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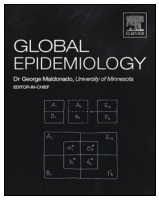

Seroconversion among children with HBsAg-positive mothers in Indonesia and factors affecting the anti-HBs titers

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ABSTRACT

Background and aim: Around 2% of newborns are at risk of hepatitis B virus (HBV) infection from their mothers. To prevent this, infants born to HBsAg-positive mothers are given hepatitis B immune globulin (HBIG) and hepatitis B (HB) vaccine as immunoprophylaxis. This study aims to investigate the efficacy of immunoprophylaxis in infants born to HBsAg-positive mothers and the contributing factors.

Methods: The study was conducted on a group of 87 children, ranging from nine months to under 36 months, born to HBsAg-positive mothers and received immunoprophylaxis within 24 h after birth followed by a national immunization schedule at the Community Health Center (CHC) in three administrative cities of DKI Jakarta. We measured the levels of HBsAg and anti-HBs, and utilized ordinal logistic regression models to identify factors that influence the anti-HBs titers after vaccination.

Results: Out of 87 children, only one child had positive HBsAg results. The data showed that 88.5% of the children had seroprotection with anti-HBs levels ≥10 mIU/mL. Additionally, 48.3% of the children had a high protective response with anti-HBs levels ≥100 mIU/mL, while 11.5% had a non-protective response. Children under one year of age, with a family history of HBV carriers, and who received five doses of the HB vaccine exhibited higher levels of anti-HBs titer category with adjusted OR 3.9 (95%CI: 1.3–11.6), 5.3 (95%CI: 1.1–27.4), and 8.3 (95%CI: 2–34.8), respectively.

Conclusion: The administration of HBIG and HB vaccine successfully prevented vertical transmission, resulting in a high seroprotection rate.

Introduction

The World Health Organization (WHO) estimated that chronic hepatitis B virus (HBV) infections affect approximately 257 million people and cause 900,000 deaths due to complications such as hepatic cirrhosis and hepatocellular carcinoma [1]. The most vulnerable population was children, with a 70% to 90% chance of contracting HBV from hepatitis B e-antigen (HBeAg)-positive mothers vertically. In areas where HBV is endemic, such as Southeast Asia, vertical transmission has become a significant route for the persistence of HBV infection, accounting for 40% to 50% of chronic infections. It is important to note that those who acquired chronic HBV infections via vertical transmission were more susceptible to developing severe liver diseases [2].

In 2013, a nationwide study revealed that the prevalence of HBV had decreased from high to moderate endemicity, dropping from 9.4% to 7.1%, due to the implementation a universal infant hepatitis B (HB) vaccination program in Indonesia [3]. However, recent data from the National Basic Health Research in 2018 showed that the prevalence of HBV had risen to 0.4% [4], with pregnant women at a higher risk of transmitting the virus vertically to their children [3]. Therefore, the Ministry of Health (MoH) has launched a triple elimination program for mother-to-child transmission (EMTCT) of human immunodeficiency virus (HIV), HBV, and syphilis. The program includes administering hepatitis B immune globulin (HBIG) and HB vaccine at birth, and serological testing to evaluate the seroprotection rate, to achieve elimination of mother-to-child transmission of HBV by 2030.

The administration of HBIG and HB vaccination can significantly reduce the vertical transmission rate of HBV infection by 85–90%, as compared to HB vaccination alone [5,6]. However, the interventions did not fully eradicate 1% to 9% of vertical transmission of HBV. Furthermore, infants living with HBsAg-positive mothers are particularly vulnerable to horizontal HBV infection, making it essential to determine

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their immunity status. The WHO recommends postvaccination serological testing of HB surface antigen (HBsAg) and antibody to HBsAg (anti-HBs) to diagnose chronic HBV infection and evaluate vaccination response [7]. Infant with positive HBsAg result need further testing of HBV deoxyribonucleic acid (DNA) and biochemical parameters of liver functions. Infant with anti-HBs titer ≥10mIU/mL was considered a seroprotective response to vaccination, although recent studies suggest that an anti-HBs >100mIU/mL may be a better indicator of seroprotection [5]. Infant with anti-HBs titer below 10mIU/mL indicates susceptibility to HBV infection and requires revaccination with three doses of HB vaccine [8].

