

RESEARCH ARTICLE



# A retrospective study of hepatitis B vaccination in preterm birth and low birth weight infants born to hepatitis B surface antigen-positive mothers: Time to close the policy-practice gap

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## ABSTRACT

National Immunization Program-version 2016 (ISIV-NIP-v2016) recommended a 4-dose hepatitis B vaccine (HepB) schedule for preterm birth (PTB) and low birth weight (LBW) infants born to HBsAg-positive mothers. However, the implementation of this immunization strategy in the past five years has not been fully evaluated in China. We reviewed the data of pregnant women and live-born infants from 24 hospitals between 2016 and 2021 in Lu'an, Anhui province, to estimate the prevalence of PTB, LBW, and hepatitis B virus (HBV) infected pregnant women. We analyzed the vaccination status of HepB and HBIG among PTB and LBW infants born to HBsAg-positive mothers. A total of 160 222 pregnant women and 159 613 live-born infants were included in this study. The estimated prevalence of PTB, LBW and HBV-infected pregnant women was 3.86% (range: 3.28%-5.10%), 2.77% (range: 2.12%-3.66%), and 3.27% (range: 3.03%-3.49%), respectively. We screened 340 PTB and LBW infants born to HBsAg-positive mothers between 2016 and 2020. We found that the coverage of HepB and HBIG among them was 100% and 99.39%. However, the timely vaccination rate of the HepB birth dose was only 78.59% and only four children (1.22%) received the 4-dose HepB as recommended by ISIV-NIP-v2016. The 4-dose of HepB for PTB and LBW infants born to HBsAg-positive mothers recommended by ISIV-NIP-v2016 was not fully implemented. A strong public health intervention should be taken to close the policy-practice gap in China in the future.

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## Introduction

Preterm birth (PTB) and low birth weight (LBW) in newborns are important global public health issues.<sup>1,2</sup> Compared with full-term infants, PTB and LBW infants are often at risk of infection and in particular with increased incidence and severity,<sup>3-5</sup> which highlights the importance of timely vaccination in this vulnerable population. However, they have an immature immune system which may impact vaccine responses.<sup>6</sup> Especially for the hepatitis B vaccine (HepB) which is widely used as a birth dose in newborns, PTB and LBW infants, may not respond as well as full-term birth infants. Existing studies have investigated the immunogenicity of HepB in PTB and LBW infants, while these results were not conclusive and varied widely among studies.<sup>7-10</sup> Therefore, the immunization strategy of HepB for PTB and LBW children varies among countries.

WHO recommends birth doses can be given to LBW and PTB infants with a birth weight of less than 2000 g but should not count as part of the primary 3-dose series.<sup>11</sup> Australasian Neonatal Medicines Formulary (ANMF) recommends PTB infants (<32 weeks gestation) or LBW infants (<2000 g) should receive a 4-dose schedule (birth,

2, 4, and 6 months of age) and then consider a booster shot at 12 months.<sup>12</sup> The US Advisory Committee on Immunization Practices (ACIP) recommends that only infants weighing <2000 g who are born to HBsAg-positive mothers should administer a 4-dose schedule (birth, 1, 2-3, and 6 months of age).<sup>13</sup>

In 2016, China officially endorsed Immunization Schedules and Instructions for Vaccines of the National Immunization Program-version 2016 (ISIV-NIP-v2016) for national use. The ISIV-NIP-v2016 recommended a 4-dose HepB schedule (birth, 1, 2, and 7 months of age) for PTB and LBW infants born to HBsAg-positive mothers. In February 2021, China endorsed Immunization Schedules and Instructions for Vaccines of the National Immunization Program-version 2021 (ISIV-NIP-v2021) which recommends that only infants weighing <2000 g who are born to HBsAg-positive mothers should administer a 4-dose schedule. Therefore, the 4-dose HepB schedule for PTB and LBW infants (regardless of birth weight) has been implemented for approximately five years in China. However, the implementation of this immunization strategy in the past five years has not been fully evaluated in China. Therefore, this study aimed to address that gap by conducting a retrospective study in Lu'an, Anhui province.

