

# Effectiveness of prevention of mother-to-child transmission practice in three provinces of Southern China

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Vaccination in prevention mother-to-child transmission (PMTCT) of hepatitis B has been recommended since plasma-derived hepatitis B vaccines became available in China in 1986; however, less study evaluated practice effectiveness of PMTCT systematically. We conducted a prospective survey to evaluate the effectiveness of PMTCT practices in 3 provinces of southern China. We selected prefectures with low timely birth dose coverage in Yunnan, Guangxi, and Hunan provinces. Infants born to HBsAg positive mothers were evaluated at 7–12 months of age. We tested hepatitis B virus (HBV) surface antigen (HBsAg) and HBV e antigen (HBeAg) of mothers and tested HBsAg of infants born to HBsAg positive mothers using Enzyme-linked Immunosorbent Assay (ELISA) at provincial CDC laboratories. We used logistic regression analysis to analyze the risk factors for HBV infection. Among 3,094 infants born to HBsAg positive mothers, 172 were positive for HBsAg (5.6%). HBeAg status of pregnant women, timely birth dose (TBD) of hepatitis B vaccine were major predictors for HBV infection of infants. PMTCT practices greatly reduced the prevalence of HBsAg among infants born to HBsAg positive mothers China. However, the effectiveness of strategies used in PMTCT varied. HBsAg screening for pregnant women, monitoring of infants born to HBsAg positive mother should be enhanced to evaluate the effectiveness of program.

## Introduction

China has been a highly endemic area for Hepatitis B virus (HBV) infection, and 30%–50% of HBV infections were attributed to mother-to-child transmission (MTCT).<sup>1</sup> The consequences of HBV infection vary by age. Approximately 5%–10% of infected adults develop chronic HBV infection, while 90% of infected infants develop chronic infection.<sup>2</sup> An estimated 21% of HBV related deaths are the result of MTCT.<sup>3</sup> Currently the 0, 1, 6 month schedule for hepatitis B vaccines is required for all children born in China. The first dose received within 24 hours after birth is considered as timely birth dose (TBD); the second and third dose should be received 1 and 6 months after birth respectively. TBD is recognized as the key strategy in preventing hepatitis B mother to child transmission. Prevention of HBV infection may be as high as 85%–95% if infants born to HBsAg positive mothers receive hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) within 24 hours following delivery and complete a 3-dose series of hepatitis B vaccine in the follow months.<sup>4</sup> Since in 2011, many provinces could not provide

HBIG for free, parents still had to pay HBIG themselves, which might reduce the coverage of HBIG.

The China national hepatitis B sero-epidemiologic surveys in 1992 and 2006 showed that the prevalence of hepatitis B surface antigen (HBsAg) positivity among childbearing women was 8.2%<sup>5</sup> and 6.6%, respectively.<sup>6</sup> Although hepatitis B vaccine plus HBIG has been recommended for children born to HBsAg positive mothers in 1986, there have been less systematic data to evaluate this prevention of mother-to-child transmission (PMTCT) practice.

## Methods

### Study design

We selected 3 provinces based on the prevalence of HBsAg. According to the National Sero-epidemiological Survey in 2006,<sup>33</sup> the prevalence of HBsAg in Yunnan province, Hunan province and Guangxi province was 3.96%, 6.19% and 11.68% respectively, which could be a good representative for the

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southern China areas. We conducted a prospective survey to evaluate the effect of PMTCT practice in 13 prefectures in the 3 provinces based on HepB vaccine coverage in 2007–2008.

### Study population

Mothers screened HBsAg positive in the hospital before delivery and had a positive confirmatory test by the provincial Center for Disease Control and Prevention (CDC) in 13 prefectures were selected as the study population. Infants born to these HBsAg positive mothers and received 3 doses of vaccines at 0, 1, 6 month schedule were followed up at 7–12 months old. Mothers received antiviral treatments were excluded from analysis.

### Investigation methods

We conducted face to face interviews of the HBsAg positive mothers when their infants were followed up at 7–12 months of age. Information obtained from mother includes maternal age, hospital level, and whether the mother received HBIG during pregnancy. Information obtained from infants included sex, birth date, premature status, birth weight, breastfeeding, and hepatitis B vaccination and HBIG immunoprophylaxis histories. Hepatitis B vaccination and HBIG immunoprophylaxis histories were obtained from immunization certificates. The low birth weight infant is defined as the weight lower than 2.5 kg at birth.

