The effects of increased dose of hepatitis B vaccine on mother-to-child transmission and immune response for infants born to mothers with chronic hepatitis B infection: a prospective, multicenter, large-sample cohort study

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Abstract

**Background:** Appropriate passive-active immunoprophylaxis effectively reduces mother-to-child transmission (MTCT) of hepatitis B virus (HBV), but the immunoprophylaxis failure was still more than 5% under the current strategy. The study objective was to investigate the effects of high dose of HB vaccine on MTCT and immune response for infants born to hepatitis B surface antigen (HBsAg)-positive mothers.

**Methods:** This was a prospective, multicenter, large-sample cohort study in four sites of China, and 955 pairs of HBsAg-positive mothers and their infants were enrolled in our investigation. The infants were given 10 μg or 20 μg HB vaccine (at age 0, 1, and 6 months) plus HB immunoglobulin (at age 0 and 1 month). Serum HBsAg, antibody to HBsAg (anti-HBs), and/or HBV DNA levels in the infants were determined at age 12 months. The safety of 20 μg HB vaccine was evaluated by adverse events and observing the growth indexes of infants.
Results: Thirteen of 955 infants were HBsAg-positive at 12 months. Stratification analysis showed that immunoprophylaxis failure rates in the 20 μg group were not significantly different from the 10 μg group, whatever maternal HBV load was high or not. But the high dose of HB vaccine significantly reduced low-response rate (anti-HBs 10–100 IU/L) (P = 0.002) and middle-response rate (anti-HBs 100–1000 IU/L) (P = 0.022) and improved high-response rate (anti-HBs ≥ 1000 IU/L) (P < 0.0001) in infants born to mothers with HBV DNA < 5 log_{10} IU/mL. For infants born to mothers with HBV DNA ≥ 5 log_{10} IU/mL, 20 μg HB vaccine did not present these above response advantages. The 20 μg HB vaccine showed good safety for infants.

Conclusions: The 20 μg HB vaccine did not further reduce immunoprophylaxis failure of infants from HBsAg-positive mothers, but increased the high-response and decreased low-response rates for infants born to mothers with HBV DNA < 5 log_{10} IU/mL.

Trial registration: Chinese Clinical Trial Registry, ChiCTR-PRC-09000459

Keywords: Hepatitis B vaccine, High dose, Mother-to-child transmission, Immune response

Background
Chronic hepatitis B virus (HBV) infection remains a serious threat to public health and is associated with cirrhosis and hepatocellular carcinoma (HCC) in China. It is estimated that the prevalence of hepatitis B surface antigen (HBsAg) in China is 5–6% at present, and about 70 million persons have chronic HBV infection, including 20–30 million chronic HB (CHB) patients [1, 2]. In high-endemic areas, mother-to-child transmission (MTCT) is the main route of HBV infection. According to guidelines for the prevention of CHB, passive-active combined immunization can reduce the rate of MTCT from 75–90% to 10%. Infants received 100 IU HB immunoglobulin (HBIG) intramuscularly and 10 μg HB vaccine within 12 h after birth, with additional HB vaccination at 1 and 6 months. However, immunoprophylaxis failure rate is 5–10% in infants born to mothers positive for HBsAg and HB e antigen (HBeAg) [3, 4].

HBIG injection in late pregnancy seems to have little effect on reducing MTCT of HBV [5–7]. At present, it is recommended that the pregnant women with high viral load take tenofovir disoproxil fumarate or telbivudine orally in the second or third trimester to reduce further the rate of MTCT, but the long-term safety of mothers and infants and hepatitis flare after postpartum discontinuation are controversial [8].

