WEEKLY EPIDEMIOLOGICAL REPORT

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Hypotonic Hyporesponsive Episode [HHE]

DPT-HBV-Hib (Pentavalent) vaccine was introduced to Sri Lankan Immunization Program commencing from 1st January 2008. Being a new vaccine, all providers were requested to closely monitor adverse effects following immunization [AEFI] due to this vaccine. Around 125,000 pentavalent immunizations may have been carried out during the first four months of 2008.

During the first four months of 2008, four hundred and seven (407) cases of AEFI following pentavalent immunization have been reported through the national AEFI surveillance system. Majority were expected AEFI following Pertussis containing vaccine such as high fever (171 cases) and allergic reactions (72 cases). 47 cases of persistent screaming, 17 cases of seizures and 17 cases of injection site abscess were also among the reported AEFI.

However, twenty two cases of acute onset of pallor, cyanosis, reduced responsiveness and convulsions (Hypotonic Hyporesponsive Episode (HHE) like syndrome) were also reported within few minutes to several hours of administration of pentavalent vaccine. Majority of these cases fully recovered without sequelae.

However, it should be noted that no HHE like events have been reported through the routine AEFI surveillance system in previous years against DPT or any other vaccine in Sri Lanka.

Other than that, During this period there were five reported infant deaths that were temporally to be associated with Pentavalent vaccine. Clinical presentations of these deaths were not directly compatible with the HHE. After the preliminary investigations, experts classified that 3 of the 5 reported deaths, one as possibly related, one as unlikely to be related and the other as unrelated to the vaccine . The classification of the remaining 2 cases were not conclusive and further review is pending.

With the collaboration of the WHO, detailed investigations into these reported events are still in progress. By considering all National committee on AEFI has decided to temporally withdraw thepentavelent vaccine from the national EPI schedule and revert back to the previous immunization schedule

Hence at this Juncture, it vital for us to be well aware of HHE as a possible AEFI following pentavalent or any other pertussis containing vaccines and keep the health personnel and parents informed on the situation. It is important to further strengthen the surveillance of HHE by detecting and reporting such cases through the routine AEFI reporting system.

Hypotonic-hyporesponsive episode (HHE) is a clinical event characterized by sudden onset of reduced muscle tone, hyporesponsiveness (i.e., less responsive than usual to verbal or other sensorial stimuli) and change of skin color (pallor or cyanosis) following immunization. Until recently there has been no generally accepted definition of HHE. To promote meaningful comparability of future data, the Brighton working group on HHE has attempted to establish a case definition for global acceptance and use in clinical trials and passive surveillance by groups with various levels of resources and in different geographic regions.

HHE has been referred to by terms like 'shock,' 'shock like syndrome', 'collapse' and 'collapse reaction'. For a proper interpretation of various studies on the occurrence, pathophysiology and consequences of HHE, more detailed information would be needed to explore, whether the same events are described by the various *ad hoc* definitions. The only published structured work put into the development of a case definition for HHE was done in a US public health service workshop on hypotonic-hyporesponsive episode (HHE) after pertussis immunization . In addition to a systematic literature search of Medline, EMBASE and the Cochrane library of vaccine studies involving human subjects between 1990 and 2000, this has served as the basis for consensus formation within the working group.

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It has been modified to serve as a single definition to be globally used in clinical trials and post-marketing surveillance by groups with various levels of resources and in different geographic regions.

HHE has been documented to occur after immunization with diphtheria, tetanus, *Haemophilus influenzae* type b, and hepatitis B vaccines. Most reported episodes have, however, followed administration of pertussis component of vaccines, and have been associated with whole-cell vaccines more often than acellular. HHE has also been observed most frequently during the primary immunization series, mainly after the first dose . Whether these features are related to characteristics of the vaccinee, an immunologic phenomenon, presence of toxic component(s) in the vaccine, combinations of the above, or some yet to be determined cause, remains unclear. Sex attribution does not seem to be a factor of relevance: a slight majority (53%) of HHE among females was demonstrated in reports to the Vaccine Adverse Event Reporting System (VAERS) in the United States while male predominance was observed in the enhanced surveillance program in The Netherlands

The reported rates following whole-cell and acellular pertussis component combination vaccines may vary from 21 to 71 episodes and 7 to 36 episodes *per 100,000 doses* , and 36 to 250 episodes and 4 to 140 episodes *per 100,000 children*, respectively. Rates vary greatly even for the same vaccine, as has been noted in the reported incidence of HHE after receipt of DTPw . These wide variations probably reflect the various case definitions and case ascertainments rather than inherent properties of different vaccines but might also be explained by variations in immunization schedules, age of the child at the time of immunization, or differences in the components contained in combination vaccines. According to the VAERS the median time to onset of signs after immunization is 3–4 h but ranges from immediately to 48 h postimmunization. Of 203 cases in children <24 months of age, 17 (8.5%) presented within 5 min following immunization, whereas 8 (67%) of 12 children older than 24 months had such an early onset . The median duration of these triad signs is 6–30 min but rarely parents may report their perception of time to entire resolution, particularly pallor, as being as long as 10 days. "Fever" in association with HHE is reported in up to one third of cases.

