Prevention of perinatal hepatitis B transmission in Haimen City, China: Results of a community public health initiative

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A B S T R A C T

In regions where hepatitis B virus (HBV) is endemic, perinatal transmission is common. Infected newborns have a 90% chance of developing chronic HBV infection, and 1 in 4 will die prematurely from HBV-related liver disease. In 2010, the Hepatitis B Foundation and the Haimen City CDC launched the Gateway to Care campaign in Haimen City, China to improve awareness, prevention, and control of HBV infection citywide. The campaign included efforts to prevent perinatal HBV transmission by screening all pregnant women for hepatitis B surface antigen (HBsAg), following those who tested positive, and administering immunoprophylaxis to their newborns at birth. Of 5407 pregnant women screened, 185 were confirmed HBsAg-positive and followed until delivery. At age one, 175 babies were available for follow up testing. Of those, 137 tested negative for HBsAg and positive for antibodies to HBsAg, indicating protection. An additional 34 HBsAg-negative babies also tested negative for antibodies to HBsAg or had indeterminate test results, were considered to have had inadequate immune responses to the vaccine, and were given a booster dose. A higher prevalence of nonresponse to HBV vaccine was observed among babies born to hepatitis B e antigen (HBeAg)-positive mothers and mothers with high HBV DNA titers. The remaining 4 babies tested positive for HBsAg and negative for antibodies, indicative of active HBV infection. The mothers of all 4 had viral loads >8 × 10⁶ copies/ml in the third trimester. Although inadequate response or nonresponse to HBV vaccine was more common among babies born to HBeAg-positive and/or high viral load mothers, these risk factors did not completely predict nonresponsiveness. All babies born to HBV-infected mothers should be tested upon completion of the vaccine series to ascertain adequate protection. Some babies of HBeAg-positive mothers with high viral load may still become HBV infected despite timely immunoprophylaxis with HBV vaccine and HBIG.

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1. Introduction

Chronic hepatitis B virus (HBV) infection is a major cause of morbidity and mortality globally, causing approximately 600,000 annual deaths due to cirrhosis, liver failure, or liver cancer [1]. HBV is endemic in many areas of the world, including Asia, Africa, and the Pacific Islands. In these regions, mother to child (perinatal) transmission is a common route of infection, due to blood exchange during the childbirth process [2]. In the absence of effective immunoprophylaxis, perinatal HBV transmission rates are 20% to 95%, depending on maternal HBV viral load and hepatitis B e antigen (HBeAg) status [3,4]. A baby infected with HBV perinatally has a 90% chance of developing chronic HBV infection (less than 10% of people infected as adults develop chronic HBV infections) [5]. One in four adults who were infected at birth will die prematurely from HBV-related liver disease [6]. There are effective methods of preventing perinatal transmission, including screening pregnant women for HBV, administering HBV vaccine to babies beginning at birth, and administration of hepatitis B immune globulin (HBIG)

Abbreviations: HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCCDC, Haimen City Center for Disease Control and Prevention; HCHWC, Haimen City Center for the Health of Women and Children; IQR, interquartile range.

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at birth for babies born to infected mothers [7]. Administration of antivirals in late pregnancy to mothers with high viral loads has also been shown to be effective in preventing perinatal transmission [4]. The recommended components of perinatal HBV prevention programs differ by region [8,9]. In 2010, the Ministry of Health in China issued a recommendation that all pregnant women be screened for HBV infection and that their infants receive immunoprophylaxis at birth [10].

In 2010, the Haimen City (China) Center for Disease Control and Prevention (HCCDC), in collaboration with the Hepatitis B Foundation, launched "Gateway to Care," a multi-year city-wide campaign focused on improving prevention and control of HBV infection, and encouraging the adoption of evidence-based HBV infection prevention measures. The campaign included HBV education of the general public, leaders, and medical care providers [11]. A perinatal HBV prevention program was an integral part of the campaign, and included the establishment of a centralized registration system for all pregnant women, testing pregnant women for HBV infection, and delivery of immunoprophylaxis to newborns. In this report we describe the outcomes of perinatal HBV prevention efforts in pregnant women screened for HBV in Haimen City, China over a 12-month period.

