 132 serious AEFI cases uploaded on the website of the Ministry of Health and Family Welfare in India. Seventy-eight of these babies were survived and 54 were died. Among those who survived, the causality assessment shows nearly 50%, were reactions to the vaccine. On the other hand not even one death was classified as vaccine related. Ninety-six percent deaths were simply classified as unclassifiable or coincidental.[17] It was noted in the paper that if a child is admitted to hospital with intractable convulsions after vaccination, if it survives, the reaction could be classified as vaccine-product related, but if it dies it will be classified as "coincidental death." If the vaccination of an infant was reported to have been followed by sudden death but the child was malnourished or otherwise unwell does not mean that causality assessment should conclude no cause and effect relationship between the vaccine and the death. The new definition completely ignores and excludes interacting causalities.[18]

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b0025 **BOX 23.4 Sudden Unexpected Death after Pentavalent Vaccine and the TOKEN Study**

p0145 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–e]

p0150 After the AEFI algorithm was revised, the deaths are now classified as "Not a case of [AEFI]" on the ground that deaths have not been reported as AEFIs in epidemiological studies involving the vaccine. However, the TOKEN study contradicts this assertion.[f]

p0155 The TOKEN study was done specifically to assess a possible causal relationship between vaccination and unexplained SUD of children between their second and 24th month of life. vonKries had previously found a statistically significantly increased standardized mortality ratio (SMR) within 2 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).

p0160 Temporal association of SUD to vaccination was examined in a self-controlled case series (SCCS) design. Parents of children who had died of SUD were requested to participate in the study. A total of 254 cases (37.6% of all the eligible cases) could be included in the study. Parental participation was more than twice as high for children who had died within 1 week after vaccination (80.0%) as for children who had not been vaccinated within 1 week prior to their death. To account for this bias, inverse probability weighted analyses were conducted in addition to the preplanned, unweighted analyses. The results obtained from these weighted analyses are regarded as more valid. The authors note that weighted analysis could only account for the selection bias among the exposed cases aged up to nine months and enrolled by the forensic institutes. Therefore, the results of the weighted analyses are likely to still overestimate the risk of SUD.

p0165 The weighted SCCS analysis, relative risk of SUD after pentavalent vaccination (first and second year of life) looking at risk period from 0 to 3 days after vaccination versus control period 4 to 28/183 days showed the 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 (first and second year of life) looking at risk period from 0 to 3 days versus control period 4 to 28/183 days showed the RR of 2.19 ($p = 0.031$, 95% CI = 1.08–4.45; Table 36 in the TOKEN Report).

p0170 It is clear from the aforementioned text that there is reasonable evidence in epidemiological studies that SUD can occur as AEFI following the 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]."

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

(*Continued*)

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BOX 23.4 Sudden Unexpected Death after Pentavalent Vaccine and the TOKEN Study (Continued)

b. Lone Z, Puliyel J. Introducing pentavalent vaccine in the EPI in India: A counsel for caution. *Indian J Med Res* 2010;**132**: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, June 12–13, 2013. *Wkly Epidemiol Rec* 2013;**88**:301–12. http://www.who.int/vaccine_safety/committee/reports/Jun_2013/en/ (accessed 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, Haemophilius influenzae type b): is there a signal? *Eur J Pediatr* 2005;**164**:61–9.

s0085 ## OTHER SUBTLE CHANGES IN THE DEFINITION OF TERMS

s0090 ### "Causal Association" Redefined

p0630 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.[19] 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.[18]

p0635 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.[19] However, these considerations

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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. 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.

p0640 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.

p0645 Box 23.5 illustrates how periodic safety reporting meant to pick up signals not noticed in the prelicensure clinical trials are misleadingly interpreted and how these reports are shielded from public scrutiny.

s0095 Biological Plausibility Redefined

p0650 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 leads from the cause to the effect), do not qualify.[8] 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 threat that vaccine manufacturers can be held responsible for marketing a defective product has diminished greatly as a consequence of these changes. How such changes provide an impetus for the manufacturers to be more reckless with regard to vaccine safety is discussed in Box 23.6.