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## Materials and methods

### Study design and subjects

This retrospective observational study was conducted in Lu'an which is a typical inland city located in the central region of China. The study subjects were those PTB and LBW infants born to HBsAg-positive mothers in Lu'an between 2016 and 2021. PTB was defined as birth before 37 completed weeks of gestation.<sup>14</sup> LBW was defined as birth weight <2500 grams.<sup>2</sup> Preterm low birth weight (PLBW) was defined as birth weight <2500 grams and gestational age <37 weeks.<sup>15</sup> Hepatitis B virus (HBV) infection was defined as the detection of HBsAg was positive in this study. We screened subjects from 24 hospitals which were selected by convenience sampling from all seven counties in Lu'an. Although these hospitals were selected by convenient sampling, they are the principal birth hospitals in each county. At least 80% of newborns were delivered in these hospitals each year, which means that the results of this study can be considered representative of Lu'an city.

### Data collection

Data collection was performed in three-stage. First, we reviewed the information on pregnant women and live-born infants from the birth medical registration record of the obstetrics department of 24 hospitals between 2016 and 2021. The basic information included the number of pregnant women, HBsAg-positive pregnant women, live-born infants, and PTB and LBW infants. Pregnant women were tested for HBsAg when they received their first antenatal health care, and at least 95% of women attending antenatal care were screened for HBV.<sup>16</sup> Therefore, we extrapolated the prevalence of HBV infection among pregnant women, the incidence of PTB and LBW, and their temporal trends in Lu'an between 2016 and 2021. Second, we reviewed the gestational age at delivery and birth weight of the infants born to HBsAg-positive mothers to screen the subjects of this study. We extracted the basic information of the eligible subjects into the structured questionnaire. Data collected in the questionnaire included the name and the ID of the pregnant woman, address, mode of delivery, gender and birth date of the infant, birth weight, gestational age at delivery, complications, and immunization of the HepB and hepatitis B immune globulin (HBIG), etc. We calculated the proportion of PTB and LBW infants born to HBsAg-positive mothers in all live-born infants and infants born to HBsAg-positive mothers, respectively. In the third stage of the study, we searched in the Anhui Immunization Information Management System (AIIMS) by matching the ID

number of the infant's mother, the name of the infant's mother, and the birth date of the infant to obtain vaccination information. The AIIMS is an internet-based management platform maintaining immunization data which was described in detail in our previous study.<sup>17</sup>

### Ethics statement

This study was approved by the Academic Council of Lu'an CDC (P2022–2203).

The authors assert that all procedures contributing to this survey comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration. Also, the data were kept confidential by all authors and those involved in the research.

### Data analysis

All collected data were entered into Microsoft Excel 2019 where data cleaning was performed. Possible differences between different years were tested by the chi-square test. All the statistical analyses were performed using IBM SPSS Statistics for Windows version 20.0 (IBM Corp, Armonk, NY, USA). Two-sided *p*-values were reported to be statistically significant at <0.05.

## Results

A total of 160 222 pregnant women were involved in this study. Of these, 5 233 (3.27%) were HBsAg-positive at antenatal screening. As shown in Table 1, the prevalence of HBV infection among pregnant women fluctuated between 2016 and 2021, with the highest rate occurring in 2018 (3.49%) and the lowest occurring in 2021 (3.03%). There was no increasing trend of HBV infection among pregnant women was observed ( $\chi^2_{\text{trend}} = 0.813, p = .367$ ). Among 159 613 live-born infants, 6161 were PTB infants (3.86%) and 4419 were LBW infants (2.77%). The overall PTB prevalence increased from 3.28% in 2016 to 5.09% in 2021, and a significant increase in annual estimated incidence was observed during 2016–2021 ( $\chi^2_{\text{trend}} = 260.227, p < .001$ ). The increasing trend of LBW prevalence was also observed, from 2.12% in 2016 to 3.66% in 2021 ( $\chi^2_{\text{trend}} = 178.693, p < .001$ ).

