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Original Article

Hepatitis B seroprotection in children aged 10 – 15 years after completion of basic hepatitis B immunizations

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Abstract

Background The prevalence of hepatitis B viral (HBV) infection in Indonesia is high. The most effective way to control HBV infection is by hepatitis B (HB) immunization. Many studies reported that hepatitis B surface antibody (anti-HBs) seroprotection declines in children > 10 years of age. In addition many factors can influence anti-HBs titer.

Objective To measure anti-HBs titer and evaluate possible factors associated with anti-HBs titer.

Methods This cross sectional study was conducted in children 10-15 years of age from ten schools at Tuminting District, Manado, North Sulawesi, from October to November 2014. All subjects had completed the hepatitis B immunization scheme. By stratified random sampling, 105 children were selected as subjects. Data was analyzed with SPSS version 22.

Results From 48 schools, we selected 10 schools from which to draw a total of 105 children, but only 23 (21.9%) children had detectable anti-HBs . Of all subjects, 76 (72.4%) were female, 78 (74.3%) had good nutritional status, and 98 (93.3%) had birth weight ≥2,500 grams. Data from immunization record books showed that 26 (24.8%) subjects received the HB-1 vaccination at ≤7 days of age and 45 (42.9%) subjects had a ≥2 month interval between the HB-2 and HB-3 vaccinations. Multivariate analysis showed that administration of HB-1 at ≤7 days of age and a ≥2 month interval between HB-2 and HB-3 had significant associations with anti-HB seroprotection in children.

Conclusion A low proportion of subjects who had completed the hepatitis B immunization scheme had detectable anti-HBs titer (21.9%). Administration of HB-1 at ≤7 days of age and a ≥2-month interval between HB-2 and HB-3 vaccinations are important factors in anti-HB seroprotection in children aged 10-15 years. **[Paediatr Indones. 2017;57:76-83. doi: http://dx.doi.org/10.14238/pi57.2.2017.76-83]**.

Keywords: *seroprotection; anti-HBs titer; factors influencing anti-HBs titer*

Hepatitis B viral (HBV) infection is a global issue because it causes severe complications, such as liver cirrhosis, portal hypertension, and hepatocelluler carcinoma.[1] *The World Health Organization* (WHO) reported that approximately 900 million people are infected with hepatitis B (HB) and 378 million people are carriers. Each year, 620,000 people with hepatitis B die. Indonesia has been classified as a moderate- to high- prevalence area, with a mean of 9.4%, indicating that 1 in 10 of Indonesia's population have been infected with HBV.[2,3] In high endemic regions, infection often occurs at an early age and is transmitted vertically from mother to child or horizontally from chronic carriers who live in the same house.[4,5] Data from the *Indonesian Ministry of Health* in 2000 showed an HBV vertical transmission of 45.9% from mother to infant, mainly occurring at birth.[6] To date, the most effective way to control HBV infection is by HBV immunization. Although seroprotection titers decline with increasing age, the immune

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memory does not wane. Evidence of the above was found in a Thai study in children who were given the recombinant HB vaccine in infancy. Protective anti-HBs titers were found in 89.8% of subjects at the age of 5 years.[7] Given that the epidemiological pattern of HB in Indonesia is similar to that in Thailand, it can be concluded that booster immunizations at age of 5 years are not needed.[8] However, other studies showed that protective anti-HBs titers at the of age 10-12 years were only 12% - 47.9%.[9-15] In addition, the *Ministry of Health* figures in 2013 show coverage of the third dose of hepatitis B immunization in Indonesia is only 75.6%, which is still below the level of minimum protection (80%).[16]

Past studies have provided evidence that many factors can influence anti-HBs titers, such as age, sex, nutritional status, birth weight, administration of HB-1 at ≤ 7 days or >7 days, an interval between HB-2 and HB-3 of <2 months or ≥2 months, maternal age at delivery, maternal education level, and parental socioeconomic level.[9,13,17-23] Yet study on factors that influence anti-HBs titers are still rare. However, anti-HBs titers varied among studies, and, to our knowledge, a study of this type has never been conducted in Manado. As such, we aimed to evaluate anti-HBs titers and some possible associated factors.