Since 1997, Indonesia has implemented a universal HB vaccination that includes administering HB vaccination at birth followed by three doses of combination vaccines including diphtheria, pertussis, tetanus and hepatitis B within the 2nd, 3rd, and 4th months. This program has significantly reduce the prevalence of HBV infection from 5 to 10% to 0–5.9 after 15 years [9]. A meta-analysis study revealed that the program could reduce the risk of vertical transmission of HBV infection to 10–15% in HBeAg-positive mothers and <1% in HBeAg-negative mothers [10]. In 2017, the MoH implemented EMTCT program to further eliminate HBV infection. For evaluating efficacy and seroprotection rate of this program, the MoH implemented a rapid diagnostic test for qualitative detection of HBsAg and anti-HBs. However, there is still limited data on the postvaccination serological testing in Indonesia. Thus, we aimed to evaluate HBsAg and anti-HBs titer in infants born to HBsAg-positive mothers who received HBIG and HB vaccination within 24 h after birth followed by a national immunization schedule to determine seroconversion rate and factors related to anti-HBs titer to immunization.

Methods

Subject and study design

We enrolled infants between nine and under 36 months old who were born to HBsAg-positive mothers at the Community Health Center (CHC) in DKI Jakarta. In the EMTCT program, all pregnant women must undergo screening for three diseases: HIV, HBV, and syphilis. The Enzyme-linked Immunosorbent Assay (ELISA) test was used to evaluate HBsAg in pregnant women. Positive results were documented in the EMTCT program registry. Participants were recruited through the EMTCT program registry, and researchers contacted their parents to perform HBsAg and anti-HBs tests at the CHC. Parents who were available to bring their children to CHC during the study period were requested to sign an informed consent form. Infants born to HBsAg-positive mothers were administered 0.5 ml (220 IU/ml) HBIG (HyperHEPB®) and 0.5 ml (10 μg) of the recombinant HB vaccine (Bio Farma) as their first HB vaccine within 24 h after birth on the anterolateral thigh in different extremities. The immunoprophylaxis was administered to the infants born in CHC or a public hospital. Afterward, they followed the national immunization schedule, which included three doses of the combination vaccine DTwP-HB-Hib simultaneously with OPV at 2, 3, and 4 months of age and IPV at 4 months of age, followed by two doses of measles-rubella vaccine at 9 and 18 months of age, and one dose of the combination vaccine DTwP-HB-Hib at 18 months of age. We recorded their vaccination history using a questionnaire and conducted face-to-face interviews with their parents or guardians at each CHC. During the interview, we collected information regarding demography, gestational age, birth weight, mode of delivery, family history of HBV carriers, and history of HBIG injection and HB vaccination series. We defined family history of HBV carrier as a history of HBsAg-positive in the household other than the mother. We measured weight and height of the participants and calculated their nutritional status using the WHO z-score for weight-for-length/height [11].

EMTCT program

As part of the routine checkups during pregnancy, this program screened for HIV, HBsAg, and syphilis for all pregnant women. However, the program did not include detection for HBeAg and HBV DNA levels, which are important for identifying infectious rates that could potentially increase the risk of mother-to-child transmission. Infants born to HBsAg-positive mothers were given 0.5 ml (220 IU/ml) HBIG and their first dose of the HB vaccine within 24 h of birth. Afterward, they must follow the national immunization schedule. At the age of nine months, their immunity status was checked by assessing HBsAg and anti-HBs titer in CHC.

Serological test

The study involved taking blood samples from participants, which were then analyzed at the laboratory of Dr. Cipto Mangunkusumo Hospital, a national referral center for government hospitals. To detect serological markers for HBV like HBsAg and anti-HBs, the laboratory used the Chemiluminescence Microparticle Immuno Assay (CMIA) method and an Architect i2000 automatic light detector, along with test reagents from the U.S.A Abbott Corporation. A serum HBsAg signal/cutoff ≥1 was considered reactive, while a signal/cutoff <1 was nonreactive. The serum anti-HBs were quantitatively measured, and we classified titers by <10 mIU/mL, 10–100 mIU/mL, and > 100 mIU/mL as a non-protective response, protective response, and high protective response to the immunization, respectively.