### Specimen collection

HBsAg screening was performed in hospitals before delivery. In order to find as many mothers with positive HBsAg as possible, reagents with high sensitivity and relatively low specificity were used in screening. Infants born to HBsAg positive were followed up at 7–12 months of age for blood collection. Then HBsAg positive blood was sent for confirmation in provincial CDC laboratories to exclude cases with false positive status. We

separated infants' serum in county level CDC laboratories, transported and stored the serum at  $-20^{\circ}\text{C}$ , and tested the serum at provincial CDC laboratories.

### Laboratory testing

All blood samples were sent to the provincial CDC to be tested for final confirmation, hepatitis B e antigen (HBeAg), and antibodies to hepatitis B e antigen (Anti-HBe) were tested for those HBsAg positive samples. In order to exclude mothers with false positive HBsAg status, Enzyme-linked Immunosorbent Assay (ELISA) tests with both high sensitivity and high specificity were used, and the reagents were purchased from Xiamen Xinchuang Production Company.

### Data analysis

Provincial CDC staff doubly entered data into Epidemiology Data (EPI Data) 3.1. Statistical Product and Service Solutions (SPSS) 13.0 was used for data analysis. We conducted multifactor logistic regression analysis using the forward stepwise (Wald) method to enter factors identified by one-way factor analysis.

### Ethical review

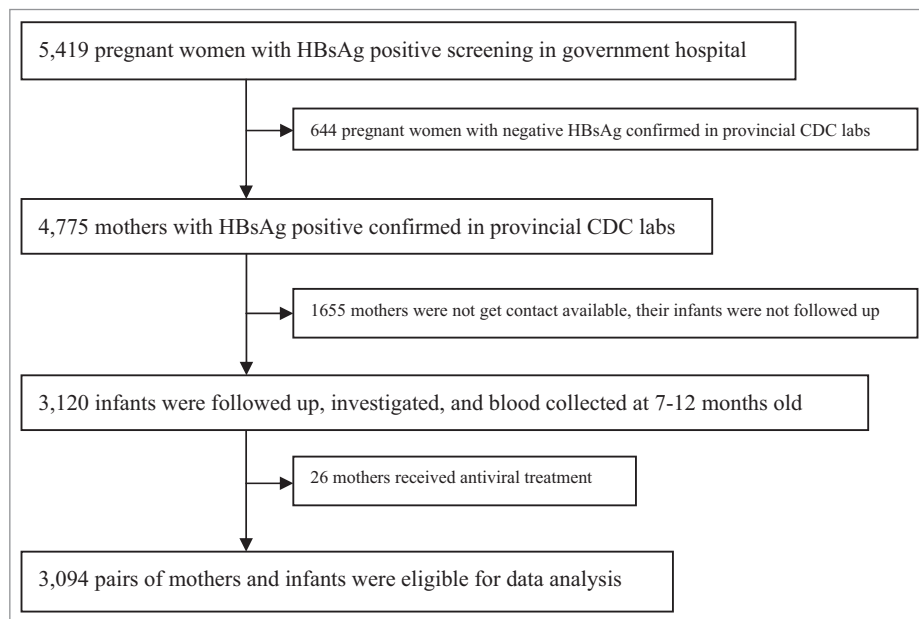
This study was approved by the China CDC Institutional Review Board. We provided the written form to mothers and explain the objectives of the study before interviewing. We obtained consent from mothers by signing the form, meanwhile, the blood of infants was collected and the questionnaires were surveyed.

## Results

There are 5,419 HBsAg-positive mothers were eligible for enrollment in hospitals in 13 prefectures in 2011. Among these, 644 mothers whose samples confirmed negative for HBsAg were excluded, 1,655 mothers were not able to be contacted till 12 months, 3,120 infants were followed up to draw blood samples at 7–12 months of age, 26 mothers received antiviral treatment were excluded. Finally, a total of 3,094 pairs of subjects were eligible for study (Fig. 1).

