

HEPATITIS B VIRUS SEROPREVALENCE AMONG CHILDREN OF HEPATITIS B SURFACE ANTIGEN-POSITIVE MOTHERS

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Abstract. Immunization is the most effective strategy to prevent perinatal transmission of hepatitis B virus (HBV). In spite of receiving both hepatitis B immunoglobulin (HBIG) and HB vaccination, some children still contract chronic HBV infection from their hepatitis B surface antigen (HBsAg) positive mothers. This study aimed to determine the seroprevalence of HBsAg positivity among children born to HBsAg-positive mothers and evaluate factors associated with this transmission. This cross-sectional descriptive study was performed at King Chulalongkorn Memorial Hospital (KCMH) during 2016-2018. Children of HBsAg-positive mothers, aged 1-18 years who received 3-5 doses of HB vaccine with or without HBIG were recruited into the study. The first dose of vaccine and HBIG were administered within 12 hours of birth. Each child was initially checked for HBsAg and hepatitis B surface antibody (anti-HBs). Each child with a positive HBsAg test was also examined for alanine aminotransferase (ALT) level and hepatitis B e-antigen (HBeAg). The previous test results for HBsAg and HBeAg of all mothers were recorded. Sixty mothers and their 73 children [41 males, mean ($\pm$ standard deviation) age of the children was 5.8 ($\pm$ 3.7) years] were included in the study. Among the 73 studied children, 9 (12%) had a positive HBsAg and 62 (85%) had a positive anti-HBs test. Four of the 9 children with a positive HBsAg test had received both HBIG and HB vaccines. Among the 9 children with a positive HBsAg test, 5 had a positive HBeAg test with a normal ALT level, 2 had a positive HBeAg test with ALT elevation and 2 had a negative HBeAg test with ALT elevation. Children born to a HBeAg-positive mother were significantly more likely to be HBsAg positive (odds ratio (OR): 2.43; 95% confidence interval (CI): 2.14-61.01; $p = 0.004$). These findings suggest current strategies used to prevent mother to child transmission of HBV infection in the study population are unsatisfactory.

Keywords: immunoprophylaxis failure, hepatitis B immunoglobulin (HBIG), hepatitis B surface antigen (HBsAg), seroprevalence, vaccine.

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INTRODUCTION

Hepatitis B virus (HBV) infection is a global health problem (Polaris Observatory Collaborators, 2018; WHO, 2019; WHO, 2016). It can cause chronic infection leading to chronic liver disease,

cirrhosis, and hepatocellular carcinoma (WHO, 2017). There were an estimated 257 million people worldwide living with chronic HBV infection in 2016 (Hutin *et al*, 2018). The highest prevalence of HBV infection has been reported to be in sub-Saharan Africa followed by the western Pacific and Southeast Asia (WHO, 2017). Without immunoprophylaxis, the rate of perinatal transmission of HBV from mother to child may be high as 80%-90% among infants born to hepatitis B e-antigen (HBeAg)-positive mothers (Li *et al*, 2015). The earlier HBV infection is contracted, the greater the likelihood it will become a chronic infection (Anonymous, 2017; Shao *et al*, 2011).

Immunization is the most effective strategy to prevent HBV infection and its devastating complications. In order to reduce the risk of contracting HBV infection, the first dose of hepatitis B (HB) vaccine should be given within 24 hours of birth, followed by at least 2 additional doses to complete the primary vaccination series (WHO, 2019). The World Health Organization recommended in 1991 the HB vaccine be included in the childhood immunization schedule for all countries by 1997 and proposed the goal of eradicating viral hepatitis, including HBV, by 2030 (Anonymous, 1992; The Lancet, 2016). HB vaccination covering 84% of infants nationwide was reported by 188 countries in 2017 (VanderEnde *et al*, 2018). Thailand has also included the HB vaccine into its Expanded Program on Immunization (EPI) since 1992. In Thailand, a survey of hepatitis B surface antigen (HBsAg) positivity among children aged < 5 years found the rate had declined from 0.4% in 2004 to 0.1% in 2014 (Chongsrisawat *et al*, 2006; Posuwan *et al*, 2016). The worldwide prevalence of HBsAg positivity among children aged < 5 years in 2015 was

estimated to be 1.3% (WHO, 2017).

