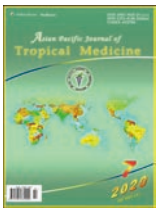

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Seroprotection after hepatitis B vaccination amongst infants aged between 12 and 24 months in Ho Chi Minh City, Vietnam

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ABSTRACT

Objective: To assess levels of HBsAb amongst infants who received hepatitis B vaccine in the Expanded Program on Immunization in Vietnam.

Methods: A cross-sectional study was carried out at 16 community health centers from February 2016 to July 2017. Eligible infants were tested for HBsAb and HBsAg. Structured questionnaires were used to collect relevant information about the demographics of the parents/caregivers and their infants after physical examination.

Results: A total of 199 eligible infants were selected with a mean age of (17.3±4.5) months. Protective antibody levels with HBsAb ⩾10 mIU/mL were detected in 68.3% of infants. Of these, antibody levels from 10 to 99 mIU/ mL were 48.5% of those tested and antibody levels ⩾100 mlU/mL were recorded as 51.5%. No cases were recorded of being infected with hepatitis B virus. The rate of positive HBsAb level in those who were not wasting and 18 months old was less than that among those who were <18 months old (*OR* 0.49, 95% *CI*: 0.26-0.92, *P*<0.05) while the infants with wasting and <18 months were less likely to be positive HBsAb than those who were not wasting and of the same age group (*OR* 0.15, 95% *CI*: 0.04-0.55, *P*<0.05).

Conclusions: Seroprotection against hepatitis B virus was low in the infants tested (at 68.3%), which suggests that the hepatitis B vaccine should be administered with one additional dose for infants between 12 and 24 months of age, particularly those with wasting.

KEYWORDS: Hepatitis B virus; Hepatitis B; Vaccine; Vaccination; Expanded Program on Immunization

1. Introduction

Vietnam has a reported high level of endemic hepatitis B virus (HBV) infection. Different areas in Northern Vietnam showed the prevalence of HBsAg was 18.8%[1], 19.05%[2] and 8.8%[3], respectively. Recently, seroepidemiological researches among the general population in Binh Thuan Province, a region in the south of Vietnam, found that a significant proportion of HBsAg and hepatitis B core antibody were reported to be 15.3% and 71.7% of those tested, respectively[4]. In 2012, the International Agency for Research into Cancer and the World Health Organization (WHO) reported that Vietnam was ranked as a country with one of the highest mortality in liver cancer, which is proven to be caused, predominately, by chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection[5,6]. A primary source of HBV-related disease has been shown to stem from infections acquired in the period of early childhood through perinatal. This is significant because infections acquired at an early age are more than likely to become chronic in nature, much more than an infection acquired

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later in life. The probability of progression to chronic infection is inversely connected with the age of patients at the time of infection. Approximately 90% of infants infected perinatally become chronic HBV carriers, if they were not vaccinated at birth within the guidelines set for HBV vaccination. The hazard for chronic HBV infection declined by about 30% for HBV-infected infants from 1 to 4 years and, particularly, below 5% for HBV-infected adults[7]. Since 1997, the HBV vaccine has been added to the Expanded Program on Immunization (EPI) in Vietnam. In 2010, the combination vaccine Quinvaxem® (which includes diphtheria, pertussis, tetanus, hepatitis B, and Hib (DTwP-HBV-Hib), developed by Crucell and Novartis, was used by the EPI of Vietnam. In Vietnam, all infants under 12 months are vaccinated at no cost to the parents and caregivers. The Quinvaxem® vaccine is injected to infants each month from 2 to 4 months[8], a total of 3 doses. After the full allocation of the immunization was complete, a study was undertaken among a sample of 131 Vietnamese infants to assess the immunogenicity of Quinvaxem®. The results of this study showed that the percentage of infants, who had protective antibodies persisting at one year after the first dose was 76.7% for HepB[9]. In another study on 384 Vietnamese children aged 5 years, the proportion of children that completed 3 doses within the specified timeframes of the HBV vaccine with seroprotection was only 28.3%[10]. The study found that decreasing the concentration of HBsAb over time can be alarming. Therefore, this study aims to assess the level of HBsAb amongst infants from 12 to 24 months who received a complete and timely HBV vaccination.

2. Materials and methods

2.1. Study design

A cross-sectional study on HBV immunization was carried out from February 2016 to July 2017. The study was undertaken in 8 out of 24 districts in Ho Chi Minh City. Among 16 Community Health Centers (CHCs), two CHCs in each district were selected for this study. A total of 199 eligible infants between 12 and 24 months were collected through a simple random selection (Figure 1).