### Characteristics of the study population

Average age for HBsAg positive mothers was 26.7 years; 1,884 (60.9%) mothers delivered infants at county-level hospitals. The HBeAg positive rate among HBsAg positive mothers was 38.1%. Among investigated infants, 1,685 (54.5%) were male; 534 (17.3%) were 7 months old; 844 (27.3%) were



**Figure 1.** Subject enrollment in the study in south China, 2011.

**Table 1.** Characteristics of the study population in 3 provinces of Southern China, 2011

Category	Guangxi (N = 524)		Hunan (N = 773)		Yunnan (N = 1797)		Total (N = 3120)	
	n	%	n	%	N	%	n	%
Age of mother (years)								
<25	183	34.9	345	44.6	877	48.8	1405	45.4
25~	174	33.2	278	36.0	544	30.3	996	32.2
≥30	167	31.9	150	19.4	376	20.9	693	22.4
Hospital level								
Prefectural or above	90	17.2	112	14.5	260	14.5	462	14.9
County	280	53.4	397	51.4	1207	67.2	1884	60.9
Township	154	29.4	264	34.1	330	18.3	748	24.2
Gender of infant								
Male	280	53.4	444	57.4	961	53.5	1685	54.5
Female	244	46.6	329	42.6	836	46.5	1409	45.6
Age of infant (months)								
7	81	15.5	80	10.3	373	20.8	534	17.3
8	134	25.6	112	14.5	598	33.3	844	27.3
9	102	19.5	173	22.4	481	26.8	756	24.4
10	106	20.2	202	26.1	181	10.1	489	15.8
11	101	19.3	206	26.7	164	9.1	471	15.2
HBeAg status of mother								
Negative	331	63.2	524	67.8	1059	58.9	1914	61.9
Positive	193	36.8	249	32.2	738	41.1	1180	38.1

8 months old; 756 (24.4%) were 9 months old; 489 (15.8%) were 10 months old; and 471 (15.2%) were 11 months old (Table 1).

#### Univariate Analysis on HBsAg Status of Infants

Among the 3,094 infants investigated, 172 were positive for HBsAg (5.6%). The HBsAg prevalence among infants born to HBeAg positive mothers (8.4%) was higher than among infants born to HBeAg negative mothers (3.8%) ( $\chi^2 = 29.11$ ,  $P < 0.001$ ). HBsAg prevalence among infants without TBD (14.1%) was higher than among infants who received a TBD (5.2%) ( $\chi^2 = 14.35$ ,  $P < 0.001$ ). HBsAg prevalence among infants with low birth weight (10.40%) was higher than among infants with normal birth weight (5.4%) ( $\chi^2 = 5.81$ ,  $P < 0.05$ ). HBsAg prevalence of infants who received 5  $\mu\text{g}$  yeast recombinant vaccine, 10  $\mu\text{g}$  yeast recombinant vaccine, and 20  $\mu\text{g}$  Chinese Hamster Ovary (CHO) recombinant vaccine were 9.9%, 5.3%, and 5.0%, respectively ( $\chi^2 = 6.54$ ,  $P < 0.05$ ). There were significant differences in HBsAg positivity between infants who received 5  $\mu\text{g}$  yeast recombinant vaccine and 10  $\mu\text{g}$  yeast recombinant vaccine, and between infants with 5  $\mu\text{g}$  yeast recombinant vaccine and 20  $\mu\text{g}$  CHO recombinant vaccine ( $\chi^2 = 6.23$ ,  $P < 0.05$ ;  $\chi^2 = 4.23$ ,  $P < 0.05$ ). There was no significant difference between infants with 10  $\mu\text{g}$  yeast recombinant vaccine and 20  $\mu\text{g}$  CHO recombinant vaccine ( $\chi^2 = 0.05$ ,  $P > 0.05$ ) (Table 2).

#### Multiple factors analysis on HBsAg status of infants

We used binary logistic regression analysis to identify factors associated with the prevalence of HBsAg of infants. Forward stepwise regression was used to include variables in a regression model. In our model, the dependent variable was the HBsAg status of infants; independent variables, such as HBeAg status of

mother, prematurity, doses of vaccine, TBD, age of infants at follow-up, and use of vaccine and HBIG in combination were included sequentially. Regression analysis showed that infants born to HBeAg positive mother had high HBsAg positive rate than infants born to HBeAg negative mothers (RR = 2.26); infants who did not receive a TBD had high HBsAg positive rate than infants who did not receive a TBD (RR = 2.87); infants more than 10 months old at follow-up (RR = 2.00), and 11 months at follow-up (RR = 2.20) had higher likelihood of HBsAg positive rate than infants who were followed up at 7 months of age. Infants vaccinated with 10  $\mu\text{g}$  yeast vaccine (RR = 0.52) or 20  $\mu\text{g}$  CHO vaccine (RR = 0.47) had lower likelihood of HBsAg positive rate than infants vaccinated with 5  $\mu\text{g}$  yeast vaccine (Table 3).

