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Original Article

Adverse events following immunization of combined diphtheria, whole-cell pertussis, tetanus, and hepatitis B (DPwT/HB) vaccine

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ABSTRACT

Background Combined vaccine of diphtheria, whole-cell pertussis, tetanus, and hepatitis B (DPwT/HB) will reduce the number of injections to children and simplify the delivery logistics. The adverse events following immunization (AEFI) of this vaccine have to be concerned since the events may increase or decrease.

Objectives To evaluate AEFI of DPwT/HB vaccine in healthy infants.

Methods A descriptive prospective study of AEFI of three doses of DPwT/HB vaccine was performed on 74 healthy infants aged two to six months at the Department of Child Health, Cipto Mangunkusumo Hospital, from July 2000 to March 2001.

Results Out of 74 infants, 68 received two doses and 67 completed the study with a total of 209 doses. Of 209 doses, adverse events were reported following 126 doses (60.3%), consisted of systemic (60.3%) and local reactions (9.5%). The three most frequent AEFI iwere mild fever (44.5%), high fever (15.7%), irritability (31.5%). Most AEFI were coincidental (51.1%), occurred after more than 72 hours (31.4%) and lasted less than 24 hours (17.7%). Systemic reactions were mostly found in 4-month-old infants (33.3%), while local reactions in 2-, 3-, and 5-month-old infants (25%), respectively.

Conclusion Most AEFI were coincidental and resolved without any complication **[Paediatr Indones 2004;44:209-214].**

Keywords: *adverse events, combined vaccines, DPwT/HB vaccine.*

Hepatitis B infection continues to be a worldwide health concern. The World Health Organization (WHO) estimated that currently, there are over 350 million chronic carriers of the hepatitis B virus worldwide. According to WHO, significant global reduction of hepatitis B infection can only be achieved through universal vaccination.[1,2] Nowadays, diphtheria, pertussis, and tetanus still warrant attention since these diseases infect millions of people with serious complications. Diphtheria, pertussis, and tetanus vaccine (DPT) has been developed since 1943, and together with the hepatitis B vaccine (HB), has been included in the WHO expanded program on immunization (EPI). Combining HB with DPT is viable since both vaccines are adsorbed and given in multiple doses. Various strategies are being investigated to produce a combined DPT/HB vaccine.

A combined vaccine would reduce the number of injections to children and simplify the delivery logistics. Besides these advantages, AEFI of these combined vaccines should be taken into consideration since the events may vary.[3-10] The objective of this study was to evaluate the adverse events following three doses of a combined diphtheria, whole-cell pertussis, tetanus, and hepatitis B (DPwT/HB) vaccine administered to healthy two- to six-month-old infants.

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Methods

The study was performed from July 2000 to March 2001 on 74 healthy two-to six-month-old infants recruited from the Growth and Development Clinic at the Department of Child Health, Cipto Mangunkusumo Hospital. The inclusion criteria were no evidence of disease or fever, no history of allergy to any components of DPT or HB, and no history of high fever, shock, unusual or persistent crying, or convulsion occurring within 48 hours after former immunization. Prior to the study, informed consent was obtained from the parents.

The combined DPwT/HB vaccine used in this study was Tritanrix HB(R), manufactured by Smith Kline Beecham. One dose (0.5 ml) of this vaccine contained ≥30 IU of diphtheria toxoid, ≥60 IU of tetanus toxoid, ≥4 IU of inactivated whole-cell *B pertussis* bacteria, and 10 mg of recombinant hepatitis B surface antigen, adsorbed onto 0.6 mg of aluminum salts and preserved with 25 mg of thimerosal and 50 mg of phenoxyethanol.

Three doses of vaccine were injected intramuscularly in the anterolateral thigh in 5-week interval. For the first 15 minutes after each vaccination, the infants were observed by a physician for any adverse event. Parents were then asked to observe their infants for 5 weeks following each vaccination for any adverse event. Parents were given diary cards to record the observations and were asked to return these cards on the following visit. These cards were designed for recording information on local and systemic reactions, time of onset, and duration of reactions. A thermometer was given to each infant enrolled. Any of the following reactions constituted a contraindication to the vaccine and excluded the infants for subsequent doses i.e., body temperature of ≥40.4°C, persistent screaming or crying for 3 hours within 48 hours following vaccination, convulsions, encephalopathy, hypotonic-hyporesponsive episode, Guillain-Barre syndrome, and shock following vaccination.