Sampling method and statistical analysis

The COVID-19 pandemic has made parents more hesitant to visit health facilities and participate in our study. Due to low compliance rate, we were unable to conduct randomized cluster sampling from all five administrative cities in DKI Jakarta. Therefore, we opted for total sampling from the CHC population in three administrative cities in DKI Jakarta; North Jakarta, Central Jakarta, and South Jakarta.

In this study, we evaluated the efficacy of a HB vaccine in HBV-vulnerable participants by assessing the anti-HBs titer response. We classified a titer below 10 mIU/mL as a non-protective response, 10–100 mIU/mL as a protective response, and above 100 mIU/mL as a high protective response. Our analysis included HBsAg testing, and we presented participant characteristics and the distribution of anti-HBs levels in both numerical and percentage formats. We employed ordinal logistic regression models to examine factors associated with anti-HBs titers, adjusting for potential confounders, such as age, sex, gestational age, birth weight, delivery mode, family history of HBV carrier, nutritional status, and dose of HB vaccination. Results were expressed as an adjusted odds ratio (AOR) with a 95% confidence interval (CI). Statistical analysis was conducted using STATA 14.

Ethics

The study was approved by The Committee of Medical Research Ethics of the Faculty of Medicine, University of Indonesia (No. KET-495/UN2·F1/ETIK/PPM.00.22/2022).

Result

A total of 87 children were involved in the study, comprising 52 boys and 35 girls. Two of the participants were twins. The age range of the participants was between 9 and 34 months. Most of the children (85.1%) received four doses of the HB vaccine. Out of the total, 7 children (8%) were born prematurely, while 5 (5.7%) had low birth weight. (See Table 1)

Out of the 87 children who were tested after receiving HBIG and HB vaccine at birth, only one child (1.1%) tested positive for HBsAg. The

Table 1
Characteristics of children born to HBsAg-positive mothers ($N = 87$).

Characteristics	n (%)
Age	
< 1 year old	24 (27.6)
≥ 1 year old	63 (72.4)
Male	52 (59.8)
Premature	7 (8)
Low birth weight	5 (5.7)
Vaginal delivery mode	31 (35.6)
Dose of HB vaccination	
4	74 (85.1)
5	13 (14.9)
Nutritional status	
Normal	79 (90.8)
Wasted	5 (5.8)
Overweight	3 (3.4)
Family history of HBV carrier	8 (9.2)
Response group to HB vaccination	
Protective response	77 (88.5)
High protective response	42 (48.3)

child was born at full term, with normal birth weight. She was delivered vaginally and had completed the routine HB vaccine series. Her family did not have a history of HBV carriers (other than her mother). Nutritional status was assessed using the WHO weight-for-length index, and her z-score was within the normal range of −0.51 SD. Furthermore, her anti-HBs titer has been classified as a non-protective response.

Anti-HBs levels varied from 0 mIU/mL to 4984.1 mIU/mL, with a mean of 344.3 ± 770.6. Of the total number of children, 77 (88.5%) demonstrated a seroprotective response (anti-HBs ≥10mIU/mL), while 42 (48.3%) had a highly protective response (anti-HBs ≥100mIU/mL). A total of 10 (11.5%) children showed non-protective response to vaccination (anti-HBs <10 mIU/mL), including 1 child who was HBsAg-positive. (See Table 1)

HB hepatitis B; HBV hepatitis B virus; nutritional status was measured using WHO z-score for weight-for-length/height < −2 Standard Deviation (SD) defined as wasted, between −2 and + 2 SD defined as normal, and > +2 SD defined as overweight/obesity [11].