2. Methods

2.1. Enhanced screening and prevention initiative

As part of the Gateway to Care city-wide campaign to raise awareness and improve prevention services for hepatitis B in Haimen City, China [11], the HCCDC enhanced its efforts to screen all pregnant city residents for HBV infection, and to follow those women who test positive until the time of delivery when immunoprophylaxis is made available for all infants. Routine prenatal blood testing for hepatitis B surface antigen (HBsAg), and collection of demographic and risk factor data was done by the Haimen City Center for the Health of Women and Children (HCHWC, a public health agency under the Haimen City Health Bureau), usually during the first trimester. Women who initially tested positive for HBsAg were referred to the HCCDC for repeat HBsAg testing, and analysis of additional HBV markers which included HBeAg: antibodies to HBsAg, HBeAg, and hepatitis B core antigen or HBeAg (anti-HBs, anti-HBe, and anti-HBc); and circulating HBV DNA levels (viral load). The women also received education and counseling regarding their test results. The HCCDC recommends that all babies born to HBsAg-positive mothers receive the first dose of HBV vaccine and 100 IU of hepatitis B immune globulin (HBIG) at their birth hospital within 12 to 24 h of birth. Delivery hospitals routinely test for HBV markers when a pregnant woman is admitted before delivery, and free birth dose and HBIG are to be given to the newborn if the woman tests positive. For this study, each woman who was identified as HBsAg-positive during prenatal screening was also given a flash card at her late pregnancy follow-up appointment to bring with her to the delivery hospital as a reminder. The babies born to HBsAg-positive mothers also received follow up HBV testing around 12 months of age, after completing the routine 3-dose course of HBV vaccination. HBV vaccine and HBIG were provided by the Haimen City government without charge to the patients and were administered at the birth hospital, where appropriate refrigeration was available. All births in this study occurred in hospitals in Haimen City.

2.2. Laboratory analysis

Routine immunoassays for HBV markers (HBsAg, HBeAg, anti-HBs, anti-HBe, anti-HBc) were performed at HCCDC using the Hepatitis B virus HBsAg (or other markers) Testing Kit manufactured by Shanghai Kehua Bioengineering Company, Ltd. HBV viral load was quantitated using the Hepatitis B Virus DNA PCR-Fluorescence Detection Kit real time PCR (Shanghai Kehua Bioengineering Company, Ltd) via real time PCR on the FluoCycle Real-time PCR Detection System manufactured by Shanghai Kehua Laboratory System Company, Ltd. This assay has a lower limit of detection of ~500 copies/ml.

2.3. Immunoprophylaxis

HBV vaccine administered to infants was a 10 μg dose from Dalian Hissen Bio-Pharm Company, Ltd. HBIG was administered as a single 100 IU dose from Sichuan Yuanda Shuyang Pharmaceutical Company, Ltd.

2.4. Data analysis

Records from women seeking prenatal care from HCHWC from July 1, 2011 through June 30, 2012 were abstracted and reviewed for program evaluation purposes and provided in fully anonymized form for the study reported herein. Ethical approval for this analysis of the program data was provided by the Ethics Review Committee of Haimen City.

Statistical analyses were performed using SAS v 9.3. For continuous variables, Wilcoxon rank sum test was used for variables where the interquartile range (IQR) is given, due to non-normality of distributions. Where mean and standard deviation are given, Student’s t-test was used. For comparison of proportions, Fisher’s exact test was used.

