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Diphtheria immunogenicity following the administration of pentavalent DTwP−HB−Hib vaccine at 4− and 8−week intervals: A randomized controlled trial

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ABSTRACT

Objective: To evaluate the effectiveness of DTwP-HB-Hib vaccination dosing intervals at eight weeks *versus* four weeks on the immunogenicity of the diphtheria component.

Methods: This is a randomized, open-label, parallel, controlled trial on healthy two-month-old infants who had not received DTwP-HB-Hib vaccinations. The infants received three doses of the vaccine either at an eight-week or four-week interval. The anti-diphtheria toxoid IgG antibody levels before and after three doses of the vaccination were measured using ELISA.

Results: Eighty infants were enrolled in this study, with 64 fulfilling the study requirements and randomized into two groups. All study participants exhibited uncertain protection against diphtheria antibodies (0.01-0.99 IU/mL) at the beginning of the study with an average of (0.023±0.009) IU/mL and (0.026±0.009) IU/mL in eight weeks and four weeks groups. Following three doses of the vaccination, the antibody level rose to an average of (1.320±0.234) IU/mL in the eight-week group and (1.307±0.186) IU/mL in the four-week group, with no statistically significant difference in the antibody levels observed (P=0.814).

Conclusions: DTwP-HB-Hib vaccinations can be administered at an eight-week or four-week interval, as they do not significantly affect the level of anti-diphtheria IgG antibodies.

KEYWORDS: Anti-diphtheria toxoid IgG antibody; DTwP-HB-Hib vaccine; Dosing interval; Immunogenicity

1. Introduction

Diphtheria, an infectious disease that results from toxin-producing bacteria, represents a considerable public health risk, particularly in environments characterized by inadequate health conditions, overcrowding, and insufficient vaccine coverage[1]. In the 1970s, before the extensive use of vaccines, it was projected that one million cases of diphtheria, resulting in 50000 to 60000 fatalities, occurred yearly in low- and middle-income countries (LMICs). Subsequent to the World Health Organization's (WHO) initiation of the Expanded Programme on Immunization in 1974, the incidence of diphtheria dropped by more than 90% from 1980 to 2000 worldwide[2]. In 2019, the national coverage of complete childhood vaccination in Indonesia, including the diphtheria vaccine, reached 93.7%. Despite the rising trend of vaccine reluctance stemming from the coronavirus disease 2019 (COVID-19) pandemic, the vaccination coverage for diphtheria in 2023 remains comparatively high at 84.63%[3,4]. Nevertheless, epidemiological data revealed discrepancies between the vaccination coverage and the incidence of diphtheria cases. By 2023, the incidence rose to 949 cases, which has increased from 541 cases in 2022, including incidence among vaccinated children[4]. Moreover, new outbreaks linked to displaced populations and infrastructural deficiencies highlight the persistent threat of diphtheria[5].

Summary

Question: In healthy infants aged two months old, what is the effect of dosing intervals of DTwP-HB-Hib vaccination on the immunogenicity of the diphtheria antibody?

Findings: Following three doses of the vaccination, the anti-diphtheria IgG antibody level was (1.320±0.234) IU/mL in the eight-week interval group and (1.307±0.186) IU/mL in the four-week interval group, with no statistical difference.

Meaning: DTwP-HB-Hib vaccinations may be given at eight- or four-week intervals, as they do not substantially influence the level of anti-diphtheria IgG antibody.