The HB vaccine is highly immunogenic and effective in preventing HBV infection even in high risk neonates born to HBsAg-positive mothers (Bialek *et al*, 2008; Bruce *et al*, 2016; Chongsrisawat *et al*, 2006; Hammitt *et al*, 2007; Poovorawan *et al*, 2013). In spite of the effectiveness of the combination of HB immunoglobulin (HBIG) and the HB vaccine starting at birth, the maternal to child transmission rate of HBV infection among mothers who are HBeAg-positive ranges about 8-10% (Lin *et al*, 2014; Wang *et al*, 2012; Zhang *et al*, 2014).

The aim of this study was to determine the seroprevalence of HBsAg among children born to HBsAg-positive mothers and evaluate the factors associated with maternal to child transmission of HBV in order to inform strategies to minimize this transmission rate.

MATERIALS AND METHODS

Participants

We conducted this cross-sectional descriptive study at King Chulalongkorn Memorial Hospital (KCMH) during 2016-2018. Study subjects were children aged 1-18 years and their mothers who were HBsAg-positive. HBeAg test results for all mothers were recorded. All children subjects had received a first dose of HB vaccine within 12 hours of birth followed by at least 2-4 additional doses of HB vaccine administered at ages 1, 2, 4, and 6 months. The vaccine given at birth and one month of age was a monovalent HB vaccine. The subsequent doses of HB vaccine were given in combination with either a diphtheria and tetanus toxoids, acellular pertussis, inactivated poliovirus and *Hemophilus influenzae* type b (DTaP-IPV-Hib-HBV) or diphtheria and tetanus

toxoids, and whole cell pertussis (DTwP-HBV). These records were reviewed and recorded. We also recorded whether the child received a dose of hepatitis B immune globulin (HBIG) within 12 hours of birth.

A venous blood sample was obtained from all child subjects to test for HBsAg and anti-HBs. Children with a positive test for HBsAg were examined physically for signs of chronic liver disease and had the following additional testing: alanine aminotransferase (ALT) and HBeAg to define the phase of HB infection. The European Association for the Study of the Liver (EASL) classifies patients with chronic HBV infection according to the presence/absence of HBeAg and serum ALT level. Patients with a normal serum ALT level were classified as having a chronic HBV infection, whereas those who had serum ALT level > 40 units per liter were classified as having chronic hepatitis B (EASL, 2017). Subjects with a history of blood transfusion, intravenous drug use, tattooing or piercing were excluded from the study. The study protocol was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University (IRB No.135/60). Written informed consent was obtained from participants and/or their parents or guardians prior to inclusion in the study.

Laboratory testing

Serum ALT levels were measured using a commercially available enzymatic test kit (ARCHITECT, Abbott Park, IL). HBV markers were analyzed using a chemiluminescent microparticle immunoassay (CMIA) test kit (ARCHITECT, Abbott Ireland, Sligo).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social

Sciences (SPSS) software for Windows, version 21.0 (SPSS Inc, Chicago, IL). Descriptive statistics, such as means and percentages, were calculated to evaluate the characteristics of the participants. Binary logistic regression analysis was performed to estimate the adjusted odds ratio (OR) with a 95% confident interval (CI) to determine the factors significantly associated with HBsAg positivity. A p -value < 0.05 was considered to be statistically significant.

RESULTS

Characteristics of study population

Table 1
Clinical characteristics of child study subjects.

Characteristics	Number (percent)
Gender	
Male	41 (56)
Female	32 (44)
Age in years	
1-3	22 (30)
4-6	27 (37)
7-10	13 (18)
11-15	10 (14)
16-18	1 (1)
Mode of delivery	
Vaginal	22 (30)
Cesarean section	51 (70)
Received HBIG	
Yes	67 (92)
No	6 (8)
HBsAg	
Positive	9 (12)
Negative	64 (88)
Anti-HBs	
Positive	62 (85)
Negative	11 (15)

HBIG: hepatitis B immune globulin; HBsAg: hepatitis B surface antigen; anti-HBs: hepatitis B surface antibody.