2.1.1. Inclusion criteria

Participants in this study were specifically infants aged 12 to 24 months. The infants received hepatitis B vaccine within the schedule recommended by the EPI in Vietnam, which involved an initial dose at birth and the three-dose series which was given to infants aged 2 months (59-88 days old), 3 months (89-118 days old), and 4 months (119-148 days old)[8].

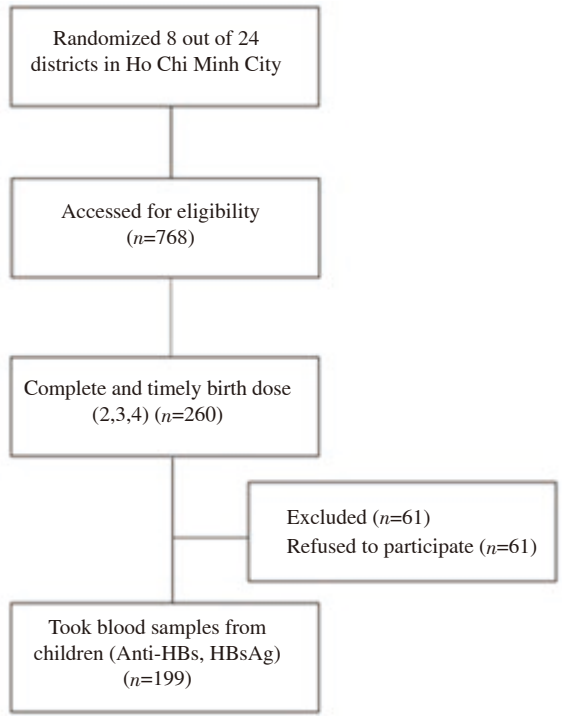

Figure 1. The study flowchart.

2.1.2. Exclusion criteria

Infants who did not have their vaccination cards to confirm the record of receiving the HBV vaccine were excluded from this study.

2.2. Data collection procedures

Structured questionnaires were used to collect information from the parents/caregivers of those tested. The first section of the questionnaire obtained baseline social demographics of infants which included age, gender, gestational age, birth weight, the nutritional status (underweight, stunting, wasting, overweight and obese), exclusive breastfeeding in the first 6 months and the age of infants start complementary foods. In the second section, blood samples were taken from infants to assess their HBsAb and HBsAg levels. It is noted that all blood samples for antibodies and antigens were obtained from infants aged 12 to 24 months, who received the full HBV vaccine (the birth dose, 2, 3, and 4 months). Approximately 2 mL of blood was obtained from each child. Then, blood samples were transported to the Ho Chi Minh City's District 2 Hospital. The concentration of HBsAg and HBsAb were performed using the Cobas e-411analyzer. The specimens spin down at 3 000×g for 15 minutes. After the centrifugation process, all sera were tested for HBsAg and HBsAb by using Roche's Elecsys HbsAg II and Anti-HBs assys (Immunoassay for the quantitative determination of HBsAg and Anti-HBs, Roche Diagnosics GmbH, Germany.

The interviews and blood tests were carried out when the parents/caregivers took their children to the CHCs for vaccination. The data collected would remain anonymous.

2.3. Variable definitions

2.3.1. Anthropometric measurements

The current nutritional position of the infant was recorded at the time of testing and was estimated by the weight-for-age Z-score (WA), the weight-for-length/height Z-score (WH), the length/height-for-age Z-score (HA), and body mass index (BMI). According to the WHO standard, classifying children's nutritional status such as stunting (HAZ < -2), underweight (WAZ < -2), wasting (WHZ < -2) and at risk of overweight (BMI –z-score > +1)[11].

2.3.2. HBV markers

The con centration of HBsAb and HBsAg were determined by using a standard ELISA kit from Roche (The Elecsys HbsAg II). Seroprotective antibody concen tration was defined as HBsAb ⩾10 mIU/mL[7] and HBV infection was defined as the seropositivity for HBsAg.

2.4. Vaccine

The vaccine used in the study is noted as being Quinvaxem®, which was a combination vaccine. Each 0.5 mL dose included ⩾30 IU purified diphtheria toxoid, ⩾60 IU purified tetanus toxoid, ⩾4 IU whole-cell pertussis, 10 μg Hib oligosac charide, and 10 μg HBsAg[12]. The vaccine was vaccinated intramus cularly into the infants' thigh area at 2, 3, and 4 months of age.

2.5. Ethical approval

The study was approved by the Ethics Council-University of Medicine and Pharmacy at Ho Chi Minh City (protocol number 125/UMP-BOARD). Additionally, the parents/caregivers of each child agreed and consented to the tests before conducting the research. All HBsAb-negative infants were invited to return to consult a hepatitis B revaccination and HBsAg-positive infants were referred to a liver specialist at the Ho Chi Minh City's District 2 Hospital.