Methods

This cross sectional study was conducted from October to November 2014 in children aged 10-15 years at the elementary, junior, and high schools in Tuminting District, Manado, North Sulawesi. Subjects were chosen randomly with stratified random sampling. Inclusion criteria in this study were: 1) children in good health, 2) had completed the HB basic immunization scheme (3 times) with an interval between HB-1 and HB-2 of 4-8 weeks and at a maximum of 12 months of age, 3) had approval from parents/guardians to participate in the study by signing a consent form following the study and approval of medical action, 4) had an health and immunization book/card (Kartu Menuju Sehat/KMS). Exclusion criteria were children with: 1) positive HBsAg, 2) malignant disease (leukemia, osteosarcoma, or lymphoma), chronic liver disease (cholestasis or HB), diabetes mellitus, diseases of immunodeficiency (HIV), chronic diseases (tuberculosis), chronic kidney disease requiring dialysis, hematology abnormalities requiring serial blood transfusion and immunosuppressant treatment use, or 3) a narcotic drug user (marijuana, morphine, or methamphetamine).

The minimum required sample size was estimated to be 97. This study was approved by the Research Ethics Committee of Sam Ratulangi University Medical School. Seroprotection status was classified as either an anti-HBs titer of ≥ 10 mIU/mL, categorized as responders (seroprotected), or an anti-HBs titers of <10 mIU/mL, categorized as non-responders. The responders were further categorized again as hyporesponder (anti-HBs titers 10-100 mIU/mL) or good responders (anti-HBs titers >100 mIU/mL). Data was analyzed with *SPSS version 22*. Bivariate data were analyzed using Chi-square and Mann Whitney test, followed by multivariate analysis, for results with P<0.05. Multivariate analysis was used to look for significance and regression coefficients. A P value <0.05 was considered to be statistically significant.

Results

This study was conducted in children aged 10-15 years at the elementary, junior, and high schools at Tuminting District, Manado, North Sulawesi. Of the 48 schools in the area, 105 study subjects were randomly chosen from 10 schools.

Characteristics of study subjects are shown in **Table 1**. Of the 23 seroprotected children, only two children had anti-HBs titers ≥ 100 mIU/mL. Two out of 105 subjects (1.9%) had mothers with a history of HBV infection. The 23 seroprotected subjects were further divided into groups based on the vaccination interval between HB-2 and HB-3, <2 months (2 subjects) and ≥2 months (21 subjects). Of the 21 subjects in the ≥2 month interval group, we found that the vaccination interval between HB-2 and HB-3 was 2 months for 10 subjects (mean anti-HBs titers 24.81 mIU/mL), 3 months for 7 subjects (mean anti-HBs titer 44.78 mIU/mL), 4 months for 1 subjects (anti-HBs titer 18.54 mIU/mL), 5 months for 1 subject (anti-HBs titer 51.27 mIU/mL), 6 months for 1 subject (anti-HBs titer 101.05 mIU/mL), and 8

Table 1. Study subjects characteristics based on age

Characteristics	Age (years)						Total N=105
	10 n=18	11 n=18	12 n=15	13 n=19	14 n=18	15 n=17	
Gender, n(%)							
Male	6	2	5	5	9	2	29 (27.6)
Female	12	16	10	14	9	15	76 (72.4)
Nutritional status, n(%)							
Undernutrition	7	7	1	5	4	3	27 (25.7)
Good nutrition	11	11	14	14	14	14	78 (74.3)
Birth weight, n(%)							
< 2,500 g	3	0	1	2	1	0	7 (6.7)
≥ 2,500 g	15	18	14	17	17	17	98 (93.3)
HB-1 administration, n(%)							
≤ 7 days	3	7	4	2	4	6	26 (24.8)
> 7 days	15	11	11	17	14	11	79 (75.2)
Interval between HB-2 and 3, n(%)							
< 2mo.	10	10	5	10	10	15	60 (57.1)
≥ 2 mo.	8	8	10	9	8	2	45 (42.9)
Maternal age at delivery, n(%)							
< 20 yrs	3	1	0	3	3	0	10 (9.5)
20-35 yrs	13	15	14	15	13	16	86 (81.9)
> 35 yrs	2	2	1	1	2	1	9 (8.6)
Maternal education, n(%)							
Elementary	2	3	2	1	0	0	8 (7.6)
Junior High	3	2	6	6	5	4	26 (24.8)
Senior High	12	12	7	10	12	11	64 (60.9)
College	1	1	0	2	1	2	7 (6.7)
Family income, n(%)							
< 2 million IDR/month	7	3	5	6	2	3	26 (24.8)
≥ 2 million IDR/month	11	15	10	13	16	14	79 (75.2)
Anti-HBs titer*, n(%)							
≥10 mIU/mL	5	5	4	2	4	3	23 (21.9)
< 10 mIU/mL	13	13	11	17	14	14	82 (78.1)

months for 1 subject (anti-HBs titer 48.84 mIU/mL) (data not shown).