A total of 73 children subjects and 60 HBsAg-positive mothers were included in the study. The mean ($\pm$ standard deviation (SD)) age of children subjects was 5.8 (± 3.7) years. The clinical characteristics of the children subjects are shown in Table 1. Eighteen of 60 mothers (30%) were positive for HBeAg testing. Among the 73 studied children, 9 (12%) had a positive HBsAg test and 62 (85%) had a positive anti-HBs test. There were 3 children subjects with a negative HBsAg test and a negative anti-HBs test. These 3 subjects received one booster dose of HB vaccine and showed an anamnestic response to booster vaccination.

The clinical characteristics of the children subjects with HBsAg positivity are shown in Table 2. Among the 9 subjects with a positive HBsAg test, 5 had HBeAg-positive chronic HBV infection, 2 had HBeAg-positive chronic hepatitis B, and 2 had HBeAg-negative chronic hepatitis B according to EASL classification. The 2 children subjects who had a positive HBsAg test and ALT elevation were confirmed by liver biopsy to have cirrhosis; they were aged 3 and 4 years. One of these two children subjects developed moderate-differentiated hepatocellular carcinoma (HCC) at age 5 years in spite of receiving pegylated interferon therapy for 48 weeks.

On binary logistic regression analysis, maternal HBeAg-positive status was significantly positively associated with the child's HBsAg positivity (Table 3). No other factors were significantly associated with the child's HBsAg positivity.

DISCUSSION

Although the combination of passive and active immunization against HBV has significantly reduced the rate of

maternal-to-child transmission of HBV, transmission still occurs (Chang, 2010; Lin *et al*, 2014; Shao *et al*, 2011). The proposed etiologies for this transmission include a high maternal viral load, intrauterine infection, emergence of vaccine-escape mutants, delayed vaccination, and hyporesponsiveness to the vaccine (Chang, 2010; Ijaz *et al*, 2006; Shao *et al*, 2011). In our study, 30% of maternal subjects had HBeAg, slightly higher than 26% reported from Singapore (Lee *et al*, 2018). In our study, 6% of child subjects whose mother was HBeAg positive became HBsAg positive, slightly lower than 7.9% reported from China (Zhang *et al*, 2014).

Our results show maternal HBeAg positivity is an indicator of active viral replication and is significantly associated with maternal to child HBV transmission in spite of timely immunoprophylaxis in children. The European Association for the Study of the Liver and The American Association for the Study of Liver Diseases have recommended antiviral therapy to reduce the risk of maternal-to-child transmission of HB in HBsAg-positive pregnant women with a HBV DNA level $>200,000$ IU/mL (EASL, 2017; Terrault *et al*, 2016). However, a multicenter study of infants whose mothers had high HB viremia levels from Thailand found no significant difference in the mother-to-child transmission rate for HBV between mothers who received tenofovir and those who received placebo (Jourdain *et al*, 2018). However, the study from Thailand might not reflect the reality of actual practice since in that study, each child received HBIG and the HB vaccine within 2 hours of birth when at our institution those are given within 12 hours of birth.

Immunization of infants against HBV has been found to reduce the risk for

Table 2
Clinical characteristics of child subjects with HBsAg positivity.

Subject	Age in years	Gender	Maternal HBeAg status	Received HBIG	Number of hepatitis B vaccine doses received	Child's HBeAg status	Serum ALT level (units per liter)
1	4	Male	Negative	Yes	5	Positive	254
2	2	Female	Negative	Yes	5	Positive	10
3	13	Male	Positive	No	5	Positive	154
4	2	Female	Positive	Yes	5	Positive	15
5	13	Male	Positive	No	3	Positive	23
6	3	Female	Positive	No	4	Negative	1,408
7	9	Male	Positive	No	4	Positive	24
8	15	Male	Positive	Yes	4	Negative	75
9	12	Male	Positive	No	5	Positive	13

HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B e antigen; HBIG: hepatitis B immune globulin; ALT: alanine aminotransferase.

Table 3
Assessment of association between selected factors and HBsAg positivity among child study subjects.

