

Report of a WHO Ad Hoc Expert Panel to Review Reports of  
Serious AEFI following administration of pentavalent and  
other vaccines - Sri Lanka, 2008

1. Background

The Expert Panel was formed by the WHO Department of Immunization, Vaccines and Biologicals (IVB) to provide expert advice on the potential causal association between selected serious AEFI cases reported in Sri Lanka in 2008 and the vaccines received by the affected infants. (Panel members are listed in Annex A.) The majority of cases were reported following use of Quinvaxem®, the liquid pentavalent (DTwP-HepB-Hib) vaccine produced by Berna Biotech Korea Corporation, resulting in an initial investigation by national authorities with WHO assistance. The panel was therefore also requested by WHO to assess, to the extent possible based on the available information for adverse events, the safety profile of Quinvaxem®.

The panel was informed that Quinvaxem® was pre-qualified by WHO in September 2006 for supply through UN agencies, and was introduced into Sri Lanka's national immunization programme on 1 January 2008. It was withdrawn in Sri Lanka on 29 April 2008 by national authorities after five deaths and other serious AEFIs were reported with temporal association with receipt of the vaccine. The other serious AEFIs were originally reported in the Sri Lankan AEFI surveillance system as "HHE-like" events and several were hospitalized.

1.1 Questions for review

The specific questions/issues presented by WHO to the Expert Panel for review were:

1. To assess the potential causal relationship of the reported AEFIs with the vaccine(s) administered in each case.
2. With respect to the adverse events reported following receipt of Quinvaxem®,
  - a. whether the reported incidence of HHE/HHE-like events is higher than expected?
  - b. whether there is an association with sudden unexpected deaths (or increased mortality) in infants?
  - c. whether there is a potential new "signal" of a specific adverse vaccine reaction?
3. To advise on further specific post-marketing studies (as relevant) to improve the knowledge of the safety of Quinvaxem®.

In addition, the following specific questions/issues raised by Sri Lankan national authorities were presented to the Expert Panel:

4. Why Sri Lanka "did not see cases of HHE prior to introduction of pentavalent vaccine, in spite of using combination vaccines for nearly 50 years". Whether the "HHE-like" cases reported in Sri Lanka following the pentavalent vaccine was of different intensity or severity when compared to similar cases reported following pertussis/HSV/Hib-containing vaccines elsewhere?
5. Even though, according to the available literature no deaths are reported following HHE, whether some of the reported deaths could be due to the occurrence of "HHE-like" illness during sleep and leading to asphyxiation?
6. Whether HHE or deaths have been reported from any other countries using pentavalent vaccine? If so, what action has been taken? (*This question was seen as more appropriately directed to WHO; therefore the panel did not address it directly.*)
7. To get the views of the panel on any quality issues of the vaccine which may have been overlooked.

## 2. Review process and definitions of categories for causality assessment

After initial discussion by the Expert Panel of the type and completeness of information available, the following approach for the review was proposed and agreed with WHO.

- In the first phase, to conduct two types of review, comprising (a) individual causality assessments of the fatal AEFI cases, and (b) review and classification of the "HHE-like" cases using the standard Brighton Collaboration case definition<sup>1</sup> to grade the level of diagnostic certainty.
- In a second phase of the review, to address all other questions to the extent possible depending on the information available. In particular, the panel noted that assessing potential safety risks associated with the pentavalent vaccine at a population level would require knowledge of several epidemiological parameters. The panel has therefore requested information on several relevant parameters (see Annex B).

For the individual causality assessment and case classification, the Expert Panel reviewed 13 fatal AEFI case reports and 20 non-fatal events. Case reports reviewed by the panel (including clinical, laboratory and pathology reports as applicable) were provided to WHO/IVB by the Epidemiological Unit, Ministry of Health and Family Welfare, Sri Lanka.

WHO also provided to the panel (based on information gathered from the investigation of the cases or other available information), relevant summary information on the Sri Lankan childhood immunization program (including general vaccine coverage data and summary data on the use of the pentavalent vaccine and other vaccines administered to the reported cases); background AEFI surveillance data from Sri Lanka; relevant available epidemiological data; summary of worldwide distribution and known safety experience with pentavalent vaccine; and a summary of the results of the pentavalent vaccine quality review and testing undertaken by WHO.