Bivariate analysis of factors influencing anti-HBs titer are shown in **Table 2**. We found that children in the reactive group had better nutritional status compared to children in non-reactive group. Among subjects in non-reactive group, we found more children who received the Hb-1 vaccination at >7 days and the interval between Hb-2 and Hb-3 vaccination was < 2 months.

Multivariate analysis of factors influenced anti-HBs titer are shown in **Table 3**. We found the HB-1 vaccination at ≤7 days of age, and a ≥ 2 month interval between the HB-2 and HB-3 vaccinations were the significant factors that influencing anti-Hbs titer.

Discussion

We designed this study to be conducted on children aged 10-15 years, due to evidence contradictory to the *European Consensus Recommendations* (ECR) that HB seroprotection lasts for at least 10 years. Moreover, the ECR found that although anti-HBs titers decline considerably with age, even to negative values, a person is still clinically protected from chronic illness due to in vitro immunologic memory that still provides protection. As such, the booster is said to be no longer needed for people who received the complete basic HB immunizations.16 However, the reality on the ground shows that despite the HB immunization program having been implemented throughout Indonesia since 1997, the prevalence of HB infection

Table 2. Bivariate analysis of factors associated with anti-HBs titer

Characteristics	Anti-HBs titer		Relative risk (95%CI)	P value
	Non reactive n=82	Reactive n=23		
Child's age, n(%)				
10 years	13 (15.9)	5		0.159
11 years	13 (15.9)	5		
12 years	11 (13.4)	4		
13 years	17 (20.8)	2		
14 years	14 (17.0)	4		
15 years	14 (17.0)	3		
Mean age (SD), years	12.59 (1.71)	12.17 (1.78)		
Gender, n(%)				
Male	21 (25.6)	8	0.65	0.192
Female	61 (78.1)	15	(0.24 to 1.74)	
Nutritional status				
Under-nutrition	18 (21.9)	9	2.29	0.048
Good nutrition	64 (78.1)	14	(0.85 to 6.13)	
Birth weight, n(%)				
< 2,500 g	5 (6.1)	2	1.47	0.329
≥ 2,500 g	77 (93.9)	21	(0.27 to 8.10)	
HB-1 administration, n(%)				
≤ 7 days	14 (17.0)	12	1.47	0.329
> 7 days	68 (83.0)	11	(0.27 to 8.10)	
Interval between HB-2 and -3, n(%)				
< 2 months	58 (70.0)	2	5.3	0.001
≥ 2 months	24 (29.3)	21	(1.95 to 14.4)	
Socioeconomic level, n(%)				
< 2 million IDR/month	25 (30.5)	1	0.1	< 0.001
≥ 2 million IDR/month	57 (69.5)	22	(0.01 to 0.8)	
Maternal age at delivery, n(%)				
< 20 years	8 (9.8)	2		0.494
20-35 years	67 (81.7)	19		
> 35 years	7 (8.5)	2		
Maternal education level, n(%)				
Elementary	8 (9.8)	0		0.239
Junior High	20 (24.4)	6		
Senior High	49 (59.7)	15		
College	5 (6.1)	2		

Table 3. Multivariate analysis of factors influencing anti-HBs titer

Variables	Regression coefficient (B)	P value
Administration of HB-1 at ≤ 7 days or > 7 days	2.223	0.02
Interval between HB-2 and -3 distance < 2 mo. or ≥ 2 mo.	3.614*	< 0.001
Parental socioeconomic level	2.289*	0.96
Nutritional status	1.742	0.076