Apart from the clinical triad of signs, there are no further investigations (e.g., laboratory examinations) helpful in confirming the diagnosis of HHE. Data from a small case series indicate that blood pressure is normal at the time of presentation . Leukocytosis due to neutrophilia is observed in children with or without HHE following immunization . There is no evidence of significant changes in insulin or glucose levels . Studies reporting on the follow-up of HHE relying on parental reporting and neurodevelopmental testing demonstrated HHE to be a self-limiting event without long-term sequelae .

Thus the pathogenesis of HHE is unknown and has been poorly studied given the constraints of investigating a condition that is rare and results in transient signs. The pathoenesis of HHE is likely to be multifactorial and may result from factors either idiosyncratic to the child or inherent in the vaccine.

Rationale for decisions about case definition

As vasovagal-syncope is clinically defined by the same triad of diagnostic signs but usually occurs in an older age group . Also, brief atonic seizures may present with a similar clinical picture as HHE; however, as defined by the Brighton Collaboration , atonic seizures are characterized by unconsciousness (rather than hyporesponsiveness) and a sudden loss of tone in postural muscles but not by pallor or cyanosis. Further, intoxication with sedative substances may present like HHE and should be ruled out by appropriate investigations (e.g. urine screening). If an intoxication explains the child's clinical signs and symptoms, this event should not be reported as HHE.

While perception of some of the clinical signs and symptoms listed in the definition and guidelines may be subjective and culturally influenced, it should be recognized that this is an unavoidable part of standard medical practice. If felt necessary in prospectively designed clinical trials, evaluation of inter-rater reliability may be done.

For this revised version, the working group for HHE concluded that, although most *reported* vaccine-related hypotonic-hyporesponsive episodes occur within the first 24 h, and virtually all within 48 h postimmunization, the lack of understanding of the pathogenesis and mechanism of the event precludes restriction to a fixed surveillance time interval such as "48 h". Surveillance that does not restrict reporting by time from vaccination to HHE onset could facilitate better understanding of these episodes by permitting examination of the age and onset distributions after current and future vaccines. Reporting of all events, without time restrictions, will still allow analysis stratified by occurrence within 48 h of immunization, if this is intended.

Likewise, although most cases are reported in children younger than 2 years of age undergoing their primary immunization series there are no data that would suggest that HHE could not occur in older individuals.

Source

Michael Buettcher , Ulrich Heininger , Miles Braun et al. Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunization in early childhood: Case definition and guidelines for data ollection, analysis, and presentation. Vaccine 25 (2007) 5875–5881.

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Table 1: Vaccine-preventable Diseases & AFP

10th- 16th May 2008 (20th Week)

Disease	No. of Cases by Province									Number of cases during current week in 2008	Number of cases during same week in 2007	Total number of cases to date in 2008	Total number of cases to date in 2007	Difference between the number of cases to date between 2008 & 2007
	W	C	S	N	E	NW	NC	U	Sab					
Acute Flaccid Paralysis	01 GM=1	00	00	00	00	00	00	00	00	01	00	34	34	00.0%
Diphtheria	00	00	00	00	00	00	00	00	00	00	00	00	00	00.0%
Measles	00	00	00	00	00	00	00	00	00	00	01	48	29	+65.5%
Tetanus	00	00	00	00	00	01 KR=1	00	00	00	01	00	14	13	+7.7%
Whooping Cough	01 CO=1	00	01 MT=1	00	00	00	00	00	00	02	00	16	17	-5.9%
Tuberculosis	150	84	23	00	26	17	00	07	13	320	199	3460	3867	-10.5`%

Table 2: Newly Introduced Notifiable Diseases

10th - 16th May 2008 (20th Week)

Disease	No. of Cases by Province									Number of cases during current week in 2008	Number of cases during same week in 2007	Total number of cases to date in 2008	Total number of cases to date in 2007	Difference between the number of cases to date between 2008 & 2007
	W	C	S	N	E	NW	NC	U	Sab					
Chicken-pox	13	10	15	00	02	10	04	05	07	67	70	2380	1450	+64.1%
Meningitis	04 CO=1 GM=3	00	01 MT=1	00	01 AM=1	02 KR=2	04 PO=4	00	02 KG=2	14	00	641	49	+1208.1%
Mumps	03	03	01	00	02	07	04	01	04	25	50	989	530	+86.6%

Key to Table 1 & 2

Provinces: W=Western, C=Central, S=Southern, N=North, E= East, NC=North Central, NW=North Western, U=Uva, Sab=Sabaragamuwa.

DPDHS Divisions: CB=Colombo, GM=Gampaha, KL=Kalutara, KD=Kandy, ML=Matale, NE=Nuwara Eliya, GL=Galle, HB=Hambantota, MT=Matara, JF=Jaffna, KN=Killinochchi, MN=Mannar, VA=Vavuniya, MU=Mullaitivu, BT=Batticaloa, AM=Ampara, TR=Trincomalee, KM=Kalmunai, KR=Kurunegala, PU=Puttalam, AP=Anuradhapura, PO=Polonnaruwa, BD=Badulla, MO=Moneragala, RP=Ratnapura, KG=Kegalle.