3. Results

3.1. Mothers

Prenatal care and delivery records for 5407 women screened for HBsAg by HCHWC were reviewed. Of these, 5129 (94.9%) tested HBsAg-negative and 278 (5.1%) initially tested positive (Fig. 1). Demographically, the women whose initial HBV tests were positive were slightly younger than those testing negative, but were similar in level of education, number of previous births, and type of delivery in the index pregnancy (Table 1). (Note that the Caesarean section rate, although high, is consistent with the general rate across China.) [12]. There were statistically significant differences in the frequency of self-reported past HBV vaccine and previous HBV testing between the women with initial positive vs. negative HBsAg tests. Women who tested initially positive for HBsAg were less likely to report previous HBV vaccination, and more likely to report previous HBV testing. Among those who reported a previous (pre-pregnancy) HBV test, the women with initially positive HBsAg tests were more likely to report that the previous test was positive, and much less likely to report not knowing the result of their previous HBsAg test than women who tested HBsAg-negative (Table 1).

The 278 women with initially positive HBsAg tests were referred to the HCCDC for repeat testing in the third trimester. Of these, 185 (66.5%, or 3.4% of the original 5407 screened) were confirmed positive on the second test, 12 (4.3%) tested HBsAg-negative, and 81 (29.1%) did not return for repeat testing (Fig. 1). The 185 women confirmed to be HBsAg positive upon repeat testing were further evaluated for the presence of anti-HBc, HBeAg, and anti-HBe, and circulating HBV DNA levels in the third trimester. In samples from 127 (68.6%) of these women, HBV viral loads were below the assay’s limit of detection (500 copies/ml). The median viral load for the remaining 58 women was 1.1 × 10^7 copies/ml (IQR 1.6 × 10^6–2.5 × 10^7). The distribution of HBV viral load in the 185 confirmed HBsAg-positive mothers is shown in Fig. 2. Forty-nine of
Fig. 1. Summary of HBV screening results for 5407 pregnant women seeking prenatal care from HCHWC from July 1, 2011 through June 30, 2102. Infants born to HBsAg-positive mothers were given HBV vaccine and HBIG within 24 h of birth (see Fig. 3). At approximately one year of age, 175 infants were screened for HBsAg and further evaluated as appropriate.

Table 1
Demographics and self-reported pre-pregnancy HBV vaccine and HBV testing status among women with initial positive vs. negative HBsAg tests.

<table>
<thead>
<tr>
<th></th>
<th>Initial test HBsAg-negative (N=5129)</th>
<th>Initial test HBsAg-positive (N=278)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age (mean ± SD)</td>
<td>25.0 (4.3)</td>
<td>26.1 (4.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Education &gt; high school N (%)</td>
<td>2094 (40.8)</td>
<td>109 (39.2)</td>
<td>0.64</td>
</tr>
<tr>
<td>Delivery (index pregnancy) N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>102 (40.0)</td>
<td>2150 (45.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>153 (60.0)</td>
<td>2616 (54.9)</td>
<td></td>
</tr>
<tr>
<td>Nulliparous N (%)</td>
<td>4065 (79.3)</td>
<td>213 (76.6)</td>
<td>0.29</td>
</tr>
<tr>
<td>Self reported pre-pregnancy HBV status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous HBV vaccine N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2208 (43.1)</td>
<td>90 (32.4)</td>
<td>0.0005</td>
</tr>
<tr>
<td>No</td>
<td>1367 (26.7)</td>
<td>99 (35.6)</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>1554 (30.3)</td>
<td>89 (32.0)</td>
<td></td>
</tr>
<tr>
<td>Previous HBV test N (%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>1243 (24.3)</td>
<td>163 (58.6)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3112 (60.7)</td>
<td>93 (33.5)</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>774 (15.1)</td>
<td>22 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Previous HBV test result N (%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Positive</td>
<td>6 (0.5)</td>
<td>143 (88.3)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1054 (84.8)</td>
<td>17 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>183 (14.7)</td>
<td>2 (1.2)</td>
<td></td>
</tr>
</tbody>
</table>

* Among those self-reporting both test and result.