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It is acknowledged that different individuals may exhibit varied responses to vaccinations. Several factors are known to generate humoral and cellular immune responses in humans[6]. Comprehending the elements that influence this variability is essential for forecasting vaccine efficacy and refining immunization programs. Genetic variations pertaining to immune system genes and environmental factors, including prior exposure to the pathogen, underlying health conditions, and lifestyle choices, significantly influence vaccine responses, alongside the characteristics of the pathogen and vaccine formulation, as well as individual immune responses. The timing and interval of vaccination doses, along with the application of adjuvants, significantly influence the immune response and ensuing protection[7]. In Indonesia, the recommended schedule for diphtheria-tetanus-pertussis (DTP) vaccination is at four-week intervals (two, three, and four months of age) for children under one year old, followed by a booster dose at eighteen months and five to seven years old[8]. The Centers for Disease Control and Prevention (CDC) recommends a course of five diphtheria-tetanus-acellular pertussis (DTaP) series administered at two, four, six, fifteen, and eighteen months, with an additional dose between four and six years of age[9]. On the other hand, the WHO recommends a dosage interval for DTP vaccinations ranging from four to eight weeks[10]. Research in Jakarta indicated that 68%-81% of children achieved long-term immunity (>0.1 IU/mL) following the administration of the DTP vaccination at four-week intervals[11]. However, in a US research where children received four doses of the DTP vaccine at 2, 4, 6, and 15-17 months of age, following the third dose, 100% (1 099 children) attained diphtheria antitoxin levels of ≥0.01 IU/mL, and 98.5% achieved levels of ≥0.10 IU/mL[12,13].

There is no evidence of the immunogenicity of the diphtheria vaccination from the diphtheria-tetanus-whole-cell pertussis (DTwP) vaccine at four weeks compared to the eight-week interval. The optimal vaccination interval against diphtheria for enhanced protection has yet to be established. This study aims to compare the anti-diphtheria toxoid immunoglobulin G (IgG) antibody levels before and after DTwP, hepatitis B, and *Haemophilus influenzae* type b (DTwP-HB-Hib) vaccination at four-week and eight-week intervals, offering recommendations regarding the appropriate vaccination interval.

2. Subjects and methods

2.1. Study setting and design

This is a randomized, open-label, parallel, controlled trial with 1:1 allocation ratio on healthy infants aged two months old who had not received DTwP-HB-Hib vaccinations which was carried out in two primary healthcare centers in Palembang, Indonesia from March to September 2021.

2.2. Sample criteria and size calculation

Healthy infants aged two months who had not previously received DTP vaccination, and whose parents provided written informed consent to participate in the study were included. On the other hand, the exclusion criteria consist of infants who have already received diphtheria and those with contraindications regarding the administration of DTwP-HB-Hib vaccines. The dropout criteria were infants who failed to attend scheduled appointments, declined to complete the study, relocated from Palembang during the study, switched to the DTaP vaccine, experienced a severe adverse reaction to the vaccine, died during the study, or had insufficient or inadequate blood samples.

The sample size was determined using the formula for unpaired numerical comparative tests of two groups with an α of 0.05, β of 0.2, the standard deviation of mean diphtheria immunoglobulin levels at four-week intervals of 0.27[14], and the minimum effect size expected by the researcher of 0.2. Therefore, 60 participants will be needed.

2.3. Randomization and intervention

Study subjects were selected from two community health centers in Palembang, Indonesia, using multistage random sampling and employing randomization using a draw box. The authors determined the treatment for each study subject by block randomization of ABBA, ABAB, AABB, and BBAA patterns. Each subject will be assigned to either the control or intervention groups. The control group will receive three doses of the DTwP-HB-Hib vaccine at four-week intervals, whereas the intervention group will receive the DTwP-HB-Hib vaccine at eight-week intervals. The administered DTwP vaccine was manufactured by PT Biofarma and provided with charge as part of the national immunization program.

Prior to the initial administration of the DTwP vaccination, blood samples were collected from the study subjects. The samples were centrifuged, and the plasma was collected for storage at 2 ℃-8 ℃. Following administering three doses of DTwP-HB-Hib vaccinations, blood samples were collected and centrifuged, and the plasma was preserved at 2 ℃-8 ℃. Proper sample handling and storage were conducted per the standard operating procedures (SOP). The level of anti-diphtheria toxoid IgG antibodies was then measured using an enzyme-linked immunosorbent assay (ELISA) kit.