Factors	HBsAg of child study subjects		OR	95% CI	p-value
	Positive n (%)	Negative n (%)			
Gender					
Male	6 (15)	35 (85)	1		
Female	3 (9)	29 (91)	0.50	0.38-7.21	0.50
Mode of delivery					
Vaginal	1 (5)	21 (95)	1		
Cesarean	8 (16)	43 (84)	1.50	0.02-1.89	0.17
Received HBIG					
Yes	4 (6)	63 (94)	1		
No	5 (83)	1 (17)	0.94	0.72-1.15	0.059
Maternal HBeAg status					
Negative	2 (4)	49 (96)	1		
Positive	7 (32)	15 (68)	2.43	2.14-61.01	0.004

HBsAg, hepatitis B surface antigen; HBIG, hepatitis B immune globulin; HBeAg, hepatitis B e antigen.

developing HCC. A study from Taiwan reported a relative risk for developing HCC of 0.26 among children and young

adults vaccinated against HBV during 1983-2011 compared to unvaccinated counterparts (Chang *et al*, 2016).

Cirrhosis and HCC development are rare in young children. Similar to a previously reported case of a 4-year-old child from Taiwan (Hsu *et al*, 1987), we found 1 case in our study that developed HCC. Risk factors for HBV-related pediatric HCC include perinatal acquisition, immunoclearance state, early seroconversion from HBeAg to anti-HBe (less than 3 years of age), HBeAg negative (pre-core mutants), Genotype B, high HBV-DNA viral loads, persistent HBV-DNA positivity, male gender, maternal HBeAg positivity, family history of HCC, and absent or incomplete HBV vaccination (Khanna and Verma, 2018). In our study, 2 children developed cirrhosis at age 3 and 4 years and one of them developed HCC at age 5 years. This finding underscores the potential seriousness of perinatally acquired HB infection.

All infants born to HBsAg-positive mothers should be considered for post-vaccination serologic testing for HBV markers, including checking anti-HBs and HBsAg testing at age 9-12 months (Schillie *et al*, 2018). Early detection of those who contract HBV infection and appropriate monitoring to identify patients who need interferon or antiviral treatment are crucial to achieve better outcomes.

None of our child subjects were in the HBsAg-negative phase of chronic HBV infection since all the subjects who were negative for HBsAg and anti-HBs developed an anamnestic response following administration of a HB vaccine booster dose. Our study had some limitations: the number of study subjects was small; it was conducted at a single medical school hospital. As a result, the HBV transmission rate and disease severity may not be applicable to the general population. Our retrospective study did not evaluate the maternal HBV

viral load and surface gene mutations in the child subjects who contracted infection which are potential causes of immunoprophylaxis failure.

In conclusion, our findings suggest current strategies used to prevent maternal to child transmission of HBV infection in the study population are unsatisfactory. Further studies are needed to determine the most effective methods to reduce this transmission rate.

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REFERENCES

- Anonymous. Expanded programme on immunization. Global Advisory Group--Part II. *Wkly Epidemiol Rec* 1992; 67: 17-9.
- Anonymous. Hepatitis B vaccines: WHO position paper - July 2017. *Wkly Epidemiol Rec* 2017; 92: 369-92.
- Bialek SR, Bower WA, Novak R, *et al*. Persistence of protection against hepatitis B virus infection among adolescents vaccinated with recombinant hepatitis B vaccine beginning at birth: a 15-year follow-up study. *Pediatr Infect Dis J* 2008; 27: 881-5.
- Bruce MG, Bruden D, Hurlburt D, *et al*. Antibody levels and protection after hepatitis B vaccine: results of a 30-year follow-up study and response to a booster dose. *J Infect Dis* 2016; 214: 16-22.
- Chang MH. Breakthrough HBV infection in vaccinated children in Taiwan: surveillance for HBV mutants. *Antivir Ther* 2010; 15: 463-9.
- Chang MH, You SL, Chen CJ, *et al*. Long-term effects of hepatitis B immunization of infants in preventing liver cancer. *Gastroenterology* 2016; 151: 472-80.