It was found that children who exhibit non-protective response to HB vaccination were tested after the age of one year. Most of these children were female, born at full term with normal birth weight, delivered via cesarean section, and had no family history of HBV carriers. Additionally, these children had a normal nutritional status and had only received four doses of the HB vaccination. (See Table 2)

The factors that predict the immune response to HBIG and HB vaccine are summarized in Table 3. We first check the proportional odds assumption before applying ordinal logistic regression models. The likelihood ratio chi-square value of 11.9 shows no difference in the coefficients between models. After accounting for other factors that could affect the results, it was discovered that children who were younger than one year old, had a family member who was an HBV carrier, and received five doses of HB vaccine had higher anti-HBs titers in response to the vaccination. Specifically, children under one year had 3.9 times higher odds of being in a higher anti-HBs titer category compared to children who were one year or older (AOR = 3.9, 95%CI: 1.3–11.6). Children with a family history of HBV carriers had 5.3 times higher odds of being in a higher anti-HBs titer category compared to children without a family history of HBV carriers (AOR = 5.3, 95%CI: 1.1–27.4). Finally, children who received five doses of HB vaccine had 8.3 times higher odds of being in higher anti-HBs titers category compared to children who received four doses of the vaccine (AOR = 8.3, 95%CI: 2–34.8).

Discussion

This study found that only one child (1.1%) had contracted HBV. Notably, the mother showed no symptoms of HBV and had no history of HIV infection, though her HBeAg and HBV DNA viral load status were unknown. It is common for people with asymptomatic HBV infection to withdraw from evaluation due to stigma. Nonetheless, the child received immunoprophylaxis within 6 h of birth. These study results are consistent with a previous study conducted in China, which reported a 0.9% infection rate when HBIG and HB vaccine were administered at birth [12]. Therefore, the administration of HBIG and HB vaccine at birth can effectively prevent the vertical transmission of HBV from the mother to the child. This promising outcome brings the EMTCT of the HB program

Table 2
Distribution of anti-HBs titers and the contributing factors ($N = 87$).

Factors	Anti-HBs (mIU/mL)		
	<10	10–100	>100
Age			
<1 year old	0 (0)	10 (28.6)	14 (27.6)
≥1 year old	10 (100)	25 (71.4)	28 (72.4)
Sex			
Male	2 (20)	23 (65.7)	27 (64.3)
Female	8 (80)	12 (34.3)	15 (35.7)
Gestational Age			
≥37 week	9 (90)	32 (91.4)	39 (92.9)
<37 week	1 (10)	3 (8.6)	3 (7.1)
Birth Weight			
≥2500 g	9 (90)	33 (94.3)	40 (95.2)
<2500 g	1 (10)	2 (5.7)	2 (4.8)
Delivery Mode			
Vaginal delivery	2 (20)	11 (31.4)	18 (42.9)
Cesarean section	8 (80)	24 (68.6)	24 (57.1)
Family history of HBV carrier			
Yes	0 (0)	3 (8.6)	5 (11.9)
No	10 (100)	32 (91.4)	37 (88.1)
Nutritional status			
Normal	10 (100)	31 (88.6)	38 (90.5)
Wasted	0 (0)	2 (5.7)	3 (7.1)
Overweight	0 (0)	2 (5.7)	1 (2.4)
Dose of HB vaccination			
4	10 (100)	31 (88.6)	33 (78.6)
5	0 (0)	4 (11.4)	9 (21.4)

HBV hepatitis B virus; HB hepatitis B.

Table 3
Association of anti-HBs titers category to HBIG and HB vaccine and the contributing factors.

Factors	UOR (95% CI)	AOR (95% CI)
Age		
≥1yo	1	1
<1yo	2.1 (0.8–5.3)	3.9 (1.3–11.6)
Sex		
Female	1	1
Male	2 (0.8–4.5)	2.1 (0.8–5.1)
Gestational Age		
<37 week	1	1
≥37 week	0.8 (0.2–3.3)	0.5 (0–8.3)
Birth Weight		
≥2500 g	1	1
<2500 g	1.6 (0.3–9)	1.2 (0−33)
Delivery Mode		
Cesarean section	1	1
Vaginal delivery	0.5 (0.2–1.2)	2.3 (0.9–6)
HBV carrier in family		
No	1	1
Yes	2.1 (0.5–9)	5.3 (1.1–27.4)
Nutritional status		
Normal	1	1
Wasted	1.9 (0.3–11)	2.9 (0.4–19.5)
Overweight	0.8 (0.1–6)	1.7 (0.2–15.5)
Dose of HB vaccination		
4	1	1
5	3 (0.9–10.5)	8.3(2–34.8)

HBV hepatitis B virus; HB hepatitis B; UOR unadjusted odds ratio; AOR adjusted odds ratio.

one step closer to attaining goal by 2030.