*=negative

in Indonesia remains high at 9.4%.[2,24] This evidence is also supported by the numbers of HB-0 immunization coverage in Indonesia at only 79.1% and DPT-HB-3 at 75.6%. Hence, the minimum standard of protection of 80% has not been reached.[16]

In addition to several previous studies, it is known that anti-HBs titers (seroprotection) decline in children with age (age ≥10 years), which varies from 12-47.9%.[9-12,14,15] Furthermore, Rathore found 24 subjects infected with HBV despite getting complete basic HB immunizations, so he suggested that the administration of a booster is needed to eradicate HB infection.[25]

In this study, titers of anti-HBs ≥ 10 mIU/mL were as follows: at age 10 years 5/18 (27.8%), age 11 years 5/18 (26.3%), age 12 years 4/15 (23.5%), age 13 years 2/19 (10.5%), age 14 years 4/18 (22.2%), and age 15 years was 3/17 (17.6%), with a mean total seroprotection at ages 10-15 years of 23/105 (21.9%).

The latest data indicate that protection after HB immunization did not last long term. However, we do not know whether the subjects in this study had formed anti-HBs that later declined, or did not have anti-HBs from the beginning, because we did not have subjects' initial data. Our findings regarding subjects with anti-HBs titers ≥ 10 mIU/mL were similar to those from other studies: Eldesoky *et al.*[11] at age >10 years were 33.3%, Lin *et al.*[14] at age > 12 years were 37.4%, Suraiyah *et al.*[15] at the age of 10-12 years were 38%, and Aswati *et al.*[9] at age 12 were 35%.

We found that 82 children had titers of anti-HBs <10 mIU/mL, while 23 children had seroprotection, with anti-HBs seroprotection titers ranging from 10.07 to 118.01 mIU/mL as well as the average of 36.45 (SD 29.21) mIU/mL (data not shown). Of the 23 seroprotective children, 21 children had anti-HBs titers <100 mIU/mL, while only 2 children had anti-HBs titers ≥ 100 mIU/mL (data not shown). Hence, the majority of children in this study (78.7%) were non-responders (anti-HBs titers <10mIU/mL); 21 children (19.4%) were hyporesponder; and only 2 children (1.9%) were good responder.22,26 We provided a booster for the 82 non-responders in accordance with the recommendation of the *Immunization Task Force of the Indonesian Pediatrics Society* (IPS).[27]

We also found that 3/105 children (2.8%) had mother with a history of HB infection, and from that, two children had titers <10 mIU/mL, but one child had anti-HBs titers ≥ 10 mIU/mL, so that the children with no seroprotection needed to be given HB booster immediately, because 45.9% HBV can be transmitted to the babies.[28,29]

We examined factors with potential to influence anti-HBs titers, such as age of the child at the time of examination of anti-HBs titers, sex, nutritional status, birth weight, administration of HB-1 at ≤ 7 days or >7 days, interval between HB-2 and HB-3 of <2 months or ≥2 months, maternal age at delivery, maternal education level, and parental socioeconomic level. Bivariate analysis of risk factors using Chi-square test revealed a significant relationship between seroprotection and administration of HB-1 ≤7 days, interval between HB-2 and HB-3 of ≥2 months, parental socioeconomic status, and child's good nutritional status. Further analysis with logistic regression revealed a highly significant positive correlation between seroprotection and interval between HB-2 and HB-3 of ≥2 months and in administration HB-1 ≤7 days, but no significant relationship between anti-HBs titers and parental socioeconomic level or nutritional status.

We observed a trend in declining anti-HBs titer with increasing age, though no statistically significant relationship was found. Similarity, Aswati *et al*. found no relationship between age and anti-HBs titers.9 In contrast, Whittle et al. found that anti-HBs titers were associated with age, where older children having lower titers (P<0.05).[30] We found no significant relationship between anti-HBs titers and gender, similar to a study by a previous study.[21] In contrast, studies in Iran and China showed that women had higher antibody responses than men.[31,32] In addition, another study showed a decline in the number of T-lymphocytes in males compared to females, with males having lower serum titers of IgM and IgG than females.[30] Differing immune responses in men and women were theorized be influenced by the sex steroid hormones, such as estrogen, progesterone, and testosterone.[33] We also found no correlation between anti-HBs titers and birth weight. This finding contrasts with the theory that low birth weight (LBW) and/or premature infants, have a low antibody titers due to passive immunity through maternal transmission, low complement level, macrophage function, and chemotactic response, as well as a lack of membrane deformability.[19] We found no relationship between the maternal age at delivery and anti-HBs titer, but there was a tendency that mother with lower educational level and age <20 years lacked knowledge and psychological readiness in child care, which may have affected the titer of anti-HBs.[34]