HB vaccine has 95% effectiveness in preventing HB infection and has a good safety record [1]. Many previous studies have shown that 20 μg HB vaccine can significantly improve the seroprotection in adults compare to 10 μg HB vaccine [9–11]. The current recommended dose of recombinant HB vaccine for infants in China is 10 μg [12]. In our previous study, after three doses of the HB vaccine, 1.4% of infants born to HBsAg-positive mothers did not achieve a protective level (anti-HBs ≤ 10 IU/L), and 3.7% of infants had a low response level (anti-HBs 10–99 IU/L) [13]. These infants face potential infective risk in their daily lives being in close contact with HBsAg-positive mothers. Vaccine type, low birth weight, and high maternal viral load have been identified as the most important risk factors for low immune response to HBV vaccine. In addition, host genetic background also plays an important role in determining the strength of immune response to vaccination, such as variants in human leukocyte antigen (HLA) region, mitogen-activated protein kinase eight polymorphisms [14]. Few studies have been reported about the effects of increased dose of HB vaccine on infants born to HBsAg-positive mothers. Therefore, we conducted a prospective, multicenter, large-sample cohort study to evaluate the effects of increased dose of HB vaccine (20 μg) on MTCT of HBV and immune response in infants born to HBsAg-positive mothers.

Methods
Study design
This was a prospective, multicenter, large-sample study. Patients were recruited from 4 hospitals in Beijing, Shijiazhuang, Taiyuan, and Tongliao, China. We evaluated and compared the effects of 20 μg HB vaccine on infants born to HBsAg-positive mothers, including immunoprophylaxis failure, immune responses to vaccine, and vaccine safety. The HBsAg-positive mothers were enrolled at 24–28 weeks’ gestation, and peripheral blood samples were collected at parturition for chemical and hematological tests. Demographic information of their infants was recorded at birth, including sex, singleton status, gestational age, birth weight, delivery mode, and 1-min APGAR scores as the baseline data. The infants were divided into two groups according to their mothers’ wishes: 10 μg (0.5 mL) recombinant HB vaccine plus HBIG (10 μg group) and 20 μg (1 mL) recombinant HB vaccine plus HBIG (20 μg group). The details of informed consent are described in Additional file 1: Appendix 1, Methods. All the vaccinations were completed at the corresponding investigational sites, and the
adverse events were recorded at each follow-up at 1, 6, and 12 months. At 12 months, peripheral serum samples were taken from infants after standard immunoprophylaxis, and their HBsAg, anti-HBs, HBeAg, anti-HBe, and HB core antibody (anti-HBc) were tested. If the infant was positive for HBsAg, HBV DNA was further tested. The fetal development and infant growth were evaluated at 12 months in both HB vaccine groups. The study protocol was approved by each institutional Ethics Committee and registered at Chinese Clinical Trial Registry (ChiCTR, No. ChiCTR-PRC-09000459).

**Patients**

Patient screening began from January 2009 to September 2010, and the last patient visit was on October 2011. The inclusion criteria for the mothers were as follows: HBsAg positive for > 6 months; age 18–45 years; and willing to cooperate with collection of documented information from 24 to 28 weeks’ gestation, the corresponding intervention measures, follow-up, and detection according to the informed consent. Major exclusion criteria for mothers were (1) infection with hepatitis C/D, human immunodeficiency virus, Treponema pallidum or Toxoplasma gondii; (2) treated with HBIG or antiviral therapy including interferon within 6 months before or during pregnancy; (3) alanine aminotransferase (ALT) ≥ 2 μmol/L, indicating cirrhosis and other liver diseases; (4) malignant tumor or definite disease in the cardiovascular, respiratory, urinary, nervous, digestive, blood, endocrine, or metabolic systems; (5) long-term use of hormones or immunosuppressive agents; and (6) taking part in other studies. The major exclusion criteria for infants were (1) prematurity (born at less than 36 weeks’ gestation), (2) birth weight < 2000 g, (3) congenital malformation, and (4) taking part in other studies.

