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

  Tozzi AE.Vaccine. 2013. Jacob Puliyel2014 Feb 04 1:10 p.m.

  DEATHS IN DEVELOPING COUNTRIES WILL COUNT FOR LESS

  Tozzi et al describe causality assessment for AEFI using criteria from the CIOMS/WHO working group on pharmacovigilence . AEFI is any untoward medical occurrence following immunization. A causal relationship is not implied. The Brighton collaboration classified reactions as very likely/certain; probable; possible; unlikely; unrelated; unclassifiable, based on temporal criteria and evidence of alternate etiological explanation. Deaths soon after immunization without an alternate explanation were classified as 'probably related to vaccine'.

  THE NEED FOR A NEW CLASSIFICATION

  With use of Pentavalent vaccine (Diphtheria, Tetanus, Pertussis, Hib and Hepatitis B) in developing countries, there have been many AEFI deaths. WHO experts investigated these deaths in Sri Lanka. They could find no alternate explanation for 3 deaths. The experts write in the report that they deleted the categories 'probable' and 'possible' from the Brighton classification and after that, although they could not attribute deaths to another cause, they were declared unlikely to be related to the vaccine. The association to vaccine should have been classified as 'probable'. The BMJ published a letter about this Saxena KB, 2010

  1. The CIOMS/WHO report came after the BMJ letter. The committee, composed of 40 members (19 were vaccine-industry representatives), proposed changes to how AEFI are investigated and reported. The 194-page document has serious implications for developing countries.

2. Case definitions for different adverse events were developed. Illogically, the inclusion criteria for the proposed case definitions are too strict to be of scientific value in most countries. For example, to diagnose 'encephalitis' one needs the child with fever and encephalopathy to live at least 24 hours after AEFI onset, and have a CSF examination, an EEG or neuro-imaging and one of these investigations must be positive, to reach a level 2 diagnosis (page 73).
3. Presume that a healthy child is vaccinated. Suppose she develops high fever within 2 hours, has convulsions, then lapsed into a coma and dies within 10 hours. (Variations of this scenario have been enacted repeatedly with Pentavalent vaccine). Using CIOMS/WHO definitions, as the encephalopathy lasted less than 24 hours, it cannot be classified as encephalitis. In many countries, the facilities for a lumbar puncture may be unavailable, much less those for an EEG and CT/MRI. Under the report's scheme, this would be labeled, "Insufficient information to distinguish both acute encephalitis and ADEM; Case unable to be definitely classified".
4. Further, on page 170 (i) (in very small print), the report says, "Such a case must be classified as 'Not an AEFI'". This last step, which classifies an "AEFI" as "Not an AEFI", is patently unscientific, illogical and Orwellian.
5. The scenario described could well have been caused by 'multisystem generalized reaction to one or more vaccine components' (page 50). The encephalopathy, fever and convulsions could follow systemic inflammatory response but CIOSM does not have case definition for this, and inability to exclude causes of encephalopathy, is sufficient to classify the reaction as 'not an AEFI'.
6. The risk is not merely theoretical. In March 2013 WHO investigated 12 deaths in Viet Nam from the same Pentavalent vaccine. The Viet Nam report stated, "no fatal AEFI has ever been associated with this vaccine". The 2008 WHO experts had earlier classified the Sri Lanka deaths as AEFI unlikely to be related to vaccine. The Viet Nam report stating 'no fatal AEFI has ever been associated with this vaccine' suggests the Sri Lanka AEFI is now reclassified as "Not an AEFI".
7. Tossi et al suggest that 'events with a consistent temporal relationship but with insufficient evidence for vaccine as a cause, according to well designated epidemiological studies – in such cases, further studies are encouraged if other similar events are identified'. There have been 54 deaths temporally related to the vaccine in India. Instead of taking them as a group the new system looks at 'individual adverse events' and then labels them as 'not an AEFI' making way for many more deaths.
8. Tossi and colleagues report different clinical scenarios (Supplementary material). The scenario in Asia is also worth considering. Pentavalent vaccine is selectively promoted in developing countries with poor surveillance systems. Eighty three deaths following Pentavalent inoculation have been reported from Asian countries Puliyel J, 2013. There is no plausible alternate explanation. Most deaths occurred after the first vaccine dose, fewer after the second, and hardly any after the third. This pattern argues against the deaths being random events.

Yet, the WHO to maintains that a cause and effect relationship has not been established.

9. This contrasts with what happened in 1998 when RotaShield was approved in the US. When intussusceptions were reported to the Vaccine Adverse Event Reporting System (VAERS) and only 12 children were affected the vaccine was withdrawn. No one needed to be 'certain'.
10. A public health expert in India, Dr Y Jain has filed a public interest petition in the Supreme Court asking for these deaths to be investigated. The petition states that in the first six months, when the 40,000 doses were administered to children in the southern state of Kerala, at least five children died. Extrapolated to the 25 million babies born in India each year, 3,125 deaths can be expected from the vaccine each year. Using the best evidence from the Minz study Minz S, 2008 the incidence of Haemophilus influenzae type b meningitis in India is 7/100,000 children under 5. Using the Unicef rapid method to estimate Hib Pneumonia 350 deaths from Hib disease will be prevented over 5 years by vaccinating one birth cohort of 25 million. 3125 deaths from AEFI cannot be acceptable to prevent 350 Hib deaths.
11. The Infant Mortality Rate (IMR) in Kerala is 14. Seven of these deaths occur in the first month. The other seven deaths occur in the remaining 11 months of the infant's first year. Pentavalent vaccine is administered six weeks after birth to babies who have survived neonatal life. Of the first five deaths from the vaccine, four occurred within 24 to 48 hours of the first dose of this vaccine. The death rate of babies in the first days after vaccination works out to be two to four times higher than Kerala's post neonatal IMR.
12. The first 14 deaths in Kerala were investigated by AEFI experts. They reported 6 children had co-morbid conditions and the other 8 died of sudden infant death syndrome (SIDS). This SIDS rate on day after vaccination is higher than the all-cause IMR.
13. Under the new scheme, fatal AEFI in developing countries will be falsely recorded as 'Not an AEFI', simply because some time or test criterion was not met. Death is the worst AEFI possible. Continued use of the CIOMS/WHO scheme will result in missing an important opportunity to pick up signals that could save lives. This is dangerous. Perhaps we need to get back to the Brighton Classification.

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