Members of the Expert Panel each reviewed (based on their clinical and vaccine safety expertise) all fatal AEFI cases for causality assessment. The panel then discussed the case reviews (by teleconference on 20 and 27 Nov as well as by email) to arrive at an overall panel conclusion on each of the cases. Members also individually reviewed all the non-fatal "HHE-like" cases to classify them as HHE or not. The outcomes of the individual reviews were then compared and compiled into a panel classification. We agreed that as HHE is a well known reaction to DPT, Hepatitis B and Hib vaccines, cases confirmed as HHE did not require individual causality assessment. Rather the focus was on addressing question 2a in the list of review questions.

WHO/IVB staff served as secretariat to the Expert Panel to facilitate the review.

### 2.1 Interpretation of causality assessment categories

The panel discussed and took into account the challenges/weakness of the current processes for individual causality assessment as well as the interpretation of the current WHO categories for causality assessment<sup>2</sup>. These terms and categories are often used in an academic context not fully applicable to the practice setting. It is therefore important that the terms used in these categories are applied with a full evaluation of all clinical and

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1. Buettcher M, Heininger U, Braun M et al. Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunization in early childhood: Case definition and guidelines for data collection, analysis, and presentation. *Vaccine* 2007; 25: 5875–5881.
  2. WHO Aide-Memoire for Causality Assessment of AEFI, accessible at <http://www.who.int/vaccines-documents/DocsPDF05/815.pdf>



epidemiological data as well as temporal relationships. Thus while the panel was guided in its statement of the final classification of causality by the WHO categories, it is important to emphasize that our causality assessment included (as to be expected) a comprehensive review of the clinical information as well as the laboratory and histopathological findings for each case, consideration of the epidemiological factors underpinning causal relationships and the current vaccine safety knowledge with respect to similar clinical events reported following immunization. Taking all these into consideration, the panel defined the categories of causality in the current assessment as stated below.

**Very likely/Certain:** A clinical event with a plausible time relationship to vaccine administration and which cannot be explained by concurrent or underlying disease, or by other drugs or chemicals.

**Unlikely:** In defining this category, the panel took note of the fact that the use of 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. Cases were classified in this review as unlikely where, in spite of not having evidence that the vaccine(s) contributed to the adverse event or the outcome of death, conclusive evidence regarding an alternate cause (or causes) of the event and outcome was lacking. This meant that we considered that classifying the AEFI in the category "unrelated" was not fully justified (as it could not be conclusively attributed to another cause). In such cases, we go further to state that the conclusion of "unlikely" means that the vaccine is not the major cause of death even in those cases where we discuss the possibility that the vaccine(s) or vaccination may have unmasked an underlying condition.

**Unrelated:** Cases were classified as unrelated if the event was conclusively attributed to another cause such as concurrent or underlying disease or other drugs or chemicals, and clearly not caused or contributed to by vaccination.

**Unclassifiable:** A clinical event with insufficient information to permit identification of a cause and thus allow an assessment of the casual relationship between the event and vaccination

### 3. Outcomes of review

The current report includes our findings from the first phase of the review (as described in section 2).

The final classification of causal association for the fatal cases is listed in Tables 1 and 2 below while a more comprehensive summary of review comments for each case is provided in Annex C. The latter includes:

- the key points the panel considered in its assessment; these included the major clinical presentation and lab or autopsy findings, "issues for interpretation" which address the arguments for or against alternate potential causes of the main adverse event and/or fatal outcome, and discussion of lacking information considered critical for a more conclusive assessment;
- notes on programmatic issues relevant to the assessment and/or highlighting areas for action;
- the panel's conclusions regarding causal association with the vaccine(s) administered; and
- where appropriate, recommendations specific to each case.

A number of programmatic issues with regard to immunization safety were highlighted by our review; a set of general recommendations to WHO (for the Sri Lankan national authorities and other countries as appropriate) is provided.

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### 3.1 Causality review of fatal AEFI cases

#### Pentavalent vaccine

Among five fatal AEFI cases reported following receipt of the pentavalent vaccine, the panel concluded that none was *very likely* or *certainly* due to the vaccination. Three were *unlikely* to be causally related to the vaccine, one was *unrelated* and one was *unclassifiable* due to insufficient information to assess a causal association (Table 1). It is important to emphasize that in the three cases classified as *unlikely* (D1, D3 and D6) we did not find evidence of a causal association with the vaccine. We considered that immunization with the pentavalent vaccine was not the major cause of the adverse event, however, we could not exclude with absolute certainty that the vaccine/vaccination could have had even a minor contribution to the clinical picture leading to death. In Case D3, our review of the data showed that it is difficult to confirm or exclude this potential minor contributory role while for case D6 we concluded that the immunization may have unmasked the clinical cascade but is unlikely to have been the major cause of death.