In the study, we screened 340 PTB and LBW infants born to HBsAg-positive mothers between 2016 and 2021, including 168 (49.41%) PTB only, 72 (21.18%) LBW only, and 100 (29.41%) PLBW. Overall, we found that the proportion of

**Table 1.** The estimated prevalence of PTB, LBW, and HBV infection of pregnant women in Lu'an, 2016–2021.

Year	No. of pregnant women	HBV infection pregnant women	HBV infection rate (%)	No. of live-born infants	No. of PTB	PTB rate (%)	No. of LBW	LBW rate (%)
2016	32910	1052	3.20	32792	1077	3.28	694	2.12
2017	35105	1081	3.08	34985	958	2.74	777	2.22
2018	22469	785	3.49	22344	858	3.84	624	2.79
2019	30301	1033	3.41	30201	1266	4.19	961	3.18
2020	23354	794	3.40	23272	1187	5.10	776	3.33
2021 <sup>a</sup>	16083	488	3.03	16019	815	5.09	587	3.66
Total	160222	5233	3.27	159613	6161	3.86	4419	2.77

<sup>a</sup>The field investigation of each hospital was carried out at different times, so the data for 2021 was only as of the survey time, not the data for the whole year.

PTB and LBW infants in all live-born infants and infants born to HBsAg-positive mothers was 0.21% (range: 0.18%-0.31%) and 6.42% (range: 5.46%-9.94%), respectively, and an upward trend was also observed during 2016–2021. As shown in Table 2, the proportion in live-born infants increased from 0.18% in 2016 to 0.31% in 2021 ( $\chi^2_{\text{trend}} = 6.552, p = .01$ ), and that in infants born to HBsAg-positive mothers increased from 5.46% in 2016 to 9.94% in 2021 ( $\chi^2_{\text{trend}} = 5.903, p = .015$ ).

The vaccination characteristics of HepB and HBIG are summarized in Table 3. Among 340 eligible subjects, we successfully followed up with 327 (96.18%) children, and their vaccination history of HepB and HBIG was collected. All children completed at least three doses of HepB, whereas the timely vaccination rate of the birth dose was only 78.59% (257/327). The distribution of the number of HepB doses (3, 4, 5, 6) was 312 (95.14%), 7 (2.14%), 2 (0.61%), and 6 (1.83%), respectively. We found that only four (1.22%) children received the 4-dose schedule of HepB as recommended immunization strategy by ISIV-NIP-v2016. Besides, we found that the administration of HBIG and timely HBIG administration was 99.39% and 93.88%, respectively.

## Discussion

This study had the objective to evaluate the implementation of the 4-dose HepB schedule for PTB and LBW infants born to HBsAg-positive mothers recommended by ISIV-NIP-v2016.

We found that 99.39% of infants born to HBsAg-positive mothers received HBIG, with a timely vaccination rate of 93.88%. However, only four (1.22%) children completed the 4-dose of HepB schedule as recommended immunization strategy, implying that the implementation of recommendations on special populations is a major public health challenge in Lu'an. In addition, we were also able to estimate the prevalence of PTB, LBW, and HBV infection in a large sample of pregnant women who attended major delivery hospitals in Lu'an.

The prevalence of PTB has increased significantly worldwide over the last decade and PTB-related complications were the leading causes of death in children younger than 5 years.<sup>1,14,18</sup> In 2014, the global estimated prevalence of PTB was 10.6%, corresponding to 14.84 million live PTB infants.<sup>1</sup> The overall PTB rate increased from 5.9% in 2012 to 6.4% in 2018 in China, with an annual rate of 1.3% increase.<sup>14</sup> In this study, we also found that PTB prevalence increased from 3.28% in 2016 to 5.09% in 2021, and a significant increase in annual incidence was noted during 2016–2021. Similarly, the increasing trend of LBW prevalence was also observed, from 2.12% in 2016 to 3.66% in 2021. The increasing number of PTB and LBW may be an important challenge to the prevention of HBV infection among newborns. It may delay HepB vaccination,<sup>2,19</sup> resulting in an increased risk of neonatal hepatitis B infection. It was estimated that almost all pregnant women gave birth in hospitals in 2015 in China.<sup>20</sup> Besides, at least 80% of newborns were delivered in 24 hospitals

**Table 2.** The proportion of PTB and LBW in all live-born infants and infants born to HBsAg-positive mothers in Lu'an, 2016–2021.