**Immunization schedule**

All infants born to HBsAg-positive mothers had the following prophylaxis schedule: the first dose of 200 IU HBIG (Chengdu Institute of Biological Products, China or Hualan Biological Engineering Inc., China) and the first dose of 10 μg (0.5 mL) or 20 μg (1 mL) recombinant HB vaccine (Hansenula yeast vaccine; Dalian Hissen Biopharm Co., China) were given intramuscularly within 2 h of birth at different sites. The second injection of the same dose of HBIG was administered at 1 month of age. The second and third doses of recombinant HB vaccines were given at 1 and 6 months of age, respectively.

**Serum biochemistry and HBV markers**

All serum specimens were tested in the hospital central laboratory. The presence of HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc was determined using an electrical chemiluminescence immunoassay (Roche Laboratories, Mannheim, Germany) or chemiluminescent microparticle immunoassay kit (Architect i2000 analyzer; Abbott Diagnostics, Abbott Park, IL, USA). All the serum samples for HBV DNA were tested by real-time polymerase chain reaction with a range of 2–8 log$_{10}$ IU/mL (Hunan Shengxiang Bio-engineering). ALT was measured by a fully automatic biochemical analyzer (AU5400; Olympus Optical, Tokyo, Japan). ALT > 40 IU/L was considered abnormal.

**Outcome assessment and definitions**

The primary outcome was immunoprophylaxis failure, which was defined as infants who were HBsAg-positive at age 12 months [15, 16]. The secondary outcome was response status of infants to HB vaccine. All the HBsAg-negative infants (successful immunoprophylaxis) were divided into 4 groups as follows: anti-HBs < 10 IU/L was defined as non-responder, anti-HBs 10–100 IU/L was low-responder, anti-HBs 100–1000 IU/L was medium-responder, and anti-HBs ≥ 1000 IU/L was high-responder [13].

**Statistical analysis**

The database was established with EpiData 3.02. Continuous variables values were expressed as the mean ± standard deviation (SD); categorical variables were expressed as percentages. The characteristics of infants who received different doses of the HB vaccine were compared by independent t-test and/or χ² test or Fisher’s exact test. The maternal HBV DNA level, ALT, and TBIL in two groups were compared by the Mann-Whitney U-test. The immunoprophylaxis failure rates (MTCT of HBV) in two doses of HB vaccines were cooperated, and the planned sample size of 955 patients was estimated to provide at least 85% power to detect an absolute difference of 3% in the proportion of infants with HBV infection at 12 months on the basis of two-tailed α = 0.05 and assuming an MTCT rate of 5% in the 10 μg HB vaccine group. A multivariate logistic regression model was fitted with a stepwise method (likelihood ratio test) using significant baseline characteristics (candidate variables such as mother age, HBV DNA ≥ 5 log$_{10}$ IU/mL, and other clinical indicators with P < 0.20 in Table 1) that had been prefiltered in univariate analysis to identify factors independently associated with vaccine dose grouping. The response rates of different degrees in infants between two doses of groups were compared by χ² test or Fisher’s exact test. The developmental indexes of infants at 12 months between two groups were compared by independent t-test or Mann-Whitney U-test. The data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) or GraphPad Prism version 5.0.
Results
Study populations
The study was performed at 4 investigational sites in China. A total of 1004 infants born to 1001 HBsAg-positive mothers (3 mothers had twins) were enrolled, and the numbers of patients enrolled from each site were as follows: 668 in Beijing, 108 in Taiyuan, 125 in Shijiazhuang, and 100 in Tongliao. At 12 months, a total of 955 infants completed the study, there were 478 infants who completed the follow-up in the 10 μg group, and 477 infants completed the follow-up in 20 μg HB group (Fig. 1); the groupings of these infants in respective site are showed in Additional file 1: Appendix 2 Table S1. The demographic characteristics of infants at birth and their mothers with chronic HBV infection in each group are shown in Table 1.