2.6. Statistical analysis

The data was calculated through Stata13 and Epidata 3.0 software, suggested percentages were reported along with their 95% confidence intervals (*CI*s), and differences in suggested percentages (qualitative variables) were carried out using *Chi*-square or Fisher's exact test. All variables that had a significance level < 0.20 in the bivariate analysis were done using logistic regression in multivariate analysis. *P*-value <0.05 was considered as statistically different.

3. Results

3.1. Demographics of infants

A total of 768 infants from 12 to 24 months old were surveyed. Of the total number approached, 260 infants (33.9%) had received a complete and timely (birth dose, 2, 3, 4 months of age) hepatitis B vaccination, but only 199 parents/caregivers agreed and signed informed consent prior to entering into the study (data not shown). The mean age of infants was (17.3±4.5) months, which comprised of 96 boys (48.2%) and 103 girls (51.8%). Among 199 participants, a majority of the infants recorded a normal birth weight (2 500-4 000 g). The rate of at-risk overweight and obese infants was the highest (34.2%) compared to infants recorded as stunting (10.1%), underweight (3.0%) and wasting (6.5%). The rate of infants who were exclusively breastfed in the first 6 months of life was shown to be rather low (22.1%) (Table 1).

3.2. Serological analyses

No HBsAg positive case was observed among these infants. It was reported that 136 (68.3%) infants had positive HBsAb seroconversion (⩾10 mIU/mL), among them 70 (51.5%) had HBsAb concentration ⩾100 mIU/mL.

Table 1. Baseline characteristics of the infants (*n*=199).

Parameters	Baseline data
Gender [*n* (%)]	
Male	96 (48.2)
Female	103 (51.8)
Age (mean±SD, month)	17.3±4.5
Age [*n* (%)]	
<18 months	120 (60.3)
⩾18 months	79 (39.7)
Mean duration after the third dose HBV (mean±SD, month)	13.3±4.5
Gestational age (>37 weeks) [*n* (%)]	176 (88.4)
Weight at birth [*n* (%)]	
Low (< 2 500 g)	15 (7.5)
Normal (2 500-4 000 g)	184 (92.5)
Nutritional status [*n* (%)]	
Underweight (WA< -2SD)	6 (3.0)
Stunting (HA< -2SD)	20 (10.1)
Wasting (WH< -2SD)	13 (6.5)
At risk overweight and obese infants (BMI⩾+1SD)	68 (34.2)
Exclusive breastfeeding for the first 6 months [*n* (%)]	44 (22.1)
The age that infants start receiving complementary foods⩾6 months [*n* (%)]	
Yes	180 (90.4)
No	19 (9.6)

WA: Weight-for-age; HA: Length/height-for-age; WH: Weight-for-length/height.

Table 2. Factors associated with HBV vaccine response (n=199).

Variables	N	HBsAb		X^2 value	P value
		≥10 mIU/mL (n=136)	<10 mIU/mL (n=63)		
Age					
<18 months	120	87 (72.5)	33 (27.5)	2.416	0.12
≥18 months	79	49 (62.0)	30 (38.0)		
Gender					
Male	96	61 (63.5)	35 (36.4)	1.975	0.16
Female	103	75 (72.8)	28 (27.2)		
Gestational age (≥37 weeks)					
Yes	176	122 (69.3)	54 (30.7)	0.671	0.41
No	23	14 (60.9)	9 (39.1)		
Weight at birth					
Low (< 2500 g)	15	8 (53.3)	7 (46.7)	1.689	0.19
Normal (2 500-4 000 g)	184	128 (69.6)	56 (30.4)		
Underweight					
Yes	6	4 (66.7)	2 (33.3)	0.008	0.93
No	193	132 (68.4)	61 (31.6)		
Stunting					
Yes	20	12 (60.0)	8 (40.0)	0.715	0.39*
No	179	124 (69.3)	55 (30.7)		
Wasting (n=198, missing 1)					
Yes	13	5 (38.5)	8 (61.5)	5.665	0.02
No	185	130 (70.3)	55 (29.7)		
At risk of overweight and obese infants					
Yes	68	44 (64.7)	24 (35.3)	0.631	0.43
No	131	92 (70.2)	39 (29.8)		
Exclusive breastfeeding for the first 6 months					
Yes	44	34 (77.3)	10 (22.7)	2.083	0.15
No	155	102 (65.8)	53 (34.2)		
The age of infants start receiving complementary foods≥6 months					
Yes	180	123 (68.3)	57 (31.7)	0.0001	0.99
No	19	13 (68.4)	6 (31.6)		

Chi square and Fisher's exact test used to a comparison between demographic charateristics of infants and the rates of HBsAb level.

Table 3. Logistic regression analysis of factors associated with HBsAb positivity.