p0655 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.[8] 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.[20]

s0100 REVISED AEFI CLASSIFICATION AND THE PRECAUTIONARY PRINCIPLES

p0660 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

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b0030 **BOX 23.5 Periodic Safety Update Reports: Unfit for Public Consumption?**

p0210 The GlaxoSmithKline Biological Clinical Safety and Pharmacovigilance's confidential report to the Regulatory Authority on Infanrixhexa (combined diptheria, tetanus and acelluar pertusis, hepatitis B, inactivated poliomyelitis and *Haemophilus influenzae* type B) vaccine for the period October 23, 2009 to October 22, 2011 [the 15th and 16th Periodic Safety Update Report (PSUR)] has been made available to the public by the Italian Court of Justice Nicola Di Leo and is available on the Internet.[a]

p0215 Section 9.3.1.1 on pages 246–249 documents an evaluation of whether the number of "sudden deaths" reported after immunization, exceeded the number that one could expect to occur by coincidence—that is from the natural background incidence of sudden death. The background incidence of 0.454/1000 live births in the first year and 0.062/1000 live births in the second year was used, with a healthy vaccine correlation factor of 0.8 applied. No allowance was made for the notoriously poor AEFI reporting rate. Table 36 on page 249 tabulates the number of sudden deaths that would be expected to occur by chance within a range of days (1–20 days) postvaccination. 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!

p0220 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 in the document sent to the regulator gives the International Event Report in 13 fatal cases. It can be seen in this sample that there were more deaths after the first dose than after the second and more after the second than after the third dose. This is a pattern commonly seen with AEFIs that are causatively related. The appropriate denominator in all these cases is the number of babies vaccinated.

p0225 Examination of the table shows that 42 deaths had taken place in the first 3 days after vaccination, 16 deaths in the next 3 days between days 3 and 5. The fact makes it apparent that many of the deaths are related to the vaccination episode.

p9230 Examining the PSUR 19 it is apparent that the deaths that were acknowledged in the PSUR 16 were deleted from the PSUR 19. The observed deaths soon after vaccination in the children older than 1 year was significantly higher than that expected by chance once the deleted deaths were restored and included in the analysis.[21] AU:2

p0230 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.

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

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b0035 **BOX 23.6 Product Liability: Protecting Patients not Patents**

p0240 Hexavalent vaccine (DTaP-IPV-HepB/Hib)—Hexavac was withdrawn by the manufacturers without giving reasons after five cases of SIDS within 48 hours of receiving the vaccine were reported by Zinka.[a] vonKries found that in the second year of life, the standardized mortality rate (SMRs) for sudden unexplained deaths (SUD) cases within one day of vaccination with the vaccine was 31.3 (95% CI = 3.8−113.1); and within two days after vaccination it was 23.5 (95% CI = 4.8−68,6).[b]

p0245 Similarly, it will be noted that the Rotasheild vaccine was voluntarily removed from the market after 12 cases of intussusceptions were reported. The background rate of intussusceptions at this age was five 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]

p0250 The vaccines were withdrawn voluntarily by the manufacturers without indicating the reasons. Whether the prospect of product liability suits influenced manufacturer caution is not clear.

p0255 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.

o0010 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 to provide clear evidence of negligence as cause of the harm before they qualify for compensation. However, this 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 the Governments. As a result, manufacturers may be emboldened to be more reckless on vaccine safety issues.

o0015 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 labeled "Consistent causal association to immunization." This scheme also could embolden manufacturers to be more reckless with regard to adverse reactions.

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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 unexpected deaths after the administration of hexavalent vaccines (diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, Haemophilius influenzae 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. http://www.who.int/bulletin/volumes/89/5/10-081901/en/ (accessed 23/10/15).

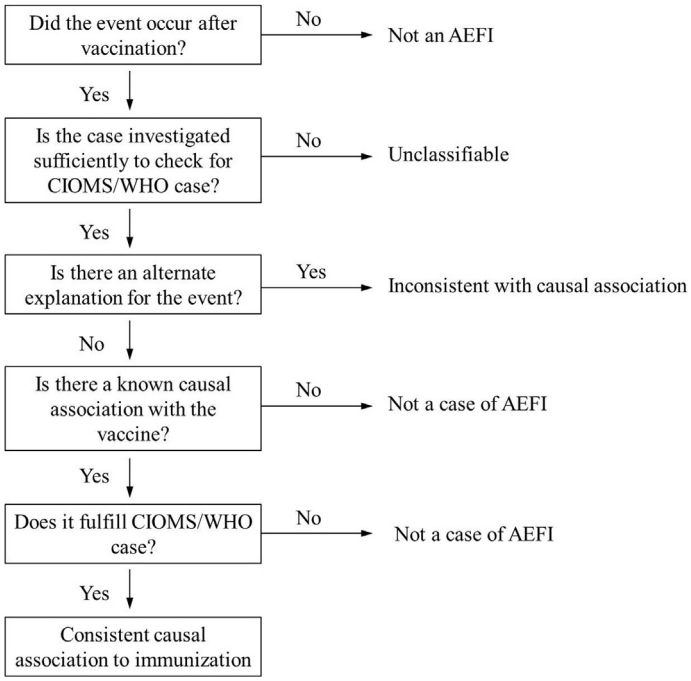
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immunization. The AEFI manual states "Allegations that vaccines/vaccination cause adverse events must be dealt with rapidly and effectively. Failure to do so can undermine confidence in a vaccine and ultimately have dramatic consequences for immunization coverage. . .."[22]