The immunization schedule had a significant positive relationship with anti-HBs titers, i.e., HB-1 administration at the age of ≤7 days and the interval between HB-2 and HB-3 of ≥2 months. A cross-sectional study by Mohammed et al. compared two immunization HB schedules and found that immune responses were similar in children who used an immunization schedule of 3, 4, and 9 months and one of 0, 2, and 9 months.[35] In addition, Damme et al. assessed anti-HBs titers 5 years after HB immunization, comparing two immunization schedules. Group A received HB vaccinations at 0 and 6 months, while group B received them at 0, 1, and 6 months. In the age group of 11-15 years, they observed anti-HBs titers of >10 mIU/mL in 79.5% of

group A and 91.4% of group B.[36]

Infants who received HB-1 immunization immediately after birth had higher seroprotection titer than other babies.[37] We found a significant association in seroprotected HB titers in infants immunized at ≤7 days compared to infants immunized at >7 days of age. However, when viewed from a number of children who are reactive after given the HB-1 ≤ 7 days in 12/23 children (52.2%) and non-reactive in 14/82 children (17.0%), this data shows there is almost no difference in the percentage and it demonstrates that the titer anti-HBs on the administration of HB-1 ≤ 7 day likely influenced by other factors.

The third dose is a determinant of antibody response as a booster dose, the longer the interval between the second and third immunizations (4-12 months), the higher the antibody titer.[37-39] We found a significant positive association between higher HB titers at an interval between HB- 2 and HB-3 immunizations of ≥ 2 months. However, when seen from the number of children who are reactive at interval of HB-2 and HB-3 immunization ≥ 2 months in 21/23 children and non-reactive in 24/82 children (29.3%), this data shows there is almost no difference in the percentage and this indicates that the anti-HBs titers at interval of HB-2 and HB-3 immunization ≥2 months likely influenced by other factors. Handayani *et al.*[40] reported a significant difference between administration of the first dose of HB vaccine at the age of ≤7 days and age> 7 days on anti-HBs titers (64.92 mIU/mL vs. 145.56 mIU/mL, respectively; P=0.038), but no relationship between HB-2 and HB-3 immunization interval and anti-HBs titers. Hepatitis B immunization at less than one week of age is intended to prevent vertical transmission from mother to baby, especially for women testing positive for HBsAg.

We found no correlation between anti-HBs titers and nutritional status of children in the multivariate analysis, although bivariate analysis show significant correlation. This result showing a nutritional status at the time of the study hence does not affect anti-HBs titers formation. A limitation of our study was that we did not obtain sufficient data to determine the subjects' nutritional status at the time they received basic HB immunizations. A Tanzanian study on children aged <5 years found 70.3% had good nutritional status, but there was no significant relationship between nutritional status and anti-HBs titers.[41] An Egyptian study examined the relationship between malnutrition and HB vaccine response in 27 infants with kwashiorkor or marasmus, and 13 healthy babies in the control group. Anti-HBs titers were significantly higher in the control group.[42]

A higher percentage of reactive subjects (95.7%) had higher parental socioeconomic status than non-reactive subjects (69.5%), but this finding was not significant on multivariate analysis. Ochirbat et al. found that children with socio-economically disadvantaged parents tended to lose seroprotection against HB compared to children of parents with good socioeconomic level.[17]

A limitation of this study was that we did not conducted HBsAg examintations on study subjects, therefore, we do not know if anti-HBs titers increased as a result of the subjects being naturally exposed to HB, or as a result of HBV immunization.

In conclusion, children aged 10-15 years have low seroprotection (21.9%) and administration of HB-1 at ≤7 days and an interval between HB-2 and HB-3 of ≥2 months are important factors associated with higher HB seroprotection. Based on our findings, we recommend giving booster to teenagers to increase the likelihood of their own seroprotection as well as decrease chances of future maternal-fetal transmission of HBV.

Conflict of Interest

None declared

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