185 (26.5%) women tested HBeAg-positive, and 136 (73.5%) were HBsAg-negative. Viral load was significantly higher in the HBeAg-positive (median 1.2 × 10^7, IQR 8.7 × 10^5–3.6 × 10^7) compared to HBsAg-negative women (median 0, IQR 0–0) (p < 0.0001).

3.2. Infants

Delivery hospital records were available for review for 183 (98.9%) of 185 babies born to mothers confirmed to be HBsAg-positive. All 183 babies (100%) received both hepatitis B vaccine and HBIG within 23 h of birth (Fig. 3). The median time was 2 h (IQR 1–4) after birth for vaccine administration, and 1 h (IQR 1–2) after birth for HBIG. For comparison, a related retrospective survey found that 98.9% of the babies born to HBV-infected women, and 98.5% of babies born to non-infected women, received birth dose of HBV vaccine in 2010 (Haimen City CDC unpublished data). All 183 babies completed the full 3-dose schedule for HBV vaccine as recommended for all infants in Haimen City. Follow up HBV marker testing was recommended by HDCDC for these 183 babies born to confirmed HBsAg-positive mothers, after completion of the vaccine series. Testing was done, on average, 365 days after birth (standard deviation 67, range 290–659 days). Serologic test results for HBsAg, anti-HBs, anti-HBc, and HBeAg from 175 babies were available. (Multiple attempts were made to test all babies born to infected women in the cohort, however 10 babies were out of town with their parents who work in other cities and they were unavailable for further testing.)

Four babies (2.3%) were found to be HBsAg-positive (indicative of active HBV infection), and all four were also HBeAg-positive, anti-HBc-positive, and had no detectable antibodies to HBsAg. All four of these HBsAg-positive babies had received HBV vaccine and HBIG no more than 11 h after birth. The mothers of all four HBsAg-positive babies were HBeAg-positive and had viral loads between 8 × 10^6 and 5 × 10^7 copies/ml in the third trimester (Table 2). Mothers whose babies became HBeAg-positive had higher viral loads than those whose babies remained negative (median 2.4 × 10^7 vs. 0, p = 0.0012) and were more likely to be HBeAg-positive (100% vs. 25.2%, p = 0.005). The transmission rate among babies of
HBsAg-positive mothers was 8.2% (4/49, 95% CI 3.2–19.2%). Within the group of HBsAg-positive mothers, however, there was no statistically significant difference in median maternal viral load for the HBsAg-positive vs. -negative babies (medians $2.4 \times 10^7$ vs. $1.2 \times 10^7$, $p = 0.46$).

A total of 171 babies tested HBsAg-negative. Of these, 137 (80.1%) tested anti-HBs positive (indicative of protection from HBV). Two of the babies testing anti-HBs-positive were also anti-HBc-positive and were therefore considered to have had and cleared transient infections (Table 2). Of the 34 anti-HBs-negative babies, 9 (26.5%) had indeterminate tests for anti-HBs, and 25 (73.5%) were anti-HBs-negative. Although it is possible that they had protective levels of antibody that had waned by the time they were tested for anti-HBs, for the purposes of this study these 34 babies were considered to have inadequate immune responses to the HBV vaccine and were referred for booster doses. The babies with inadequate response to vaccination were more likely to have HBsAg-positive mothers (relative risk 1.7, 95% CI 1.0–3.0), and higher maternal HBV viral loads than babies who seroconverted to anti-HBs-positive after vaccination ($p = 0.04$) (Table 3). The median viral load was lower than the limit of detection for both groups, but the IQR was broader for those with inadequate response (Table 3).

Delivery records were also sought for the 81 initially HBsAg-positive mothers who did not go to the HCCDC for confirmatory HBsAg testing during their pregnancies. Of these 18 (22.2%) had no records found, indicating that they did not deliver in a Haimen City hospital, or did not complete the pregnancy. Of the 63 (77.8%) with birth records, all babies received both the birth dose of HBV vaccine and one dose of HBIG administered within 24 h of birth, but these babies were not followed for HBV infection and vaccine response endpoints. Mothers who had not returned for confirmatory HBsAg testing were less likely to be nulliparous than those who did (67.9% vs. 80.0%, $p = 0.03$) but did not differ significantly on other demographic variables.