The Ministry of Health in Indonesia has been considering implementing evaluation of the anti-HBs titer test for a few years, but it has not been put into practice yet, or only used qualitative method. This may be due to the belief that most children already have protective results (anti-HBs ≥10 mIU/mL). However, our recent study shows otherwise, with a positive result of 88.5% of children having protective anti-HBs (≥10 mIU/mL), and 48.3% having high protective anti-HBs (>100mIU/mL). We found that 11.5% of the children had a non-protective response. These findings are different than a previous study in the Special Region of Yogyakarta, Indonesia, where only 73.1% of children developed protective anti-HBs following HB vaccination. The difference could be because our study participants received HBIG and HB vaccine at birth then followed by national immunization schedule, while in the Yogyakarta study, participants only received the HB vaccine [13]. Conversely, our study found that the rate of children who developed protective anti-HBs was lower than in China, where the rate was 99.3%. This difference could be due to the lower coverage rate of the HB vaccine in Indonesia, which was 70% compared to up to 98% in China [5,14]. Additionally, the pandemic has played a significant role in causing parents to be hesitant to bring their children to health centers for immunization.

Many factors can affect how well the body responds to the HB vaccine, such as obesity, smoking or drug use, young age, gender, certain medical conditions like kidney failure, HIV or HCV infection, diabetes, cancer, organ transplantation, and immunosuppression. Other factors that may play a role include parental HBV status, maternal HBV-DNA, genetic factors such as human leukocyte antigen (HLA) class II gene polymorphisms, and feeding patterns [13,15]. Studies show that genetic factors account for 70–90% of the vaccine response, while the remainder is either unknown or due to environmental factors. Additionally, research indicates that antibody levels decline with age, especially in children over 5 years old. Conversely, children under 1 year old tend to have higher antibody levels and a greater percentage of protective antibodies than older children [5,16]. Our study confirms these findings, suggesting that anti-HBs levels are highest in infants but decrease with age.

Our studies have indicated that receiving additional doses of the HB vaccine is associated with higher anti-HBs titers. This finding contrast with previous studies, which found that children who received HBIG and three doses of HB vaccine had comparable levels of anti-HBs titers compared to those who only received HB vaccine [17]. Similar with our study, a study conducted in India found that four doses of the recombinant HB vaccine produced higher levels of anti-HBs titers than three doses. Furthermore, a systematic review in Indonesia demonstrated that a national immunization program led to a decrease in the positivity of HBsAg. However children born to HBsAg-positive mothers were still at risk of having lower anti-HBs titers [18,19]. Therefore, providing a booster dose of the HB vaccine at eighteen months old, following the national immunization program, is an effective method of building immunity for children and reducing their susceptibility to infection.

Recent research conducted in Central Iran revealed that approximately 20.4% of family members who have intra-familial HBV carriers had anti-HBs levels of at least 10 mIU/ml, with children displaying the highest prevalence [20]. Our study also confirmed that children from families with HBV carriers exhibited higher anti-HBs titers and had adequate immunity to HBV. A study about intra-familial transmission of HBV in Indonesia shows that children with HBV carriers in the household and HBsAg-positive parents are at a higher risk of intra-familial transmission of HBV [21]. Therefore, children with HBsAg-positive mothers must maintain protective anti-HBs titers of at least 10 mIU/mL to prevent vertical and intra-familial transmission in the future. The low rate of HBV infection reported in children with HBsAg-positive mothers reveals the effectiveness of universal vaccination programs in preventing HBV transmission [20].