#### Other vaccines

Among the eight fatal AEFI cases reported following receipt of other vaccines, the panel concluded that one was *unlikely* to be causally related to the vaccine(s) received, four were *unrelated* and three were *unclassifiable* due to insufficient information to assess a causal association (Table 2). As before, it is important to emphasize that we did not find evidence of a causal association with the vaccines received by Case D2, classified as *unlikely*, however, we were unable to exclude with absolute certainty even a minor contribution by the vaccine/vaccination to the clinical picture leading to death. The panel concluded that there was sufficiently strong indication that death in this case was more likely caused by other underlying medical problems.

### 3.2 Review and classification of non-fatal AEFI cases

Our preliminary findings are that at least six of the non-fatal cases are not compatible with a diagnosis of HHE<sup>3</sup>. A further review of the specific levels of diagnostic certainty is required to reconcile in some cases the interpretation by individual reviewers of the signs and symptoms as reported. The full outcomes of this component of the review are to be provided in a follow up report. Based on our current findings, we conclude that the occurrence of HHE following the pentavalent vaccine use in Sri Lanka is within the recognized incidence.

## 4 Conclusions and recommendations of the Expert Panel

### 4.1 Conclusions regarding case reviews

We commend the relevant national authorities in Sri Lanka for the care taken to gather as much data as possible for the assessment of these cases. Among the 13 fatal AEFI cases reviewed; a reasonable amount of information permitting classification was available in ten cases. Based on this information, none of those ten cases was found to have conclusive evidence of a causal association with the vaccines administered.

Overall, we concluded that there was no evidence of a causal relationship between administration of the pentavalent vaccine and any of the five deaths reported as temporally associated with that vaccine. Although we classified three of the deaths as *unlikely* to be related, the data did not support pentavalent vaccine as the primary or major cause of death in any of those cases and other causes were more likely. However, the data available did not permit us to conclusively determine the primary cause of death in each case.

Of the other fatal AEFIs temporally associated with other vaccines, we also found no evidence of a causal relationship with the vaccines/vaccination. As before we emphasize that

<sup>3</sup> Case #: NF3, NF5, NF6, NF8, NF12, NF20



in the case we classified as *unlikely* to be related, the data did not support the administered vaccines or vaccination as the primary or major cause of death and other causes were more likely.

In the cases in which we classified as *unlikely* we also did not find any signs confirming clinical entities known to be potentially associated with vaccines (such as anaphylaxis). The panel also ruled out HHE as the mechanism of death in any of the cases.

Of note, we were unable to conclude on the potential causal association for four of the 13 fatal cases reviewed (i.e., *unclassifiable*) due to insufficient information. This is a very frequent pitfall with individual causality assessment in all settings, and especially when clinical workup of patients and/or subsequent AEFI investigations have not been thorough and/or critical information has not been adequately documented.

With specific regard to the pentavalent vaccine (including consideration of the cases who were administered the HepavaxGene vaccine produced by Berna Biotech Korea Corporation), the data presented by these reported AEFI cases do not provide evidence of a safety concern. Further our review of the data so far indicates that although HHE was apparently unrecognized in Sri Lanka prior to the use of this pentavalent vaccine, the cases of HHE reported do not show an increase above the expected reporting rate.

In order to correctly interpret a cluster of deaths with the aim of identifying potential "signals", it is crucial to examine background mortality rates in the age-specific population in the same region/setting. The total number of deaths reported temporally following vaccinations - as reviewed by the panel - is 13; of those, five deaths occurred following 124,672 pentavalent vaccinations over an approximate 3 month period. Based on the overall infant mortality rate in Sri Lanka of 11.2 per 1000 live births (2003 estimate), a live birth rate (1999) of 17.3 per 1000 population and a population (2005) of 19.67 million, an estimated number of 3,800 infant deaths may be expected per year (i.e., 10 to 11 infant deaths per day). A rough comparison of these figures suggests that the deaths reported (with temporal association to vaccination) are not in themselves an unexpected number of infant deaths in this setting. However, further examination of the mortality data, including death rates by age in first year of life, cause-specific death rates and most common causes of death among infants in Sri Lanka would be important for any real comparisons to be made. The panel will consider making such comparisons should the relevant data (as requested) become available.

Of particular note was the finding of poor weight gain in four of the deaths reported following immunization; this suggests that further investigation is warranted to examine the incidence of nutritional status in serious illnesses that may occur after immunization and be wrongly attributed to immunization.