2.4. Statistical analysis

Data were subsequently analyzed utilizing SPSS version 27. Descriptive statistics encompass the baseline characteristics of study participants, including sex, breastfeeding status, and birth weight. The interpretation of the anti-diphtheria toxoid IgG antibody levels is as follows: ≥1.0 IU/mL indicates long-term immunization protection, ≥0.1 IU/mL signifies the presence of immunization protection, 0.01-0.099 IU/mL reflects uncertain protection, and <0.01 IU/mL denotes no protection. The IgG antibody levels among the groups were

compared at the beginning and after administering three vaccine doses using the independent test for normally distributed data or the Mann-Whitney *U* test for non-normally distributed data. The adverse effects after vaccination were evaluated using the *Chi*-square test or Fisher's exact test when the conditions for the former were not met.

2.5. Ethics and clinical trial registration

The ethical approval for this research was granted by the Research Ethics Committee of the Faculty of Medicine at Universitas Sriwijaya (Approval number: 018-2021) on 20th January 2021. Informed consent was obtained from all guardians before participation in compliance with institutional and national ethical standards. This study was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000058407) on 9th July 2025.

3. Results

The study was done from March to September 2021. Eighty subjects were enrolled at the beginning of the study, where 36 and 44 subjects were randomized to receive DTwP-HB-Hib vaccinations at eight-week or four-week intervals, respectively. Twelve subjects declined to participate in the second sampling, three subjects' blood samples got lysis, and one subject's sample was insufficient, making 64 subjects fulfilled the study requirements (Figure 1). Most are female (34/64; 53.1%) and exclusively breastfed (43/64; 67.2%). The mean birth weight was 3.1 kilogram. The characteristics of the study subjects can be seen in Table 1.

Table 1. Characteristics of the study subjects [*n* (%)].

Characteristics	8-week interval, (*n*=32)	4-week interval, (*n*=32)	*P* value
Sex			
Male	16 (50.0)	14 (43.8)	0.616[a]
Female	16 (50.0)	18 (56.3)	
Breastfeeding			
Exclusive breastfeeding	22 (68.8)	21 (65.6)	0.790[a]
Non-exclusive breastfeeding	10 (31.3)	11 (34.4)	
Birth weight (mean±SD; kilogram)	3.147±0.324	3.103±0.308	0.582[b]

[a]*Chi*-square test, [b]independent sample *t*-test. Significant if $P<0.05$.

All study participants exhibited uncertain protection against diphtheria (anti-diphtheria toxoid IgG antibody levels of 0.01-0.99 IU/mL) at the beginning of the study. On the other hand, all subjects showed long-term protection (anti-diphtheria IgG antibody levels of ≥0.1 IU/mL) after the third vaccine administration. No statistical differences were found between the groups before and after intervention ($P>0.05$). Further findings can be found in Table 2 and Figure 2.

Table 2. The anti-diphtheria toxoid IgG antibody level in the 4-week and 8-week interval groups.

Anti-diphtheria toxoid IgG antibody level (IU/mL)	Mean±SD	Median (Min-Max)	Between-group effect size (4- and 8-week) (95% *CI*)	*P* value
Pre-intervention				
8-week interval	0.023±0.009	0.025 (0.01-0.04)[b]	0.000 (0.000–0.010)[c]	0.285[c]
4-week interval	0.026±0.009	0.030 (0.01-0.04)[b]		
Post-intervention				
8-week interval	1.320±0.234[a]	1.28 (1.01-1.92)	-0.013 (-0.118–0.093)[d]	0.814[f]
4-week interval	1.307±0.186[a]	1.25 (1.02-1.82)		

[a]Normally distributed data, [b]non-normally distributed data, [c]Hodges–Lehmann median difference, [d]mean difference, [e]Mann-Whitney *U*-test, [f]independent sample *t*-test. Significant if $P<0.05$.