p0665 Fig. 23.2 shows how all cases AEFI are classified as not causally related except those that are known adverse effects of vaccine.

p0670 The AEFI-denialism is a clear violation of the "precautionary principle' 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.[11] This new AEFI classification scheme which 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 extend reasonably practicable, protect life.

p0675 Paradoxically the AEFI algorithm is said to be for vaccine safety. Perhaps we need a scheme for public safety rather than vaccine safety.



f0015 **FIGURE 23.2** Pathway to achieving "consistent causal association to immunization" status.

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s0105 CONCLUSION

p0680 The purpose of this exercise in AEFI-denialism is first and foremost to prevent the undermining confidence in vaccines. However, the scheme does not seem to be working. Indeed, public skepticism seems to be increasing rather than diminishing with these efforts at reassurance that vaccines are safe.[22] Epidemics of vaccine preventable disease have resulted.[24]

p0685 The response in some States in the United States has been to make vaccination mandatory for admission to public schools. 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.[25] How these forces will interact is anyone's guess but the present scenario augur badly for voluntary vaccination.

REFERENCES

1. 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. <http://jacob.puliyel.com/download.php?id = 213> [accessed 19.10.15].
2. WHO. Safety of Quinvaxem (DTwPHepB-Hib) pentavalent vaccine. May 10, 2013. <http://www.who.int/immunization_standards/vaccine_quality/quinvaxem_pqnote_-may2013/en/> (accessed 15.10.15].
3. Puliyel J, Mathew JL, Priya R. *Incomplete reporting of research in press releases: ettu, WHO? Indian J Med Res*, 131. 2010p. 588–9.
4. Saxena KB, Banerji D, Qadeer I, Kurian NJ, Priya R, Shiva M. "Antivaccine lobby" replies to the BMJ.. *BMJ* 2010;**341**:c4001.
5. Tuoi Tre News. Vietnam suspends Quinvaxem vaccine following 9 deaths. Tuoi Tre News [Internet]. May 5, 2013 [cited June 22, 2013]. <http://tuoitrenews.vn/society/9330/viet-nam-suspends-quinvaxem-vaccine-following-9-deaths> [accessed 01.11.15].
6. WHO. Safety of Quinvaxem (DTwP-HepB-Hib) pentavalent vaccine. May 10, 2013. <http://www.who.int/immunization_standards/vaccine_quality/quinvaxem_pqnote_-may2013/en/> [accessed 15.10.15].
7. Hume DA. In: Selby-Bigge LA, Nidditch PH, editors. *Treatise of Human Nature*. Oxford: Clarndon; 1739.
8. Henry E. Brady 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.
9. Mackie JL. Causes and conditions. *American Philosophical Quarterly* 1965;**2**:245–64.
10. 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. http://mccagueborlack.com/uploads/articles/43/hd-pm-py_proving-causation.pdf?1299245845.
11. 1998 Wingspread Statement Wingspread Statement on the Precautionary Principle http://www.gdrc.org/u-gov/precaution-3.html.
12. Center for Disease Control and Prevention. Rotavirus Vaccine (RotaShield) and Intussusception. http://www.cdc.gov/vaccines/vpd-vac/rotavirus/vac-rotashield-historical.htm.