As more HBeAg-positive mothers with or without high load of HBV DNA prefer to choose high dose of HB vaccine (20 μg) for their infants, therefore, both the HBeAg-positive rate and HBV DNA levels in mothers in the 20 μg group were higher than those in the 10 μg group (both \(P < 0.001\), Table 1). Further, we used multivariable logistic analysis to screen the possible founders (in Table 1) that lead to the differences between the high and low vaccine groups. Results showed that the high level of maternal HBV DNA (≥5 log_{10} IU/mL) was the independent factor of differences in baseline characteristics between two dose groups (\(P < 0.001\)) (OR = 0.481, 95% CI 0.362–0.639). Therefore, we did stratified analysis in the following investigation according to the maternal HBV DNA level.

The outcomes to HB vaccines in infants born to HBsAg-positive mothers
Of the 955 infants after the standard immunization schedule, 13 infants were positive for HBsAg at 12 months, who were considered as immunoprophylaxis failure, and 942 were negative for HBsAg, who were considered as immunoprophylaxis success. The total rate of immunoprophylaxis failure was 1.4% (13/955). The characteristics of infants and their mothers between the two outcomes are shown in Additional file 1: Appendix 2 Table S2; high level of maternal HBV DNA and HBeAg-positive were the major differences between immunoprophylaxis failure and success. Among the 13 HBsAg-positive infants, 5 were in the 10 μg group and 8 were in the 20 μg group. The baseline characteristics of the infants at birth and HBV infection status at age 12 months are shown in Table 2. At 12 months, all the 13 HBsAg-positive infants were positive for HBeAg and anti-HBc.

The response differences to HB vaccine between low-dose and high-dose groups
Regarding the influence of high level of maternal HBV DNA, we compared the immunoprophylaxis failure rate and response status of infants between 10 μg and 20 μg groups by stratified analysis. There were 601 infants born to HBsAg-positive mothers with HBV DNA < 5 log_{10} IU/mL, 350 were in the 10 μg group and 251 were in the 20 μg group. None of the infants was positive for HBsAg in the 10 μg group (0%, 0/350), and 1 was positive in the 20 μg group (0.4%, 1/251); the immunoprophylaxis failure rates between two groups were not significantly different (\(P = 0.418\), Table 3). However, the high-response rate in the 20 μg group (42.2%, 106/251) was evidently higher than that in the 10 μg group.

| Variables                      | 10 μg (n = 478) | 20 μg (n = 477) | \(P\) value |
|--------------------------------|----------------|----------------|-------------|
| Maternal data                  |                |                |             |
| Age (years)                    | 27.3 ± 4.5     | 26.8 ± 4.6     | 0.076       |
| HBeAg positive                 | 154 (32.2%)    | 270 (55.0%)    | < 0.001     |
| HBV DNA (log_{10} IU/mL)       | 2.6 ± 2.9      | 3.5 ± 3.2      | < 0.001     |
| HBV DNA ≥ 5 (log_{10} IU/mL)   | 128            | 226            | < 0.001     |
| ALT (IU/L)                     | 15.2 ± 8.6     | 15.6 ± 13.4    | 0.593       |
| TBIL (μmol/L)                  | 9.9 ± 6.5      | 9.3 ± 4.0      | 0.161       |
| Infant data at birth           |                |                |             |
| Sex (male)                     | 264            | 270            | 0.669       |
| Gestation days                 | 277.0 ± 6.9    | 278.4 ± 7.3    | 0.450       |
| Birth mode (vaginal delivery)  | 184 (38.4%)    | 210 (44.0%)    | 0.083       |
| Birth weight (g)               | 3625 ± 349.0   | 3508 ± 380.1   | 0.150       |
| 1-min APGAR                     | 9.6 ± 0.1      | 9.5 ± 0.2      | 0.140       |

Abbreviations: ALT alanine aminotransferase, HBeAg hepatitis B e antigen, HBsAg hepatitis B surface antigen, HBV hepatitis B virus, TBIL total bilirubin
(22.9%, 80/350) \( (P < 0.001) \); on the contrary, the low-response rate \( (P = 0.002) \) and middle-response rate \( (P = 0.022) \) in the 20 \( \mu \)g group were both lower than those in the 10 \( \mu \)g group (Table 3). There was no difference in non-response rate between two groups (Table 3).