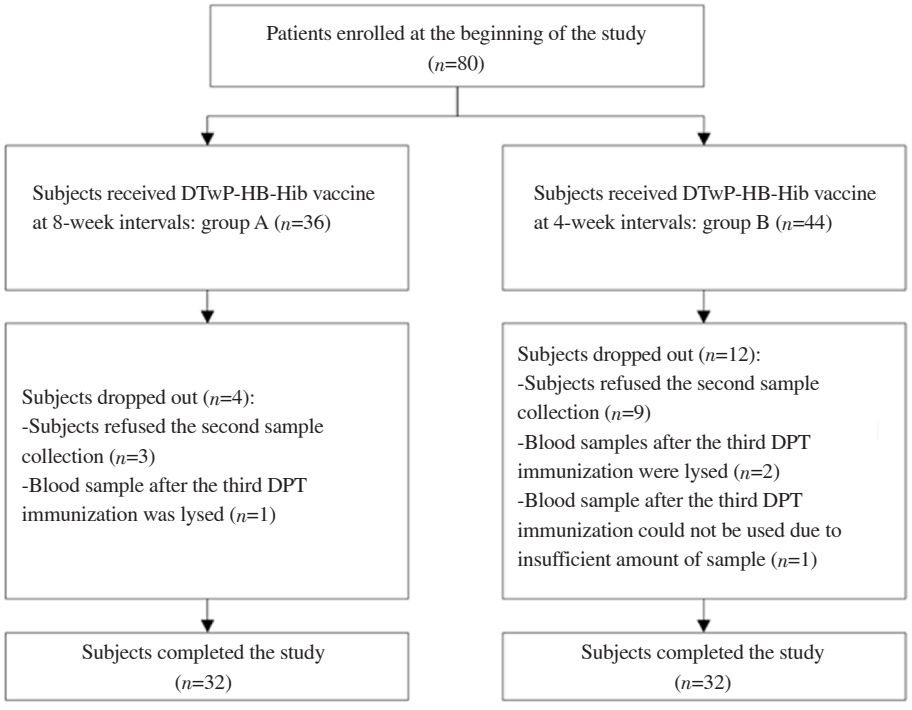

Figure 1. Trial workflow.

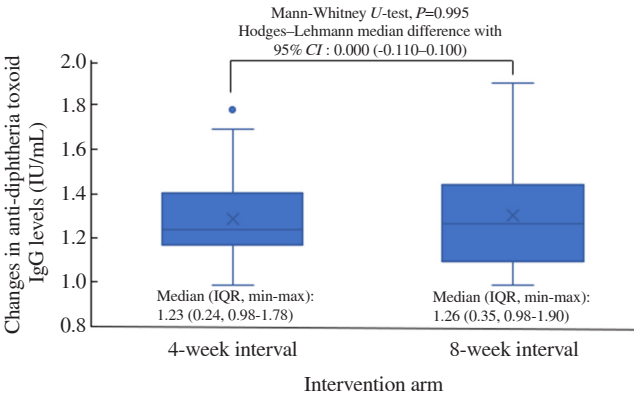

Figure 2. Changes in anti-diphtheria toxoid IgG levels after the third dose administration of DTwP-HB-Hib vaccination.

No severe adverse reactions were seen among 64 study subjects following vaccination in this research. No adverse reactions were observed in the study subjects 30 minutes post-vaccination. Local edema at the injection site occurred in less than 20% of the subjects. Local pain at the injection site was observed in 12.5% of patients following the first DTwP vaccine, with the prevalence diminishing after the second and third doses of DTwP. Table 3 indicated that the incidence of local pain following the first dose of the DTwP vaccine was significantly higher in the 4-week interval group compared to the 8-week interval group (P=0.027). Post-vaccination fever occurred in 29.7% of subjects following DTwP-1, with a subsequent decline observed after the second and third doses. No subject developed seizure subsequent to vaccination.