## Discussion

HBsAg status of pregnant women is an important influencing factor for PMTCT of HBV, particularly the HBeAg is a strong predictor.<sup>7</sup> Study has shown that without intervention, 90% of infants born to HBeAg positive and HBsAg positive mothers will become chronic HBV carriers, while 30% of the infants born to HBsAg positive and HBeAg negative mothers will become chronic HBV carriers.<sup>8</sup> A meta-analysis of PMTCT showed that the probability that infants born to HBsAg positive mothers will become HBsAg carriers can be reduced by 90% by timely vaccination with hepatitis B vaccine and administration of HBIG.<sup>4</sup> Regression analysis showed that infants born to HBeAg positive mother had 2.26 fold high HBsAg positive rates than infants born to HBeAg negative mothers. This study also showed that HBsAg prevalence among infants decreased significantly by TBD vaccination and/or HBIG administration. However, the HBeAg

**Table 2.** Univariate Analysis of HBsAg Prevalence among Infants in 3 provinces of Southern China, 2011

Variables	N	HBsAg Positive Infants		Statistical Tests
		n	%	
Age of mother (years)				
<25	1405	82	5.8	$\chi^2 = 1.15, P = 0.563$
25~	996	49	4.9	
≥30	693	41	5.9	
Hospital level				
Prefectural or above	462	17	3.7	$\chi^2 = 3.65, P = 0.16$
County	1884	111	5.9	
Township	748	44	5.8	
HBeAg status of mother				
Negative	1914	73	3.8	$\chi^2 = 29.11, P < 0.001$
Positive	1180	99	8.4	
Mother received HBIG during pregnancy				
Yes	309	13	4.2	$\chi^2 = 1.71, P = 0.425$
No	2531	147	5.8	
Unknown	254	12	4.7	
Gender of infant				
Male	1685	96	5.7	$\chi^2 = 0.14, P = 0.714$
Female	1409	76	5.4	
Age of infant (months)				
7	534	19	3.6	$\chi^2 = 9.20, P = 0.056$
8	844	48	5.7	
9	756	37	4.9	
10	489	33	6.7	
11	471	35	7.4	
Premature infant				
Yes	144	11	7.6	$\chi^2 = 1.24, P = 0.265$
No	2950	161	5.5	
Low birth weight infant				
Yes	125	13	10.4	$\chi^2 = 5.81, P = 0.016$
No	2969	159	5.4	
Feeding method				
Breast fed	1882	115	6.1	$\chi^2 = 2.78, P = 0.095$
Bottle fed	1212	57	4.7	
Hepatitis B vaccine dose				
5 μg yeast vaccine	172	17	9.9	$\chi^2 = 6.54, P = 0.038$
10 μg yeast vaccine	2585	138	5.3	
20 μg CHO vaccine	337	17	5.0	
Vaccine and HBIG combination				
Yes	2271	123	5.4	$\chi^2 = 0.33, P = 0.564$
No	823	49	5.9	
TBD				
Yes	2995	158	5.2	$\chi^2 = 14.35, P < 0.001$
No	99	14	14.1	
Total	3094	172	5.6	

status of mothers remained the main risk factor for HBV infection.

Timely received birth does is the key measure for infants born to HBsAg positive mothers, which is effective in preventing MTCT. The HBsAg prevalence among infants who did not receive a TBD (14%) was much higher than among infants that received a TBD (5.2%), and was highly significant in the regression analyses. The World Health Organization (WHO) recommends that even in areas with low chronic HBV prevalence, a TBD should be administered within 24 hours of delivery. For infants born to HBsAg positive mothers, HBIG should be administered with the vaccine.<sup>2</sup> As a high chronic HBV prevalence area, China has made use of a TBD as a priority strategy

when hepatitis B vaccines were included into Expanded Program on Immunization (EPI) management in 1992. A major programmatic effort to increase the TBD rate was started in 2004. A national sero-survey in 2006 showed that as the TBD rate increased between 1992 and 2006, and that the HBsAg prevalence rate in the population that received a TBD was significantly lower than in the population not receiving a TBD.<sup>9</sup>