Variables	Frequency of HBsAb≥10 mIU/mL (%)	Odds ratio (95% *CI*)	P value
Model 1: Multiple logistic regression model			
Age			
≥18 months	49 (62.0)	0.55 (0.29-1.03)	0.063
<18 months	87 (72.5)	Reference	
Gender			
Male	61 (63.5)	0.69 (0.37-1.30)	0.253
Female	75 (72.8)	Reference	
Low birth weight (<2 500 g)			
Yes	8 (53.3)	0.52 (0.17-1.57)	0.249
No	128 (69.6)	Reference	
Exclusive breastfeeding for the first 6 months			
Yes	34 (77.3)	1.63 (0.73-3.63)	0.231
No	102 (65.8)	Reference	
Wasting			
Yes	5 (38.5)	0.26 (0.08-0.88)	0.031
No	130 (70.3)	Reference	
Model 2: Age and Wasting in the interaction model			
Non-wasting and Age <18 months	82 (76.6)	(reference group)	
Non-wasting and Age≥18 months	48 (61.5)	0.49 (0.26-0.92)	0.028
Wasting and Age <18 months	4 (33.3)	0.15 (0.04-0.55)	0.004
Wasting and Age≥18 months	1 (100.0)	Unable to estimate	

Z-test was used for coefficients of logistic regression model.

3.3. Factors associated with or without HBsAb

Comparisons in baseline characteristics of infants in groups with and without HBsAb seroconversion were presented in Table 2. Infants without HBsAb seroconversion (n=63) was more wasting than those with seroconversion (n=136, P<0.05). The multivariate analysis and interaction modelwere presented in Table 3. The rate of positive HBsAb level in those who were not wasting and 18 months old was less than that among those who were <18 months old (*OR* 0.49, 95% *CI*: 0.26-0.92, P<0.05) while the infants with wasting and <18 months were less likely to be positive HBsAb than those who were not wasting and of the same age group (*OR* 0.15, 95% *CI*: 0.04-0.55, P<0.05)

4. Discussion

In this study of 199 infants who received 3 full doses of HBV vaccine, only 68.3% of infants had protective HBsAb >10 mIU/mL at (17.3±4.5) months of age. Several possible explanations may account for this result. Firstly, it may be related to the age of infants, WHO reported that the levels of HBsAb decline over the time[7], and the low seroprotection level could be appropriate. However, some previous studies found that the prevalence of infants with anti-HBs >10 mIU/mL were high such as in the study of Aspinall, TNH and Capeding were 91.4%[15], 93.1%[9], and 92.9%[16], respectively. This can be explained due to the age of infants in these studies being younger than this study. Obviously, in the pre-vaccination time period for the booster dose [infants aged (12.0±3.0) months], the proportion of seroprotection was 76.4%[15] and 76.7%[9], which were similar to our results. Similarly, Rey's study on 114 infants under 4 years of age in Senegal, who completed the 3 doses of Quinvaxem®, the rate of infants with anti-HBs ⩾10 mIU/mL was also low at 58%[17]. Additionally, the results of the multivariate analysis in this study showed there was a significant difference between age of infant, wasting, and the concentration of HBsAb, particularly after adjustments, the age of infants (in months) and nutritional status were associated with HBsAb positive seroconversion, whereby the infants with wasting and <18 months old had a lower positive HBsAb seroconversion than those who were not wasting and of the same group. Additionally, the rate of positive HBsAb level in those who were not wasting and 18 months old was less than that among those who were <18 months old. These findings were also reported by Thang VT[10].

Secondly, some other researches showed storage conditions in CHCs[13] could also have some impact on the results. However, this study could not clarify this issue being a factor, thus further studies are needed on larger populations in order to scrutinize fully the vaccines, as well as their storage and delivery. Besides, the current evaluation of vaccination programs needs to also ensure vaccine quality and storage, thus being able to verify that vaccine recipients were genuinely protected.

The results emphasized the importance of collaboration between the national EPI and national programs in order to control hepatitis B in infants. WHO indicated that there was no evidence for a booster dose of hepatitis B vaccine after completion of the primary vaccination series in routine the EPI[7]. Nevertheless, additional researches should be carried out to investigate the life-long protection of the hepatitis B vaccine and the necessity for booster doses in different groups of the community[18]. Vietnam has a reported high level of endemic hepatitis B virus infection and based on these results, we noticed that one additional dose of hepatitis B vaccine may be necessary when the infant was between 12 and 24 months old, particularly those with wasting

Conflict of interest statement

We declare that we have no conflict of interest.

Authors' contributions

HG designed the study and wrote the protocol. HG, PLA, and BQV interpreted the data, managed the analyses of the study. HG and NNL were the contributors to the analysis and interpretation of the data. All authors read and approved the final manuscript.

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