4. Discussion

This study aims to evaluate whether different dosing intervals of the DTwP-HB-Hib vaccine have a different effect on the immunogenicity of the diphtheria component. Prior to the vaccination, the anti-diphtheria IgG levels of all study participants ranged from 0.01 to 0.099 IU/mL, indicating uncertain protection against diphtheria. Following the administration of three doses of DTwP-HB-Hib vaccines, all study participants reached an anti-diphtheria IgG level of >1.0 IU/mL, regardless of the dosing interval, which indicates that the infants have long-term vaccination protection against diphtheria. A comparable result to this study was observed in a previous study by Fadlyana *et al*. in 2016, which examined 160 healthy infants and compared the level of anti-diphtheria IgG before and after administering the DTP vaccine[11]. They found that the mean geometric titer (GMT) against diphtheria before the DTP vaccine was 0.008 IU/mL (no protection) and rose to a level of 0.217 IU/mL (under immunization protection) after three doses of the DTwP vaccine[11]. This result was also supported by Rusmil *et al*., who found that infants aged 6-11 weeks old had a level of >0.01 IU/mL (99.7% of all subjects) or >0.1 IU/mL (84% of all subjects) after the administration of three doses of DTP with a four-week interval[14].

Research investigating the impact of different interval on immunogenicity of diphtheria components is uncommon. At the end of this study, no significant difference was observed in anti-diphtheria toxoid IgG antibody levels between the eight-week and four-week interval groups (P=0.814). This outcome aligns with the study by Conway *et al*., which examined the impact of varying DTP and polio vaccination intervals on the immunogenicity of infants born at ≤31 weeks of gestation[15]. The vaccination schedules were as follows: group A received vaccinations at three, four, and five months; group B at three, four, and five months with a booster at eighteen months; and group C at three, four, and ten months. All participants demonstrated sufficient immunity to diphtheria one month post-third immunization, with no statistically significant differences in mean antibody titers. However, the outcome differed in the ≥32 weeks of gestation category, as statistically significant differences were observed between group A and C, with higher antibody titers in group C[15]. In addition, a 1987 study in the US by Wilkins *et al*. revealed that children with the DTP vaccine given at eight-week interval had higher antibody titers compared to those who received the shots at 3-7 week interval[16]. On the other hand, in 1992, Booy *et al*. compared the immunogenicity of the DTP vaccine given with a schedule of two, three, and four months *versus* three, five, and nine months in the UK[17]. Similar to this study, they first discovered that the antibody level reached a protective level in all groups after vaccination. Nevertheless, they further found that the mean GMT of the diphtheria antibody was 7 IU/mL in the two, three, and four-month intervals and 3.87 IU/mL in the three, five,

Table 3. Side effects after the administration of DTwP-HB-Hib vaccination [*n* (%)].

Vaccine	After 1st dose of the DTwP-HB-Hib vaccine			After 2nd dose of the DTwP-HB-Hib vaccine			After 3rd dose of the DTwP-HB-Hib vaccine		
side effects	8-week interval	4-week interval	*P*-value*	8-week interval	4-week interval	*P*-value*	8-week interval	4-week interval	*P*-value*
Local									
Pain	1 (3.1)	7 (21.9)	0.027	1 (3.1)	3 (9.4)	0.306	0 (0.0)	2 (6.3)	0.246
Edema	1 (3.1)	3 (9.4)	0.306	1 (3.1)	3 (9.4)	0.306	0 (0.0)	1 (3.1)	0.500
Systemic									
Fever	12 (37.5)	7 (21.9)	0.137	8 (25.0)	6 (18.8)	0.382	7 (21.9)	5 (15.6)	0.375

*Data were analyzed using Fisher exact test. Significant if P<0.05.

and nine-month intervals. They suggested that administering the DTP vaccination at 4-week intervals yielded higher antibody levels.