In the 354 infants born to mothers with high load of HBV DNA \( (\geq 5 \log_{10} \text{IU/mL}) \), 128 were in the 10 \( \mu \)g group and 226 were in the 20 \( \mu \)g group. Among them, 5 infants (3.9%, 5/128) were HBsAg-positive in the 10 \( \mu \)g group and 7 infants (3.1%, 7/226) were HBsAg-positive in the 20 \( \mu \)g group. The immunoprophylaxis failure rates between two groups were not obviously different \( (P = 0.922) \). Interestingly, there were no significant differences in response rates of various levels between two groups, from non-response to high-response (Table 3). These were different from the infants born to mothers with low load of HBV DNA.

**High dose of HB vaccine safety for infants**

Of the 955 infants who finished follow-up, the adverse events were reported in 9 infants: 4 in the 10 \( \mu \)g HB vaccine group (0.8%, 4/478) and 5 in the 20 \( \mu \)g HB vaccine group (1.0%, 5/477). Among the 9 infants, 5 had adverse injection reactions (local swelling and induration) to the first dose of vaccine (2 in the 10 \( \mu \)g group and 3 in the 20 \( \mu \)g group). Additionally, 2 cases developed fever (1 in each group), and 2 had hives (10 \( \mu \)g group). No severe adverse events were reported to vaccination.

We also evaluated the safety of 20 \( \mu \)g HB vaccine by observing the growth indexes of infants at age 12 months. There were no differences in these growth indexes between the two groups, except for body length, which was longer in the 20 \( \mu \)g vaccine group \( (P = 0.04) \) (Table 4), but still within the normal range of Chinese children’s growth and development indicators [17]. The results suggested that 20 \( \mu \)g HB vaccine is safe for infants.

**Discussion**

This is a prospective, multicenter, large-sample cohort study. We compared the effects of increased dose (20 \( \mu \)g) and routine dose (10 \( \mu \)g) of HB vaccine combined with HBIG on infants born to HBsAg-positive mothers. Our results revealed that high dose of HB vaccine did not reduce MTCT of HBV, but could decrease low-response rate, middle-response rate, and increase high-response rate for those infants born to mothers with low viral load (HBV DNA \( < 5 \log_{10} \text{IU/mL} \)). However, for those infants born to mothers with high viral

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**Table 2** Main characteristics of HBV-infected babies in two different doses of HB vaccine

| Variables                  | 10 \( \mu \)g (n = 5) | 20 \( \mu \)g (n = 8) |
|----------------------------|------------------------|----------------------|
| **At birth**               |                        |                      |
| Sex (M)                    | 4                      | 2                    |
| Gestation days             | 278.6 ± 3.5            | 277.5 ± 2.1          |
| Birth mode (vaginal delivery) | 2                  | 4                    |
| Birth weight (g)           | 3480 ± 165.5           | 3300 ± 131.3         |
| Fetal distress             | 1                      | 2                    |
| 1-min APGAR                | 9.6 ± 0.2              | 9.6 ± 0.18           |
| **At 12th month**          |                        |                      |
| HBeAg +                    | 5                      | 5                    |
| Anti-HBc                   | 5                      | 8                    |
| HBV DNA detectable         | 3\(^{a}\)              | 6\(^{b}\)            |
| HBV DNA \( (\log_{10} \text{IU/mL}) \) | 6.7 ± 0.3 | 6.5 ± 0.2 |

\(^{a}\)10 \( \mu \)g: samples of 2 cases were unavailable

\(^{b}\)20 \( \mu \)g: 1 case HBV DNA < 100 IU/mL, samples of 2 cases were unavailable

**Abbreviations:** HB hepatitis B, Anti-HBc antibody to hepatitis B c antigen, HBeAg hepatitis B e antigen, HBV hepatitis B virus
load (HBV DNA $\geq 5 \log_{10} \text{IU/mL}$), the above response advantages of 20 $\mu$g HB vaccine were nearly not obvious.