Parents were asked to bring their infants to the clinic or emergency room if any reaction occurred. All of the AEFI were reported to AEFI committee Ministry of Health for AEFI classification audit based on The WHO Western Pacific (1999) classification of AEFI.[11,12] The audit was performed on 5th-6th July 2003.

Results

A total of 74 infants were enrolled, 68 infants received two doses of the vaccine, and 67 infants completed the study, so that the total dose administered were 209. Of the 7 infants who were withdrawn from the study, 2 was due to convulsion following immunization of the first and third doses of the vaccine. **Table 1** shows the characteristics of infants enrolled in this study. Five weeks of age were added to all infants in the following doses.

TABLE 1. CHARACTERISTICS OF THE INFANTS ENROLLED IN THIS STUDY.

	First dose n(%)	Second dose n(%)	Third dose n(%)
Sex			
Male	39(53)	35(52)	35(52)
Female	35(47)	33(48)	32(48)
Total	74(100)	68(100)	67(100)
Age (months)*			
2	41(55)	0(0.0)	0(0)
3	22(30)	39(57)	0(0)
4	7(10)	20(29)	38(57)
5	4(5)	6(9)	20(30)
6	0(0)	3(4)	6(9)
7	0(0)	0(0.0)	3(4)
8	0(0)	0(0.0)	0(0.0)
Total	74(100)	68(100)	67(100)

Note: *ages of infants were assessed in months, according to month in the category.

Of a total of 209 doses, adverse events were reported following 126 doses (60.3%) consisting of 126 systemic (60.3%) and 20 local reactions (9.5%). There were 262 adverse events reported. More than one events may be found in one dose. Two cases of general convulsion were reported in three-month-old and four-month-old male infants. The seizures were accompanied by high fever (40.5°C and 39.8°C, respectively), occurred in 11.5 and 16 hours following the first and third doses of the vaccine, each resolved within 1-5 minutes. No sequelae was reported and no hospitalization was needed for these reactions. Difference in proportions with increased number of doses given was not statistically significant for systemic ($p=0.750$) and local reactions ($p=0.149$). **Table 2** shows adverse events following each dose of this combined vaccine.

TABLE 2. ADVERSE EVENTS FOLLOWING EACH DOSE OF COMBINED DPWT/HB VACCINE.

	1st dose N=74 n (%)	2nd dose N=68 n (%)	3rd dose N=67 n (%)	TOTAL N=209 n (%)
Systemic reactions				
Mild fever*	34 (46)	27 (40)	32 (48)	93 (45)
High fever†	14 (19)	10 (15)	9 (13)	33 (16)
Irritability	25 (34)	25 (37)	16 (24)	66 (32)
Vomiting	9 (12)	7 (10)	4 (6)	20 (10)
Malaise	5 (7)	4 (6)	3 (5)	12 (6)
Diarrhea	5 (7)	3 (4)	1 (2)	9 (4)
Wheals‡	4 (5)	1 (2)	1 (2)	6 (3)
Convulsion	1 (1)	0 (0)	1 (2)	2 (1)
Pale	1 (1)	0 (0)	0 (0)	1 (1)
Local reactions				
Pain	1 (1)	0 (0)	0 (0)	1 (1)
Swelling	10 (14)	4 (6)	5 (8)	19 (9)

Note: N = total number of vaccine given in each dose.
n = number of particular adverse events reported following each dose.
% = percentages of doses administered that were accompanied by a particular adverse events.
* = the body temperature 37.5-38.5°C.
† = the body temperature >38.5°C.
‡ = one to three mosquito bite-like wheals localized on the cheeks, arms, or legs of the infants.

A total of 262 adverse events were reported to AEFI Committee Ministry of Health for a classification audit. **Table 3** shows the classification of AEFI of DPwT/HB in this study according to the audit results.