The variation in intervals may influence vaccines' immunogenicity because longer interval could facilitate the production of more antibodies, hence potentially providing superior protection to individuals. The discrepancies in the results observed between this study and the prior study might be attributed to numerous factors. First, the genetic factor is a determinant influencing the immunogenicity of vaccinations[7]. This may also explain why DTwP-HB-Hib or other vaccines are advised to be administered on varying schedules across different countries, as the schedules are tailored to the response from the society. Previous studies evaluating the interval of DTP vaccines were undertaken in the US and the UK, while this study explores the immunogenicity of vaccines within the Indonesian population. Consequently, genetic heterogeneity and lifestyle variations stemming from cultural differences may account for the discrepancies. Moreover, the prior studies differed from the interval examined in this research. Wilkins *et al*. compared the vaccine interval of eight weeks *versus* three to seven weeks, whereas Booy *et al*. compared the interval of four-week against eight or sixteen-week interval[16,17]. Therefore, none of these prior studies are genuinely comparable to this study.

This study utilized DTwP vaccines, which have been proven by multiple reliable investigations, to elicit greater adverse reactions than the DTaP vaccine[18]. In this study, the most common side effect experienced by the subject was fever (23.4%), followed by localized pain at the injection site (7.3%). This finding differed from Jong *et al*., who identified fever and irritability as the predominant side effects following the administration of the DTwP vaccine at five-week intervals[19]. In this study, no seizure side effects were recorded. This finding was similar to the study in Lithuania that administered DTP at a six-week interval and the study in Spain that administered the vaccine at an eight-week interval[20,21]. No studies before had compared the incidence of adverse effects on DTP administration with different dosing interval.

Based on this study, the incidence of localized pain at the injection site was significantly higher in the four-week interval group compared to the eight-week interval group after DTwP-1. Two studies by Gustaffson *et al*. (1996) and Greco *et al*. (1997) studied the reactogenicity of the DTwP vaccine compared to the DT vaccine given at an eight-week interval[22,23]. Gustaffson *et al*. studied the adverse events 24 hours post-vaccination, while Greco *et al*. studied the adverse events 48 hours post-vaccination[22,23]. These two studies concluded that the incidence of fever (>38 ℃) was twelve times higher after DTwP administration, and the incidence lowered after the second and third dose. The incidence of local reactions such as pain, edema, and redness at the injection site was also higher in DTwP than DT vaccines; then, the incidence diminished in the following doses. This finding was supported by Barkin *et al*. study in 1985, who found that the fever risk was eleven times higher, and the risk of local side effects were three times higher in the DTwP vaccine than in DT[24]. Study by Cody *et al*. also reported an increased risk of fever, irritability, pain, and edema 48 hours after DTwP vaccination by two to five fold[25]. This evidence was in line with the finding of this study, where fever occurred in 29.7% of study participants after the first dose, and the incidence was lowered on the following doses.

One of the limitations of this study is that the sample size of this study is relatively small. Several participants did not finish the research and were classified as dropouts. Factors such as lysed blood samples have been mitigated by researchers by adhering to appropriate sampling and transportation protocols as outlined in the SOP for handling DTwP-HB-Hib vaccinations. Another limitation is that the vaccine used in our study was a combination of DTwP-HB-Hib. Therefore, our findings may not be generalized to other diphtheria vaccines that come in a different combination form.

To summarize, this study found no significant difference between the anti-diphtheria toxoid IgG levels after DTwP-HB-Hib vaccination at four-week *versus* eight-week intervals. In both groups, the IgG levels increase from uncertain protection to long-term protection after three doses of DTwP-HB-Hib vaccines. Our study recommends that DTwP-HB-Hib vaccines can be administered at either four-week or eight-week intervals between doses. In addition, our findings suggest that a four-week interval provides immunogenicity comparable to that of an eight-week interval, potentially enabling faster coverage and earlier protection. In the future, further studies can also be done with larger sample size to follow study subjects and measure their anti-diphtheria IgG level at six months after their third dose of DTwP.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Authors' contributions

A.K. developed the study design and theoretical formalism. A.K. and M.Y.R. performed data collection. M.Y.R. performed data analysis. A.K. wrote the first draft of the manuscript. M.D. and Y.I. contributed in theoretical formalism and manuscript editing. All authors read and approved the final manuscript.

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