4. Discussion

Public health disease prevention programs usually work best when there is awareness of the problem and engagement in the solution at multiple levels of the health care system. This paper reports the outcomes of enhanced perinatal HBV prevention efforts in Haimen City, China. These efforts were instituted as part of a focused campaign to raise public and provider awareness of HBV infection, its impact in the population, and the available tools for prevention and control of infection. Along with education of the public and health care providers, a high priority was placed on the screening of all pregnant women, follow-up and education for all those found to be infected, and delivery of post-exposure prophylaxis to their newborns. HBV perinatal prophylaxis for infants born to infected mothers, including both HBV vaccine and HBIG within 12 to 24 h of birth, was shown to be feasible and very effective in

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**Table 2**

Maternal and infant characteristics for 6 infants found to be HBsAg-positive and/or anti-HBc positive.

<table>
<thead>
<tr>
<th>Baby HBsAg-positive/anti-HBc-positive/anti-HBs-negative</th>
<th>Maternal HBsAg</th>
<th>Vaccine/HBIG timing (hours after delivery)</th>
<th>Delivery method</th>
<th>Infant follow-up testing (days after birth)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$8 \times 10^6$</td>
<td>+</td>
<td>11</td>
<td>Cesarean</td>
</tr>
<tr>
<td>2</td>
<td>$2 \times 10^7$</td>
<td>+</td>
<td>2</td>
<td>Cesarean</td>
</tr>
<tr>
<td>3</td>
<td>$3 \times 10^7$</td>
<td>+</td>
<td>1</td>
<td>Vaginal</td>
</tr>
<tr>
<td>4</td>
<td>$5 \times 10^7$</td>
<td>+</td>
<td>1</td>
<td>Vaginal</td>
</tr>
</tbody>
</table>

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**Fig. 2.** Distribution of maternal HBV DNA levels during the 3rd trimester for HBsAg-positive women. Stars indicate the viral load of 4 mothers whose babies tested HBsAg-positive at one year old.

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**Fig. 3.** Cumulative distribution of time of HBV vaccine and HBIG administration to babies born to HBsAg-positive mothers 1 to 24 h after delivery. (N = 183).
preventing perinatal transmission in this population, where it has been instituted as part routine care in an enhanced public health program [11].

For the group reported in this study, which had especially good adherence to a standard immunoprophylaxis protocol, the overall infection rate among the babies born to infected women was low (4/175 babies screened, 2.3%). These results are similar to that seen in other studies and speak to the fact that the intervention (HBV vaccine and HBIG) was highly successful, preventing perinatal transmission of HBV infection in 97.7% of babies screened [13–16]. All of the HBsAg-positive babies were born to mothers who were HBsAg-positive (4/49, 8.2%), and had maternal viral loads $>8 \times 10^6$ copies/ml in the third trimester. Follow-up testing of babies showed that among those not infected, there is a higher prevalence of nonresponse to HBV vaccines among those born to HBeAg+ mothers. Moreover, in the two babies who may have experienced transient infections, one was born to a mother who was HBeAg-negative and had a viral load lower than the detection limit of the assay. As noted above, public health officials administered booster doses of vaccine to all babies showing inadequate response to the first course of vaccine. Of 18 babies retested thus far, 15 (83.3%) had converted to anti-HBs-positive, indicating a response to the booster vaccine.