Although some studies have shown that the efficacy of low-dose vaccines (2.5 μg) is similar to the efficacy of 5 μg vaccines after 8 y of follow-up,<sup>10</sup> there has been a common belief that higher-dose vaccine will yield higher the antibody titer after vaccination and better immunologic persistence.<sup>11</sup> For infants born to HBsAg positive mothers, because the immunization strategy

**Table 3.** Multiple Factor Logistic Regression Analysis on HBsAg Status of Infants in 3 provinces of Southern China, 2011

Variables	Category	Frequency	RR	RR 95%CI	P
HBeAg status of mother	Negative*	1914	1		
	Positive	1180	2.26	1.653.10	0.000
TBD	Yes*	2995	1.00		
	No	99	2.87	1.525.40	0.001
Vaccine dose	5 µg yeast vaccine*	172	1		
	10 µg yeast vaccine	2585	0.52	0.310.90	0.018
	20 µg CHO vaccine	337	0.47	0.230.96	0.038
Age of infants (months)	7*	534	1		
	8	844	1.58	0.912.72	0.103
	9	756	1.42	0.802.52	0.228
	10	489	2.00	1.113.60	0.021
	11	471	2.20	1.233.94	0.008
Vaccine and HBIG combination	Yes*	2271	1		
	No	823	0.91	0.641.30	0.601
Low birth weight infants	Yes*	125	1		
	No	2969	0.66	0.351.25	0.198

after delivery is post-exposure prophylaxis, it has been thought to be necessary to increase the vaccine dose. The guidelines for prevention and treatment for chronic hepatitis B in China recommend that infants born to HBsAg positive mothers receive high-dose hepatitis B vaccines (10 µg yeast or 20 µg CHO).<sup>12</sup> In our study, 95% of infants were vaccinated with 10 µg yeast or 20 µg CHO vaccines. The HBsAg prevalence among infants immunized with 10 µg yeast or 20 µg CHO vaccines was lower than among infants immunized with 5 µg yeast vaccines. It suggested that higher vaccine dose provided better PMTCT.

HBIG has high concentration of anti-HB antibodies that can rapidly neutralize virus and prevent HBV infection. However, this passive immunization is not long-lasting, and so it is only an adjunct to HBV TBD vaccination. In the United States, pregnant women are recommended to be screened for HBsAg prior to delivery, and infants born to HBsAg positive mother are recommended to be given hepatitis B vaccines and HBIG simultaneously.<sup>13</sup> In Chinese Taiwan, only pregnant women positive for both HBsAg and HBeAg are recommended to receive vaccine and HBIG together.<sup>14</sup> Studies have shown that the protective efficacy of vaccine combined with HBIG for infants born to HBsAg-positive, HBeAg-positive pregnant women is better than vaccination alone, but that there is no difference in efficacy between vaccine in combination with HBIG and vaccination alone for infants born to HBsAg-positive, HBeAg-negative women.<sup>2,15</sup> Studies show that 10 µg/0.5 ml vaccine without HBIG provides strong protection of infants born to HBsAg positive mothers.<sup>16</sup> In our study, there was no significant difference in the HBsAg positivity rate between infants who received vaccine only and infants who received both vaccine and HBIG. However, we found that for infants born to mothers positive for both HBsAg and HBeAg, the protective rate with the combination of 10 µg yeast or 20 µg CHO vaccines and HBIG (93%) was better than when 10 µg yeast or 20 µg CHO vaccine (88%) was used without HBIG. Considering the supply capacity, safety, and cost of HBIG, the combination of vaccine and HBIG for all infants born to HBsAg positive mothers should be seriously considered.

Hepatitis B vaccine induces good immunologic memory, and booster vaccination is not currently recommended.<sup>17</sup> However, some infants have poor response to HBV vaccination that can be identified at post-vaccination serological testing. In the United Kingdom, it is common practice to offer a booster dose to infants at high risk of HBV infection through intimate contact with HBsAg positive mothers who are found to have anti-HBs titers < 100 IU/ml.<sup>18</sup> In the United States, CDC recommendation for HBsAg negative infants with anti-HBs < 10 IU/ml at post-vaccination serological testing are to be provided an additional 3-dose series of HBV vaccine followed by retesting to confirm protection 2 months after completion of the series.<sup>13</sup>