Most AEFI occurred in 4-5 hours following immunization (22.1%) and lasted for 2-3 hours (21.4%). Mild fever was mostly reported in 4-5 hours following immunization (21%) and resolved within 2-3 hours (25%). Most high fever in this study occurred in more than 72 hours (8 out of 33 cases) and resolved within 2-3 hours (7 of 33 cases). Irritability was mostly reported in 2-3 hours following immunization (24%) and resolved within 2-3 hours (23%). Two cases of febrile convulsion occurred in 11.5 and 16 hours following immunization, respectively and each ceased in 1-5 minutes. Most vomiting, diarrhea, malaise, and wheals occurred in more than 72 hours following immunization, and lasted less than 24 hours. A case of local pain was reported in 2-3 hours following immunization and resolved spontaneously within 24 hours. Local swelling was frequently reported in 2-3 hours (7 out of 19 cases) and disappeared spontaneously in 14-15 hours. Pale was reported in one dose, occurred in 20 minutes following immunization and resolved within 15 minutes. There was one event of local pain which occurred in 2-3 hours and lasted for 24 hours.

Most AEFI was reported in 4-month-old infants (36.5%). The adverse events spread almost evenly between sexes. **Table 4** shows systemic and local reactions following DPwT/HB based on age and sex.

Discussion

Of 209 doses, 126 (60.3%) were followed by adverse events. These results were less than those reported in similar previous studies in Spain (100%),[5] Lithuania (>90%),[6] and Greece (100%).[7] The

TABLE 3. CLASSIFICATION OF AEFI OF DPWT/HB ACCORDING TO THE AUDIT BY AEFI COMMITTEE MINISTRY OF HEALTH

	I		II		III		IV		V		TOTAL	
Adverse events	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Mild fever	0	0.0	0	0.0	50	19.1	43	16.4	0	0.0	93	35.5
High fever	0	0.0	0	0.0	14	5.3	19	7.3	0	0.0	33	12.6
Irritability	0	0.0	0	0.0	30	11.5	36	13.7	0	0.0	66	25.2
Vomiting	0	0.0	0	0.0	11	4.2	9	3.4	0	0.0	20	7.6
Convulsion	0	0.0	0	0.0	2	0.8	0	0.0	0	0.0	2	0.8
Malaise	0	0.0	0	0.0	0	0.0	12	4.6	0	0.0	12	4.6
Pale	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0	1	0.4
Diarrhea	0	0.0	0	0.0	0	0.0	9	3.4	0	0.0	9	3.4
Wheals on cheek/arm/leg	0	0.0	0	0.0	0	0.0	6	2.3	0	0.0	6	2.3
Local swelling	0	0.0	0	0.0	19	7.3	0	0.0	0	0.0	19	7.3
Local pain	0	0.0	0	0.0	1	0.4	0	0.0	0	0.0	1	0.4
Total	**0**	**0.0**	**1**	**0.4**	**127**	**48.5**	**134**	**51.1**	**0**	**0**	**262**	**100**

Note: The WHO *Western Pacific* (1999) classification of AEFI:[11,12]
I.Programmatic errors, II. Injection reaction, III. Vaccine reaction, IV. Coincidental, V. Unknown.
%=Percentages of adverse events reported.

TABLE 4. SYSTEMIC AND LOCAL REACTIONS FOLLOWING DPWT/HB BASED ON AGE AND SEX

	First dose n (%)	Second dose n (%)	Third dose n (%)	Total n (%)
Systemic reactions				
Sex				
Male	25 (53)	21	21 (52)	67 (53)
Female	22 (47)	18	19(48)	59 (47)
Total	47	39	40	126 (100)
Age (months)				
2	33 (70)	0	0 (0)	33 (26.2)
3	10 (21)	23	0 (0)	33 (26.2)
4	2 (4)	11	29 (73)	42 (33.3)
5	2 (4)	4	8 (20)	14 (11.1)
6	0 (0)	1	2 (5)	3 (2.4)
7	0 (0)	0	1 (3)	1 (0.8)
Total	47	39	40	126 (100)
Local reactions				
Gender				
Male	6	3	3	12
Female	5	1	2	8
Total	11	4	5	20
Age (months)				
2	5	0	0	5
3	3	2	0	5
4	1	1	2	4
5	2	1	2	5
6	0	0	1	1
7	0	0	0	0
Total	11	4	5	20

adverse events in this study included 126 systemic (60.3%) and 20 local reactions (9.5%). A former study in Thailand found systemic and local reactions in 64% and 9% of total doses, respectively.[4] A study in Spain reported systemic reaction in 73.9% and local reaction in 59.2%.[5]

According to the audit results of AEFI Committee Ministry of Health, most adverse events reported in this study were coincidental (51.1%). These audit results confirmed the AEFI reports from Vaccine Safety Committee, Institute of Medicine (IOM).[11-14]

Most systemic reactions were found in 4-month-old infants (33.3%). Local reactions were mostly reported in 2-, 3-, and 5-month-old infants. These adverse events were spread almost evenly between sexes. There was no previous report about the proportion of local and systemic reactions based on age and sex.

