LETTER

Deaths following pentavalent vaccine and the revised AEFI classification

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We are concerned about the changes effected by the WHO to the assessment methodology of adverse events following immunisation (AEFI)(1), which make it almost impossible to classify adverse events (deaths in this case) noticed for the first time in phase IV post-marketing surveillance, as "consistent causal association to immunisation".

The sequence of events leading up to this revision of the causality classification is revealing (2). A pentavalent vaccine Quinvaxim (Crucell) was introduced in Sri Lanka on 1 January 2008(3). Four months later, after five deaths due to AEFI, the vaccine was withdrawn by the government. The WHO team which investigated the AEFI reported that in three of the deaths there was plausible temporal association with vaccination, and the deaths could not be attributed to concurrent disease or other drugs or chemicals. Using the standard WHO Brighton classification of AEFI in vogue at that time(4), these three deaths had to be classified as "probably" related to immunisation. However, this WHO team investigating the Sri Lanka deaths wrote in the report that they deleted the categories "probable" and "possible" from the Brighton classification and concluded the AEFI were "unlikely" to be related to the vaccine. This ad libitum alteration of the Brighton classification was reported in the *British Medical Journal*(5).

Following this incident, the AEFI classification was formally revised. In the new algorithm, deaths seen during post-marketing 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. If the vaccine caused a significant increase in deaths in the small controlled trials, the vaccine would not be licensed. After licensure, all deaths that are seen in the larger post-marketing phase are simply labelled as coincidental deaths or unclassifiable. Delays in acknowledging the link with vaccination can result in unnecessary and avoidable deaths.

In May 2013, the Ministry of Health of Viet Nam suspended the use of pentavalent vaccine Quinvaxim (Crucell) because it had been associated with 12 deaths(6). However, the WHO team that investigated the Viet Nam deaths employed the revised WHO classification of AEFI (1), which had just been published. They reported: "Quinvaxem was prequalified by WHO. ... no fatal adverse event following immunisation (AEFI) has ever been associated with this vaccine"(7). Memory of the deaths in Sri Lanka in 2008 had been erased by then.

We are also concerned about the way the WHO has redefined "cause and effect"in AEFI. According to the revised AEFI Manual, the term "causal association"refers to "a cause and effect relationship between causative factor and a disease 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), the cardiac decompensation would not be considered causally related to the vaccine as before(8), 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 of deaths in children after receiving pentavalent vaccine were in those with some pre-existing 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(3).The consequences of using the new classification are illustrated starkly in the causality assessment of 134 serious AEFI cases in India, approved by the National AEFI committee and uploaded on the website of the Ministry of Health and Family Welfare (9). Of these AEFI reported between 2012 and 2016, 78 babies survived hospitalisation and 58 died. Among those who survived, the causality assessment suggests that 37 (47.4% of reactions) were vaccine-product-related reactions (A1) (Table 1). On the other hand, 52 (96%) of those who died, had reactions that were classified as unclassifiable (D) or coincidental due to something other than vaccine (C). Not even one case was classified as a vaccine-product-related reaction (A1).

Table 1
Causality classification of 132 cases approved by the National AEFI committee

Causality classification categories	Survived (n=78)	Died (n=54)
A1 Vaccine product-related reaction	47.4% (37)	0% (0)
A2 Vaccine quality-related reaction	0% (0)	0% (0)
A3 Immunization error-related reaction	12.8%(10)	0% (0)
A4 Immunization anxiety-related reaction	2.6% (2)	0% (0)
B1 Temporal relationship but insufficient definitive evidence for vaccine causing event	1.3% (1)	1.9% (1)
B2 Conflicting trends of consistency and inconsistency with causal association	17.9% (14)	1.9% (1)
C Coincidental underlying or emerging condition, or condition caused by something other than vaccine	14.1% (11)	53.7% (29)
D Unclassifiable	2.6% (2)	42.6 (23)

Thus, in a child who is admitted to hospital with intractable convulsions after vaccination, if s/he survives, the reaction could be classified as vaccine-product-related, but if s/he dies, it will be classified as "coincidental death – underlying or

emerging condition, or condition caused by something other than vaccine" (C) or "unclassifiable" (D).

Given that a causal association between AEFI and vaccination is usually difficult to prove, the purposes of the precautionary principle and scientific enquiry are best served if one acknowledges, where appropriate, that the association of death with vaccine is "probable" or "possible" although it is difficult to be "certain". Also in the new scheme of evaluating AEFI there is no transparent mechanism to decide when reactions labelled as (B) "Indeterminate" will be evaluated as a new signal. These ambiguities erode confidence in the scheme's ability to evaluate rare adverse events and act decisively to protect children.

AEFI reporting is said to be for vaccine safety. In view of the above, it is necessary that the AEFI manual be re-evaluated and revised urgently. Safety of children (child safety) rather that safety for vaccines (vaccine safety) needs to be the focus.

Jacob Puliyel *(Puliyel@gmail.com),St Stephens Hospital, Delhi 110 054, INDIA;* ***Anant Phadke*** *(anant.phadke@gmail.com), All India Drug Action Network (AIDAN), Ameya Ashish Co-operative Housing Society, Kothrud, Pune 411 038, INDIA*

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