This analysis is based on administrative data collected by the HCCDC for program evaluation. There was no control or untreated group, so we cannot know directly what the transmission rate would have been without the immunoprophylaxis. Women who chose to participate in this program were similar to those who initially tested HBsAg-positive but did not participate except that the non-participants were less likely to be nulliparous. Perinatal transmission rates have been estimated at 85% and 31% for HBsAg-positive and –negative mothers, respectively [17]. Our study and others have shown that this transmission rate is greatly reduced with effective and timely immunoprophylaxis at birth. In this very high risk population, with a maternal HBsAg prevalence >5% and HBeAg prevalence among HBsAg-positives >26%, the potential impact of timely intervention is high, as it would be for other similar populations worldwide. It appears, however, that even with optimal timing of this intervention, some infections still occur, possibly in utero [18,19], 4/175 babies tested (2.3%) in our study. In some parts of the world, the use of antiviral medications in late pregnancy is becoming a more common practice, especially for mothers with high viral load and detectable HBeAg. With the use of antivirals, however, consideration of the appropriateness of long-term treatment and the risk of postpartum flare or viral load rebound must be a factor in the decision [4]. (In this study, there were no women receiving antiviral treatment during pregnancy and it is not offered by physicians in Haimen City.)

HBV perinatal prevention programs should ideally include follow-up of babies born to infected mothers to detect infections and monitor vaccine response. Follow-up of infants is not a routine practice and for this study, significant efforts were made to test the majority of babies born to infected women within the one-year period. In this study, we noted a high proportion (~20%) of babies who received timely immunoprophylaxis at birth and tested either negative or indeterminate for anti-HBs at approximately 1 year of age, consistent with findings in another studies [20,21]. Public health officials from HCCDC are now following these babies after delivery of booster doses of vaccine. It is important to note that inadequate response or nonresponse to HBV vaccine was more common among babies born to HBeAg-positive and/or high viral load mothers, but these risk factors did not completely predict nonresponsiveness. It is important to further evaluate infected pregnant women for their HBsAg status and viral load, and to do follow-up antibody testing for all babies born to infected mothers to ascertain whether they are adequately protected from infection in the future.

In many ways, the community setting in Haimen City, China during this time period was ideal for effective perinatal prevention. As part of the Gateway to Care campaign, the general population’s awareness and knowledge of HBV infection had been raised, and health care providers throughout the community had received training on HBV prevention and treatment. Particular care was taken to make personnel at all levels of the medical care system aware of the need to screen pregnant women and perform appropriate and timely immunoprophylaxis for their babies. To replicate the success of the Haimen City campaign elsewhere, there should be a similar commitment to public and provider education, availability of immunoprophylaxis at delivery, and continued monitoring of both mothers and babies to identify HBV infection, prevent perinatal transmission, and ensure vaccine protection of babies.

### Conflict of interest statement

The authors have declared that no competing interests exist.

### Author contributions

Participated in conducting the research: PH LQ GC. Analyzed the project results: AAE CC JMB GC. Prepared first draft: AAE. Contributed to revisions of manuscript: AAE CC WTL JMB GC. All authors have approved the final article.

### Ethics statement

This study used anonymized records from women seeking perinatal care from HCHWC. The authors’ use and analysis of this data was reviewed and approved by the Medical Ethics Review Committee of Haimen City.

### Acknowledgements

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**Table 3**

Maternal characteristics for babies with adequate vs. non/indeterminate antibody response to 3 doses of HBV vaccine. (All mothers were confirmed HBsAg-positive.)

<table>
<thead>
<tr>
<th></th>
<th>Vaccine responders (N=137)</th>
<th>Vaccine nonresponders (N=34)*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother HBeAg-positive [N (%)]$^4$</td>
<td>30 (21.9)</td>
<td>11 (38.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Mother HBV viral load median (IQR)$^4$</td>
<td>$&lt;5 \times 10^7$ ($&lt;5 \times 10^6$–$2 \times 10^7$)</td>
<td>$&lt;5 \times 10^7$ ($&lt;5 \times 10^6$–$9 \times 10^7$)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

$^4$ Excluding HBsAg-positive babies (N=4).

$^5$ From maternal testing in third trimester.
Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.01.054.

References