Our univariate analysis showed no statistically significant differences in HBsAg prevalence among infants in the follow-up age groups ( $P = 0.056$ ). Also, no significant differences were showed among the provinces ( $P = 0.168$ ). Since we used the same the vaccines, test methods, inclusion and exclusion criterion in our study with a strict quality control throughout the process, it was reasonable to find no difference among these provinces. Our multivariable factor analysis showed HBsAg prevalence increasing with infant age at follow up, especially for infants followed up at 10 or 11–12 months, compared with infants followed up at 7 months ( $OR > 2$ ). Others have suggested that follow-up age is important, since increasing follow-up age is associated with increased likelihood of becoming positive HBsAg.<sup>2,19–22</sup> At this stage there was no concrete evidence indicating whether this trend was due to medical reasons or just coincidence. This might be due to horizontal transmission to infants lacking protective antibodies who lived with HBsAg positive mothers or other caregivers. However, proof of horizontal transmission is difficult to obtain.<sup>23,24</sup> Our study showed that post-vaccination serological testing might be necessary. HBsAg and anti-HBs should be measured when infants are 7–9 months of age and have received the complete vaccination series in order to identify infants without protective antibodies who should be revaccinated with HBV vaccine. So we have initialed a long-term cohort study on children born to HBsAg positive mothers to figure out whether there was occult infection by serological and DNA tests, and explore the

consistence of HBV gene between mothers and children who might be at risk for horizontal transmission by gene sequencing analysis.

Some studies have shown that HBIG administration during pregnancy, childbirth delivery method, and infant feeding method influence the HBsAg status of infants born to HBsAg positive mothers,<sup>25</sup> however, this finding is controversial with those studies have shown that Caesarean birth does not reduce MTCT of HBV,<sup>14,26,27</sup> and breastfeeding does not increase risk of HBV infection<sup>28-31</sup> if infants receive a timely birth dose of HBV. The WHO recommends breastfeeding infants born to HBsAg positive mothers, assuming the infants receive the TBD. In our study, we did not find that HBIG administration during pregnancy, delivery or feeding method to be related to the HBsAg prevalence rate in infants on follow up.

There are several limitations to our study. We did not analyze age differences among the HBsAg positive mother subjects, although older women have higher HBsAg and HBeAg prevalence rates. Blood samples of infants <1 year were too small to test anti-HBs, anti-HBc and other markers. We only surveyed infants at 7–12 months old, and long-term impact of PMTCT was not evaluated. A major correlation for mother-to-infant transmission for HBV is the HBV DNA levels of the mothers. Furthermore, recent studies in Taiwan revealed that HBV DNA level is the key predictor/effector for infants infection.<sup>32</sup> In our study, there was no available data on DNA level since most provincial CDC did not have the capacity on DNA tests. During the follow up period, we tried many methods to get access to mothers in our study, but 1655 mothers were still lost. Among them, 641 could be traced but refused to be followed due to privacy (233), unwillingness to be tested again (372) and unknown reasons (36), while 1014 were unable to be traced due to migration (895) and unknown reasons (119). These subjects lost would bring some bias into our study, while the lost happened randomly, currently we could not figure out the direction and size of the potential bias.

Although numerous studies have been done to evaluate the immunogenicity of hepatitis B vaccine, few studies have evaluated comprehensive PMTCT practices in China. In our study,

we chose 3 provinces that with different HBsAg prevalence to be a representative of whole China to show a more comprehensive and reliable results on PMTCT. We can draw some conclusions from our results. First, screening for HBV infection during pregnancy is essential to identify HBV transmission risk during childbirth, and to provide an opportunity for immunoprophylaxis with hepatitis B vaccine and HBIG timely after birth. Since HBsAg screening is not universally implemented among pregnant women, immunization with hepatitis B vaccine within 24 hours of birth for all newborns is still a key strategy to prevent HBV infection during childbirth. Second, for infants born to HBsAg positive mothers, high-dose hepatitis B vaccine should be given as soon as possible after birth. Third, it may be more cost effective to give immunoprophylaxis according to mother's HBeAg status by providing high-dose vaccination only for infants born to HBsAg-positive, HBeAg-negative mothers, and reserve the combination of HBIG with high dose vaccine for infants born to both HBsAg and HBeAg positive mothers. Further study should evaluate the long term impact of prevention.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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