#### **4.2 Recommendations**

A number of programmatic issues with regard to immunization safety were highlighted by our review; we focus our recommendations mainly on those issues that we consider to be (i) safety-related (i.e., the recommendation would potentially prevent or reduce severity of similar cases) and (ii) related to the investigation or assessment of reported AEFIs (i.e., the recommendation would potentially help with investigation/assessment of similar cases in Sri Lanka or other similar settings). We recognize that a number of these recommendations will require further careful consideration by WHO or the relevant national authorities with regard to practicality/feasibility, cost-effectiveness with available resources, and the impact likely to be achieved, all of which are likely to differ from country to country.

Where relevant, we have made recommendations for specific cases in the case summaries in Annex C. Some of those are equally applicable to the detection and reporting, investigation or management of similar AEFIs in Sri Lanka and other settings and are included in the more general recommendations listed below.

1. Review or establish a standard autopsy protocol to assist in investigation of deaths that have occurred following immunization.
2. Review or establish protocols for cases in which post-mortem is refused such as ability to obtain specimens for virology and bacteriology. Whenever possible, if sepsis is suspected in AEFIs, bacterial cultures should be done pre-mortem.
3. Establish standard procedures for conducting a verbal autopsy and educate health professionals on the importance of obtaining verbal autopsies; a more detailed history about the child's health and nutritional status in the months prior to the death as well as the family situation needs to be emphasized. Details of health and nutritional status are especially useful in confirming or supporting other non-immunization related factors or underlying illness that may have contributed to death.
4. Establish procedures for specific investigation of sudden unexplained death following vaccination including a verbal autopsy; refer point 3 above with respect to verbal autopsies.
5. Whenever possible, drug and toxicology screen (minimum by history and documentation of suspected drug or toxic substance) should be done in cases of sudden unexplained death following vaccination.
6. Emphasize the importance of collecting information on the death scene including how infants are put to sleep (prone versus supine) in all cases where infants die unexpectedly. Investigation of the death scene is critical in all unexpected deaths and in deaths occurring outside of a health facility even when not considered as unexpected. Such information is of critical value in the assessment of the death as many deaths in this age group may be wrongly attributed to a vaccination when it may actually have been due to SIDS or other events such as aspiration. Standard guidelines for the investigation of the scene of death would be useful and may be included in the verbal autopsy protocol.
7. Emphasize the importance, in investigation of AEFIs, of reviewing and using in analysis vital statistics and specific epidemiological data such as neonatal and infant mortality rates (including sudden unexpected death rates), background occurrence of childhood illnesses and most common causes of morbidity and mortality in specific populations by age.
8. Emphasize the importance of collecting information on other infants immunized in same session as well as non-immunized children in the population; specifications on what data to collect should be included in national guidelines for AEFI surveillance. (Refer WHO guidelines).
9. Where relevant, investigate at a population level the occurrence of deaths or other serious AEFIs (i.e., requiring hospitalization) in severely malnourished children. For example, if serious adverse events are frequently occurring among severely malnourished infants a more comprehensive investigation/review in the population may be warranted. Such a situation may however, only be recognized by improving the collection of background health and nutritional data on individual case reports. Background information on nutritional status, such as recording of birth weight and progressive weight taken at each immunization visit, would enhance the ability to assess the importance of nutritional status as a parameter in true vaccine reactions or in coincidental illnesses that may present as and be reported as AEFIs.
10. Establish procedures/guidelines for request of further information about health status in infants with severe failure to thrive before vaccination. Vaccinators should be taught to recognize when such infants warrant further investigations (does not mean should not be immunized but may need to be referred on for more care).

11. Where relevant, investigate at a population level the occurrence of deaths or other serious AEFIs in premature infants (see 9 above for similar rationale). Sudden unexpected deaths are known to occur more frequently in premature babies with apnoea.
12. Educate health professionals about the risk of cough and cold remedies in young infants as well as risk of prolonged use of acetaminophen (Morb Mortal Wkly Rep. 2007 Jan 12;56(1):1-4 and Mohd Zain etc al Singapore Med J, 2006 Feb;47(2):134-7).
13. Review or establish guidelines/procedures for health screening, where possible, to identify babies with unrecognized congenital heart disease so that they may be referred for further investigation and care.
14. Ensure education of health professionals at appropriate levels on the importance of prompt diagnosis and management of serious illnesses presenting after immunization (and importance of not being distracted by a history of immunization/reported AEFI).
15. Ensure feedback to HCWs on the outcome of all investigations of serious AEFI, both in cases where a causal link with vaccination is found and also where there is lack of any evidence that the vaccine is involved.