- Chongsrisawat V, Yoocharoen P, Theamboonlers A, *et al.* Hepatitis B seroprevalence in Thailand: 12 years after hepatitis B vaccine integration into the national expanded programme on immunization. *Trop Med Int Health* 2006; 11: 1496-502.
- European Association for the Study of the Liver (EASL). EASL 2017 Clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; 67: 370-98.
- Hammitt LL, Hennessy TW, Fiore AE, *et al.* Hepatitis B immunity in children vaccinated with recombinant hepatitis B vaccine beginning at birth: a follow-up study at 15 years. *Vaccine* 2007; 25: 6958-64.
- Hsu HC, Wu MZ, Chang MH, Su IJ, Chen DS. Childhood hepatocellular carcinoma develops exclusively in hepatitis B surface antigen carriers in three decades in Taiwan. Report of 51 cases strongly associated with rapid development of liver cirrhosis. *J Hepatol* 1987; 5: 260-7.
- Hutin Y, Nasrullah M, Easterbrook P, *et al.* Access to treatment for hepatitis B virus infection - Worldwide, 2016. *MMWR Morb Mortal Wkly Rep* 2018; 67: 773-7.
- Ijaz S, Khulan J, Bissett SL, Ferns RB, Nymadawa P, Tedder RS. A low rate of hepatitis B virus vaccine breakthrough infections in Mongolia. *J Med Virol* 2006; 78: 1554-9.
- Jourdain G, Ngo-Giang-Huong N, Harrison L, *et al.* Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. *N Engl J Med* 2018; 378: 911-23.
- Khanna R, Verma SK. Pediatric hepatocellular carcinoma. *World J Gastroenterol* 2018; 24: 3980-99.
- Lee LY, Chan SM, Ong C, *et al.* Comparing monovalent and combination hepatitis B vaccine outcomes in children delivered by mothers with chronic hepatitis B. *J Paediatr Child Health* 2018; 55: 327-32.
- Li Z, Hou X, Cao G. Is mother-to-infant transmission the most important factor for persistent HBV infection? *Emerg Microbes Infect* 2015; 4: e30.
- Lin X, Guo Y, Zhou A, *et al.* Immunoprophylaxis failure against vertical transmission of hepatitis B virus in the Chinese population: a hospital-based study and a meta-analysis. *Pediatr Infect Dis J* 2014; 33: 897-903.
- Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol* 2018; 3: 383-403.
- Poovorawan Y, Chongsrisawat V, Theamboonlers A, Crasta PD, Messier M, Hardt K. Long-term anti-HBs antibody persistence following infant vaccination against hepatitis B and evaluation of anamnestic response: a 20-year follow-up study in Thailand. *Hum Vaccin Immunother* 2013; 9: 1679-84.
- Posuwan N, Wanlapakorn N, Sa-Nguanmoo P, *et al.* The success of a universal hepatitis b immunization program as part of Thailand's EPI after 22 years' implementation. *PLoS One* 2016; 11: e0150499.
- Schillie S, Vellozzi C, Reingold A, *et al.* Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep* 2018; 67: 1-31.
- Shao ZJ, Zhang L, Xu JQ, *et al.* Mother-to-infant transmission of hepatitis B virus: a Chinese experience. *J Med Virol* 2011; 83: 791-5.
- Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology* 2016; 63: 261-83.
- The Lancet. Towards elimination of viral hepatitis by 2030. *Lancet* 2016; 388: 308.
- VanderEnde K, Gacic-Dobo M, Diallo MS, Conklin LM, Wallace AS. Global routine vaccination coverage - 2017. *MMWR Morb Mortal Wkly Rep* 2018; 67: 1261-4.
- Wang WL, Shu ZJ, Zhou LX, Zhao YR. Clinical characteristics of hepatitis B virus infection in middle school students born after the universal infant vaccination program in

- Shanghai, China. *Arch Virol* 2012; 157: 901-5.
- World Health Organization (WHO). Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. Geneva: World Health Organization; 2016.
- World Health Organization (WHO). Global hepatitis report, 2017. Geneva: World Health Organization; 2017.
- World Health Organization. Hepatitis B vaccines: WHO position paper, July 2017 - Recommendations. *Vaccine* 2019; 37: 223-5.
- Zhang L, Gui XE, Teter C, *et al.* Effects of hepatitis B immunization on prevention of mother-to-infant transmission of hepatitis B virus and on the immune response of infants towards hepatitis B vaccine. *Vaccine* 2014; 32: 6091-7.