Maternal HBV infection status, such as HBeAg positivity, HBV DNA, and intrauterine infection, is thought to be important for HBV MTCT [18–20]. Considering the importance of maternal virological factor, we performed stratified analysis to our findings according to the maternal HBV load. Data in each group showed that 20 $\mu$g HB vaccine did not significantly reduce the MTCT of HBV, whatever maternal HBV load was high or low. The reasons for immunoprophylaxis failure are not completely clear now. It is reported HBV breach of the placental barrier largely occurs in late pregnancy because of the thinner trophocyte layer, which forms the chorionic vascular membrane that facilitates HBV passage through the thinner placental barrier [21]. Therefore, administration of nucleoside analogs during late pregnancy, such as tenofovir dipivoxil fumarate and telbivudine, is beneficial for HBsAg-positive mothers with a high viral load and could effectively reduce the intrauterine HBV infection and increase the protection of vaccine and HBIG for infants [22–24].

Although 20 $\mu$g HB vaccine did not reduce MTCT of HBV, it did influence the immune response of infants, compared with 10 $\mu$g HB vaccine. For example, for the infants born to mothers with low level of HBV DNA ($< 5 \log_{10} \text{IU/mL}$), 20 $\mu$g HB vaccine significantly increased the high-response rate and reduced the low-response rate. A related investigation on 1192 infants born to HBsAg-positive mothers reported that 20 $\mu$g HB vaccination reduced the risk of low responsiveness in infants with HLA-II risk genotype of HBsAg-positive mothers [25]. Some investigations on healthy individuals also demonstrated that 20 $\mu$g HB vaccine could increase the anti-HBs level compared with 10 $\mu$g HB vaccine [10, 11]. Therefore, some researchers think that for the immune non-responders and low-responders, more inoculations, a higher concentration of HB vaccine to increase the immunogenicity is reasonable [3], especially for those born to mothers whose HBV DNA are $< 5 \log_{10} \text{IU/mL}$.

However, in those infants born to mothers with high viral loads ($\geq 5 \log_{10} \text{IU/mL}$), 20 $\mu$g HB vaccine did not show the response advantages like those happened in infants born to mothers with low viral loads. Our results suggest that maternal HBV DNA levels might be related to the responses of their infants to HB vaccine, but the mechanism is still unknown. Lazizi et al. and Badur et al. demonstrated the relationship between unresponsiveness to HB vaccine in newborns and HBV DNA from maternal peripheral blood mononuclear cells [26, 27]. Some researchers have reported that transfer of maternal cells to newborn circulation participates in the immune response in an antigen-specific manner [28, 29]. Zhang et al. found that high maternal titer of anti-HBs can transplacentally impair immune response of infants towards HB vaccine [30]. Whether a similar mechanism can explain our results, it needs further research. In light of these findings, reducing maternal viral load in late pregnancy and increasing HB vaccine dose of infants might be advantageous to produce more effective immune response to HB vaccine for infants.