Table 3: Laboratory Surveillance of Dengue Fever 10th - 16th May 2008 (20th Week)

Samples	Number tested		Number positive *		Serotypes									
					D_1		D_2		D_3		D_4		Negative	
	GT	AH	GT	AH	GT	AH	GT	AH	GT	AH	GT	AH	GT	AH
Number for current week	06	10	00	00	00	00	00	00	00	00	00	00	00	00
Total number to date in 2008	77	50	07	13	00	00	04	05	01	04	00	00	02	00

Sources: Genetech Molecular Diagnostics & School of Gene Technology, Colombo [GT] and Genetic Laboratory Asiri Surgical Hospital [AH]

* Not all positives are subjected to serotyping.

NA= Not Available.

Data Sources:

Weekly Return of Communicable Diseases: Diphtheria, Measles, Tetanus, Whooping Cough, Human Rabies, Dengue Haemorrhagic Fever, Japanese Encephalitis, Chickenpox, Meningitis, Mumps.

Special Surveillance: Acute Flaccid Paralysis.

National Control Program for Tuberculosis and Chest Diseases: Tuberculosis.

Table 4: Selected notifiable diseases reported by Medical Officers of Health

10th– 16th May 2008 (20th Week)

DPDHS Division	Dengue Fever / DHF*		Dysentery		Encephal-itis		Enteric Fever		Food Poisoning		Leptos-pirosis		Typhus Fever		Viral Hepatitis		Human-Rabies		Re-turns Re-ceive
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	%
Colombo	29	770	00	71	00	06	02	50	00	57	09	181	00	02	02	60	00	01	**85**
Gampaha	08	463	00	68	00	05	00	28	00	66	06	162	00	04	03	65	00	01	**64**
Kalutara	09	234	07	142	00	09	01	39	00	16	09	164	00	02	00	19	00	00	**75**
Kandy	03	97	03	104	00	04	02	23	00	30	26	152	04	44	03	76	00	00	**68**
Matale	00	54	03	110	00	01	01	23	00	02	30	340	00	01	01	17	00	00	**58**
Nuwara Eliya	00	12	09	101	00	01	03	117	00	107	01	16	01	31	01	63	00	01	**85**
Galle	01	54	03	51	00	08	00	10	00	42	03	168	01	09	00	04	00	03	**76**
Hambantota	01	47	00	35	00	03	01	06	00	06	01	49	01	51	00	04	00	00	**55**
Matara	05	109	02	79	00	04	00	20	00	02	03	167	03	96	01	06	00	01	**65**
Jaffna	02	46	05	65	00	01	04	174	00	05	00	00	01	132	00	20	00	00	**63**
Kilinochchi	00	00	00	03	00	00	00	00	00	00	00	02	00	00	00	01	00	00	**00**
Mannar	00	24	00	07	00	06	00	95	00	00	00	00	00	00	00	11	00	00	**00**
Vavuniya	00	10	03	21	00	02	00	01	00	09	00	04	00	00	00	03	00	00	**50**
Mullaitivu	00	00	00	01	00	00	00	06	00	12	00	00	00	00	00	04	00	00	**00**
Batticaloa	01	76	03	37	00	02	02	13	01	19	00	01	00	01	01	67	00	05	**45**
Ampara	00	09	02	89	00	00	00	04	00	00	00	12	00	00	00	04	00	00	**29**
Trincomalee	01	156	00	40	00	00	00	07	00	03	00	11	00	11	00	09	00	00	**20**
Kurunegala	02	193	02	134	00	10	00	25	00	10	02	95	00	15	01	22	00	04	**72**
Puttalam	10	224	00	41	00	02	00	76	00	18	00	06	00	26	00	19	00	02	**44**
Anuradhapur	00	107	02	41	00	04	00	08	00	04	20	133	01	10	00	10	00	02	**47**
Polonnaruwa	01	41	09	54	00	01	00	20	00	06	00	30	00	00	00	15	00	00	**86**
Badulla	02	42	13	194	00	03	01	58	00	13	03	19	01	62	01	59	00	01	**73**
Monaragala	00	35	07	106	00	01	00	25	00	19	05	65	02	56	00	13	00	00	**55**
Ratnapura	01	121	02	109	00	20	02	41	00	42	03	89	00	66	01	36	00	00	**50**
Kegalle	01	167	00	180	00	20	01	30	00	00	03	104	00	35	00	282	00	00	**55**
Kalmunai	01	21	07	99	01	03	00	09	00	10	00	00	00	02	00	14	00	00	**69**
SRI LANKA	**78**	**3112**	**82**	**1982**	**01**	**116**	**20**	**908**	**01**	**498**	**124**	**1970**	**15**	**656**	**15**	**903**	**01**	**21**	**59**

Source: Weekly Returns of Communicable Diseases (WRCD).

***Dengue Fever / DHF** refers to Dengue Fever / Dengue Haemorrhagic Fever.

****Timely** refers to returns received on or before 24 May, 2008 Total number of reporting units =238. Number of reporting units data provided for the current week: 183

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