Mild fever was the most common systemic reaction reported in this study (45%), followed by irritability (32%) and high fever (16%). The study in Lithuania showed that irritability occurred in 61% of doses, mild fever in 25.9% of doses, and high fever in 0.87% of doses.[6] The Greece study reported mild fever (41.9%), irritability (39.5%), and high fever (3.2%).[7] Vomiting was reported following 9.5% of doses in this study. A study in Bogor showed that vomiting occurred in 7.69-12.82% of doses.[15] In this study, malaise, diarrhea, and wheals were reported following 5.7%, 4.2%, and 2.8% of doses, respectively, and classified as coincidental events according to the audit results of AEFI Committee, Ministry of Health. There is no report about these events in previous studies.

Febrile convulsion was reported following 2 doses (0.9%) of the vaccine in this study. No sequelae was found following these reactions. The Advisory Committee on Immunization Practices (ACIP) reported that convulsion with or without fever occurred following 0.05% doses of DPT vaccine, less than that reported in this study.[16] However, it is stated in the literature that approximately 2-5% children younger than 5 years old have experienced febrile convulsion, greater than that found in this study.[17] In this study, pale was reported in 1 doses (0.5%) and classified as an injection reaction according to the audit results of AEFI Committee Ministry of Health. There is no report about convulsion and pale following immunization of DPwT/HB from previous studies.

Local swelling was the most common local reaction reported in this study (9%), followed by local pain (0.5%). The study in Lithuania showed that local pain occurred in 52.9% of doses, and local swelling was found following 38.7% of doses.[6] The study in Greece reported local pain (21.8%) and swelling (17.7%).[7] Another study in Bogor found that local pain occurred in 42.05-46.67% of doses, and local swelling occurred in 14.87-22.05% of doses.[15]

Adverse events mostly occurred in 4-5 hours following immunization and lasted for 2-3 hours. The study in Bogor reported that most adverse events occurred in the first day and lasted less than 3 days. In this study, mild fever was mostly reported in 4-5 hours following immunization and resolved within 2-3 hours. The study in Bogor showed that mild fever mostly occurred in the first day, and resolved within 1.28-1.31 days.[15] Most high fever in this study occurred in more than 72 hours and resolved within 2-3 hours, while Sundoro [15] noted that high fever

occurred in the first day, and lasted for 1.2-1.7 days.[15]

Irritability was mostly reported in 2-3 hours following immunization and resolved within 2-3 hours. Sundoro reported that irritability mostly occurred in the first day, and lasted for 1.6-1.8 days.[15] Two cases of febrile convulsions occurred in 11.5 and 16 hours following immunization and each ceased in 1-5 minutes. There is no report about this event in other studies.

Most vomiting, diarrhea, malaise, and wheals occurred in more than 72 hours following immunization, and lasted less than 24 hours. A case of local pain was reported in 2-3 hours following immunization and resolved spontaneously within 24 hours. The Bogor study showed that vomiting and local pain were frequently reported in the first day and disappeared spontaneously in 1-2 days.[15] Local swelling was frequently reported in 2-3 hours and disappeared spontaneously in 14-15 hours. Study in Bogor found that local swelling mostly occurred in the first day, and lasted for 1.53-1.97 days.[15] No event was followed by sequelae and needed any hospitalization. The difference results in systemic and local reactions among these studies may be due to the subjectivity of the observers (parents) in reporting AEFI, and the different observation time among these studies.

We concluded that most AEFI in this study were coincidental, occurred and lasted less than 24 hours. No complication and hospitalization were reported following the AEFI. However, there were some limitations of this study, such as subjectivity of the observers (parents) in reporting AEFI, incapability to cover rare AEFI, and non-controlled study. A randomized controlled study of combined versus non-combined vaccines, with large samples and strict AEFI reporting observation, would be necessary in the future.

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