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13. 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. http://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf.
14. Soriano A, Nesher G, Shoenfeld Y. Predicting post-vaccination autoimmunity: Who might be at risk?. *Pharmacol Res.* 2015;**92**:18−22.
15. Berkovic SF, Harkin L, McMahon JM, Pelekanos JT, Zuberi SM, Wirrell EC, et al. De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. *Lancet Neurol.* 2006;**5**:488−92.
16. Rigolet M, Aouizerate J, Couette M, Ragunathan-Thangarajah N, Aoun-Sebaiti M, Gherardi RK, et al. Clinical features in patients with long-lasting macrophagic myofasciitis. *Front Neurol* 2014;**5**:230.
17. Puliyel J, Phadke A. Deaths following pentavalent vaccine and the revised AEFI classification. Ind J Med Ethics. Published online: July 4, 2017. doi:10.20529/IJME.2017.063
18. Legge D, Puliyel J. Enhancing community confidence in vaccines safety. *BMJ* 2017;357 doi:10.1136/bmj.j2449 (Published 19 May 2017)
19. Advisory Committee on Causality Assessment, Collet JP, MacDonald N, Cashman N, Pless R. Monitoring signals for vaccine safety: the assessment of individual adverse event reports by an expert advisory committee. *Bull World Health Organ* 2000; **78**:178−85.
20. No authors listed. Global Advisory Committee on Vaccine Safety, June 12−13, 2013. *Wkly Epidemiol Rec* 2013;**88**:301−12. http://www.who.int/vaccine_safety/committee/reports/Jun_2013/en/ (accessed on 1/11/15).
21. Puliyel J. Sathyamala C. Infanrix hexa and sudden death: a review of the periodic safety update reports submitted to the European Medicines Agency. Online first Available here http://www.issuesinmedicalethics.org/articles/infanrix-hexa-and-sudden-death-a-review-of-the-periodic-safety-update-reports-submitted-to-the-european-medicines-agency/
22. WHO. The Causality assessment of adverse event following immunization User manual for the revised WHO classification WHO/HIS/EMP/QSS. March 2013. http://www.who.int/vaccine_safety/publications/aevi_manual.pdf?ua=1.
23. NE. MacDonald. Vaccine hesitancy: Definition, scope and determinants. *Vaccine*, **33**(34), 4161−4164. Sci Dev Net. Parental doubt drives drop in vaccination. http://www.scidev.net/global/health/news/parental-doubt-drives-vaccination.html.
24. Clemmons NS, Gastanaduy PA, Fiebelkorn AP, Redd SB, Wallace GS; Centers for Disease Control and Prevention (CDC). Measles − United States, January 4−April 2, 2015. *MMWR Morb Mortal Wkly Rep* 2015;**64**(14):373−376. Measles − United States, January 4−April 2, 2015.
25. Tavernise S, Louis CS. Vaccine Issue Arises at Republican Debate, to Doctors' Dismay. The New York Times, September 17, 2015. http://www.nytimes.com/2015/09/18/health/republican-presidential-debate-vaccines.html?_r=0.

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Abstract

WHO has recently revised how adverse events after immunization (AEFI) are classified. According to this new algorithm, only reactions that have been previously acknowledged, in epidemiological studies to be caused by the vaccine, are classified as a vaccine-product–related-reaction. In the new algorithm, deaths seen during postmarketing surveillance cannot be classified as "consistent with causal association with vaccine" if the vaccine did not cause a statistically significant increase in deaths in the small Phase 3 trials. It goes without saying that if the vaccine caused a significant increase in deaths in the small control trials the vaccine would not be licensed. After licensure, all deaths that are seen in the larger postmarketing phase are simply labeled as coincidental deaths or unclassifiable and the association with vaccine may never be acknowledged. The resulting paradox is evident. If a child is admitted to hospital with intractable convulsions after vaccination, if she survives, the reaction could be classified as vaccine-product related, but if she dies it will be classified as "coincidental death." The term "causal association" has itself been altered. A causal association can now only be used where a cause and effect relationship between causative factor and a disease has occurred "with no other factor intervening in the processes." This would mean that AEFI in children with an underlying heart disease who may develop symptoms of cardiac decompensation after vaccination (due to a vaccine-caused elevation in temperature or stress from a local reaction at the site of vaccination), would not be considered causally related to the vaccine although vaccination contributed to cardiac failure in this specific situation. This is of particular concern since the Global Advisory Committee on Vaccine safety documented that a large number deaths in children after receiving pentavalent vaccine were those with some preexisting heart disease. Acknowledgment of this link to vaccination and caution during vaccination of children with heart problems has saved lives according to the WHO report. The new definition of "cause and effect" is potentially harmful to children with underlying diseases as it removes the impetus to provide them special care during immunization. In view of the above, it is necessary that the AEFI manual be revaluated and revised urgently. The authors point out that AEFI reporting is said to be for vaccine safety. Safety of children (child safety) rather than safety for vaccines (vaccine safety) needs to be the emphasis. The way it is done now—simply denying deaths, erodes confidence in the system to pick up safety signals and to evaluate potential dangers with new vaccines.

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