- Jacob Puliyel2014 Mar 21 03:07 a.m.edited

  Williams and colleagues have described assessment of AEFI employing the algorithm described by Halsey < PMID: 22507656>.

  I have posted two very detailed comments to an article by Tozzi Tozzi AE, 2013 which discusses the same subject of the revised WHO Classification of AEFI. I will not repeat the points I have made there but it may be viewed here.

  As this is a matter of patient safety I think it is important that the experts who understand the new scheme must explain why the revision was needed and that it will not miss opportunities of picking up new signals. The question is whether the new scheme would have picked up and flagged the signal of adverse-effects like the RotaShield-reactions, had the scheme been in use in 1999. The purpose of this posting is to invite the learned authors of this article on causality assessment to respond to the issues raised in the postings to the Tozzi article and I propose to flesh out those concerns a little further in the context of the article in Pediatrics by Williams and colleagues.

  1) Williams and colleagues Williams SE, 2013 suggest that the first step in the general approach to evaluating serious AEFI is to establish a clear diagnosis using Brighton Collaboration case definitions.

  The second step is to consider known biological mechanisms.

  Neither of these would have been evident when the intussusceptions signal was picked up by the old scheme (and the vaccine was withdrawn expeditiously preventing unnecessary distress to thousands of babies). Even today although a case definition has been developed for 'intussusceptions', the biological mechanism is not clearly defined and so the second step described by Williams et al cannot be completed.

  It was reported recently that Pentavalent vaccine (DPT co-administered with measles vaccine (MV) and yellow fever (YF) vaccine) is associated with increased mortality compared to MV + YF alone Fisker AB, 2014. It is pertinent to mention that the biological mechanisms involved are not understood.

  Neither is the biological mechanism for increased female mortality in recipients of the high-titer Edmonston-Zagreb vaccine known, although this was first noticed 2 decades ago. < PMID: 8237989>, Aaby P, 1993.

  2) It will be instructive to look at how the new algorithm has failed to flag up the deaths following Pentavalent vaccine used in Asia (DPT + Hib + Hepatitis B) and as a result, numerous children continue to be exposed to the risks of this vaccine.

  The glossary of the User Manual for the [Revised WHO classification](who.int/vaccine*safety/publications/aevi*manual.pdf) suggests ways and means to rule out

a causal association. It defines causal association as a cause-and-effect relationship between the causative factor and a disease with no other factor intervening in the process.

There have been many deaths following use of this Pentavalent vaccine in Sri Lanka. The committee WHO vaccine safety examined 19 deaths in Sri Lanka, 14 of them between 2010 and 2012. In six of the 19, a congenital heart disease was reported.

Does preexisting congenital heart disease rule out a causal association between the vaccine and the deaths? Under this definition the 6 deaths in children with heart disease were not causally related to the vaccination.

The older Advisory Committee on Causality Assessment Collet JP, 2000 looked at the problem more logically and holistically. For example it noted that elderly persons with concomitant or preceding chronic cardiac failure can develop cardiac decompensation after influenza vaccination due to a vaccine-caused elevation in temperature or from stress from a local reaction at the site of vaccinating. The vaccine is considered to have contributed to cardiac failure in this specific situation. It is obvious that with the older method of assessment of AEFI, caution would have been exercised when administering influenza vaccine to persons with preceding chronic cardiac failure, to avoid decompensation.

The deaths in children with heart disease following administration of Pentavalent vaccine could well be due to decompensation. The Pentavalent vaccine must be used with caution in the presence of an underlying heart condition albeit asymptomatic. However detection of asymptomatic heart disease prior to vaccination in developing countries is impractical where the vaccine is administered by health workers who are barely literate. Is it prudent to use the vaccine under these circumstances given the findings of the Sri Lanka investigation? The new system disregards this real danger.

3) Step 2 Checklist 4 of the revised [WHO classification for causality assessment](who.int/vaccine*safety/publications/aevi*manual.pdf) asks to check if the event can occur independently of vaccination (background rate). Thus it seems that until the deaths from vaccine AEFI are frequent enough as to increase the age specific mortality-rate in a statistically significant manner, they are to be ignored.

The question of what background rate to use is not addressed specifically and this can further confound objective assessment of the AEFI. The Pentavalent vaccine in Asia is administered after 6 weeks of age. Would the local post-neonatal infant mortality rate (PN IMR) in the community before introduction of the vaccine be the comparator?

Most of this post-neonatal IMR is made of babies who are very sick with pneumonia, diarrhea, sepsis, meningitis etc. The fact that the AEFI babies were brought by the mother for routine immunization suggests that the child was not sick and the mother did not consider the child was likely to die in the next day or two. The comparator must really be the SIDS rate in the locality for babies of a comparable age.

Deaths in Bhutan were investigated and local newspapers reported on the various official explanations. It was argued that the deaths could have been due to encephalitis although there was little evidence for it. Officials explained that the encephalitis death rate in the years after the vaccine was introduced (even after adding AEFI deaths) had not increase significantly. This was sufficient grounds to accept the 'coincidental encephalitis' theory. One cheeky health official however pointed out that there were no cases of meningo-encephalitis reported among children below one year, in the eight months when Pentavalent vaccine was suspended in Bhutan.

4) Another factor related to the deaths following Pentavalent vaccine is that the vast majority have occurred after the first dose and fewer after the second dose. A random event or coincidental SIDS cannot explain these deaths. However the new algorithm does not take this important factor into consideration.

For all these reasons it would appear that the new algorithm is not a comprehensive means to assess serious adverse events. Its use will delay withdrawal of vaccines that result in serious AEFI and in the end it will erode confidence in the entire immunization programme and those who administer it.

Can I suggest that we need to go back use older scheme namely Brighton Classification of AEFI till we find a better method to assess AEFI.

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  See:Combined hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type B vaccine; Infanrix™ hexa: twelve years of experience in Italy. [Hum Vaccin Immunother. 2014.]

- This article was mentioned in a comment by Jacob Puliyel2014 Mar 05 04:45 a.m.

  See:Guidelines for collection, analysis and presentation of vaccine safety data in surveillance systems. [Vaccine. 2009.]