There were limitations in our study. We did not further test HBV DNA levels in HBsAg-negative infants at 12 months, although occult HBV infection has been

### Table 3: The response differences to HB vaccine in infants born to HBsAg-positive mothers in two groups

| Infant response | Maternal HBV DNA $< 5 \log_{10} \text{IU/mL}$ | $P$ value | Maternal HBV DNA $\geq 5 \log_{10} \text{IU/mL}$ | $P$ value |
|----------------|---------------------------------|---------|---------------------------------|---------|
| Failure        | 0 (0%) (n = 350)                | 0.418   | 5 (3.9%) (n = 128)              | 0.922   |
| Non-responder  | 11 (3.1%) (n = 251)             | 0.387   | 6 (4.7%) (n = 226)              | 0.052   |
| Low-responder  | 67 (19.1%) (n = 128)            | 0.002   | 17 (13.3%) (n = 226)            | 0.452   |
| Middle-responder | 192 (54.9%) (n = 128)          | 0.022   | 62 (48.4%) (n = 226)            | 0.244   |
| High-responder | 80 (22.9%) (n = 128)            | < 0.001 | 38 (29.7%) (n = 226)            | 0.868   |

### Table 4: Developmental index of infants between two doses of HB vaccine at 12 months

| Developmental index | $10 \mu$g (n = 478) | $20 \mu$g (n = 477) | $P$ value |
|---------------------|---------------------|---------------------|---------|
| Weight (kg)         | 10.6 ± 1.5          | 10.6 ± 1.3          | 0.89    |
| Body length (cm)    | 77.5 ± 3.9          | 78.0 ± 3.8          | 0.04    |
| Head circumference (cm) | 46.3 ± 1.3       | 46.4 ± 1.3          | 0.43    |
| Abdominal fat thickness (cm) | 1.5 ± 0.5     | 1.7 ± 2.9           | 0.13    |

**Abbreviation:** HB hepatitis B
reported at a low frequency in HB-vaccinated children, especially in those with absent or low anti-HBs levels [31, 32]. This factor might influence the accuracy of immunoprophylaxis failure and non-response rates of the HB vaccine. Additionally, the long-time prevention of 20 μg HB vaccine on these infants needed further follow-up and investigation.

Conclusion
In conclusion, increasing dose of HB vaccine (20 μg) did not further reduce the MTCT of HBV, but was helpful to enhance more effective immune response for infants born to mothers with low load of HBV DNA, by increasing high-response rate and decreasing low-response rate and middle-response rate. Our study is expected to provide clinical basis for further improving the strategy of enhancing protection of HB vaccine for infants in the perinatal period.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12916-021-02025-1.

Additional file 1: Appendix 1. Methods. The main contents of informed consents; Statistics used in Table S2. Appendix 2. Table S1. The infants who completed the final follow-up at their respective investigational sites. Table S2. The comparison of characteristics of the failure infants and successful infants and their mothers.

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Authors’ contributions
DZP and PC managed and supervised the study. CY, ZH (Hua Zhang), MJ, DEH, LZS, and LJY supervised the study development of respective investigational sites. ZH (Hua Zhang), TRH, ZYX, GHM, ZBS, JYX, and FLP involved in the sample collection and assembly of the clinical data. ZXH and ZHB analyzed all the data. ZXH drafted the manuscript, and ZHB undertook the interpretation of the data. LJ and ZH (Hui Zhuang) gave suggestion of investigation, and LJ modified the draft. All the authors reviewed and approved the final version of the manuscript.

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Availability of data and materials
In accordance with the current national law and consensus of researchers in this study, the data used in this study is only available for the researchers participating in this project. Thus, we are not allowed to distribute or make publicly available the data to other parties.

Declarations

Ethics approval and consent to participate
The ethical approval for this study was obtained by the Ethics Committee of Beijing Youan Hospital, Capital Medical University (NO 200907). Written consents were obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Abbreviations
ALT: Alanine aminotransferase; anti-HBc: Hepatitis B core antibody; anti-HBs: Hepatitis B surface antibody; HB: Hepatitis B; HBsAg: HB e antigen; HBIG: Hepatitis B immunoglobulin; HBsAg: HB surface antigen; HBV: Human immunodeficiency virus; MTCT: Mother-to-child transmission; OR: Odds ratios; SD: Standard deviation; TBL: Total bilirubin.

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Competing interests
The authors declare that they have no competing interests.

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