According to a meta-analysis study, premature and low birth weight children demonstrated reduced anti-HBs titers following HBIG and HB vaccine administration [22,23]. However, our study revealed no interval estimation difference in anti-HBs titers between premature and low birth weight children, and their term and normal birth weight counterparts, after the administration of HBIG and HB vaccine. The limited sample size of the study may have contributed to this outcome. Our findings align with a study by Tüfekci et al. that also demonstrated no discernible difference in anti-HBs titers between low birth weight children and normal birth weight children [24]. Therefore, administering HBIG and HB vaccine at birth can be considered for premature and low birth weight babies to develop a protective immune response against HBV infection.

Obesity is linked to a higher risk of nonprotective response to the HB vaccine, which increases in line with body mass index (BMI). Additionally, obese individuals are at risk of HBV-vaccine mutations [25,26]. Malnutrition, on the other hand, does not appear to have an impact [27]. Our study showed no difference in anti-HBs titers in the children who are underweight, overweight, and have normal z-score. Therefore, administering HBIG and HB vaccine according to the national immunization program benefits our children regardless their nutritional status.

The rate of non-responsiveness may vary in different studies, which were 9% in children aged 9–15 months and 5–30% in immunocompetent people [28,29]. In our study, the rates of the non-proctective response group were 11.5%, which is higher than the previous study. In the non-proctective response group, further examination is needed to rule out the possibility of occult HBV infection [30]. But, due to the limitation of our national insurance program funding, evaluation of HBV-DNA was not an essential part of the program. Revaccination with three doses of vaccine containing 20 μg HBsAg was recommended for non-proctective response group to lower the risk of HBV infection [29]. After revaccination, the non-proctective response group should have experienced seroconversion rate of 88.9–90% (anti-HBs ≥10mIU/mL) [28,30]. Therefore, national immunization program had to be encouraged among children in Indonesia, particularly in children born to HBsAg-positive mothers, and evaluation of anti-HBs titers had to be implemented extensively.

There were several limitations in our study. First, our study was conducted during the peak of the COVID-19 pandemic causing a higher rate of noncompliance to follow the study. As a result, fewer children were enrolled from only 3 out of 5 cities of DKI Jakarta. Nevertheless, we found that the children that noncompliance to follow the study does not differ much from our study population. Thus, our study result can represent study population. Second, the policy of our national insurance limited further evaluation of children who did not exhibited protective response to HB vaccine. Therefore, the prevalence of occult hepatitis B infection in children born from HBsAg-positive mothers was unknown. Third, the mothers were not evaluated for HBeAg titer and HBV-DNA after positive HBsAg result, leading to an unknown infectious rate. This happens due to stigma surrounding HBV infection and pandemic factors, which make people reluctant to seek medical care.

Although this research had some limitations, it was the first study that evaluated seroconversion of anti-HBs following the administration of HBIG and HB vaccine in children born to HBsAg-positive mothers in Indonesia. The findings of this study could be helpful for the Ministry of Health (MoH) in evaluating the factors that contribute to vertical transmission of HBV in Indonesia. Additionally, further analysis of the non-proctective response group group may reveal more information about the possibility of occult HBV in the population and the potential of early intervention.

Conclusion

The administration of HBIG and HB vaccine at birth successfully prevented vertical transmission of HBV in children born to HBsAg-positive mothers. Compliance with the national immunization

program up to 18 months old may provide optimal immune response to HBV. Therefore, it is suggested to endorse the national vaccination program and evaluate the anti-HBs titers for a more effective reduction of HBV infection.

Patient consent statement

We ensured that all participants were fully informed of the objectives and their right to privacy in this research. Before participation, each participant provided written informed consent. Children were enrolled only after their parents or legal guardians agreed to and signed the consent form.

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CRediT authorship contribution statement

Angga Wirahmadi: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Hartono Gunardi:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Bernie Endyarni Medise:** Supervision, Investigation, Writing – review & editing. **Hanifah Oswari:** Supervision, Methodology, Writing – review & editing. **Teny Tjitra Sari:** Methodology, Formal analysis, Software. **Nastiti Kaswandani:** Resources, Formal analysis, Validation. **Mulya Rahma Karyanti:** Resources, Methodology, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gloepi.2024.100135.

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