Year	No. of live-born infants	No. of infants born to HBsAg-positive mothers	No. of PTB and LBW infants born to HBsAg-positive mothers				Proportion in all live-born infants (%)	Proportion in infants born to HBsAg-positive mothers (%)
			PTB only	LBW only	PLBW	Total		
2016	32792	1063	32	16	10	58	0.18	5.46
2017	34985	1094	34	15	17	66	0.19	6.03
2018	22344	797	33	13	8	54	0.24	6.78
2019	30201	1048	21	18	23	62	0.21	5.92
2020	23272	805	23	8	20	51	0.22	6.34
2021 <sup>a</sup>	16019	493	25	2	22	49	0.31	9.94
Total	159613	5300	168	72	100	340	0.21	6.42

<sup>a</sup>The field investigation of each hospital was carried out at different times, so the data for 2021 was only as of the survey time, not the data for the whole year.

**Table 3.** Vaccination status of HepB and HBIG among PTB and LBW infants born to HBsAg-positive mothers.

Characteristics of vaccination	No. of infants (N=327)	Proportion (%)
Doses of HepB		
3 doses	312	95.41
4 doses <sup>a</sup>	7	2.14
5 doses	2	0.61
6 doses	6	1.83
Received the 4-dose schedule of HepB as recommended by ISIV-NIP-v2016		
Yes	4	1.22
No	323	98.78
Administration time of HepB		
Within 24 h	257	78.59
Over 24 h	70	21.41
Administration of HBIG		
Yes	325	99.39
No	2	0.61
Administration time of HBIG		
Within 24 h	307	93.88
Over 24 h	18	5.50

<sup>a</sup>Despite 7 children received 4 doses of HepB, 3 of them did not conform to the time schedule recommended by ISIV-NIP-v2016. They just administrated a booster dose 4–12 months after completing the 3-dose primary HepB vaccination

where this study was conducted. Therefore, the results of the current study may spark local public health authority concerns as the findings can reflect the real situation of Lu'an.

China has the world's largest burden of HBV infection and it was estimated that there are about 86 million HBsAg-positive carriers (6.1% prevalence) in 2016.<sup>21</sup> Furthermore, there are approximately one million infants were born to HBsAg-positive mothers every year in China, implying China still faces challenges to achieving the goal of hepatitis B elimination by 2030.<sup>22,23</sup> The current study showed that the total prevalence of HBV infection among pregnant women in Lu'an was 3.27% between 2016 and 2021, which was lower than that of the average level in China (3.99%) from a national observational study.<sup>16</sup> One of the possible reasons may be due to pregnant women included in this study were almost born between the 1980s and 2000s, implying that some of them might benefit from the national immunization policy on infants and children. Previous studies reported that chronic infection occurs in 80–90% of infants infected in the first year of life and 30–50% of children infected in the first 5 years of life but in less than 5% of those who acquire infection in adulthood.<sup>24,25</sup> In other words, prevention of HBV infection in children and infants is the bedrock of reducing the burden of hepatitis B. In this study, we found that all children completed at least three doses of HepB, whereas the timely vaccination rate of the first dose of HepB was only 78.59%. PTB and LBW were common reasons for delayed vaccination, as parents or doctors perceive preterm and low birth weight infants as medically fragile even after their health has improved and their weight increased.<sup>19,26</sup>

Previous studies have demonstrated that PTB infants were more likely to be infected by HBsAg-positive mothers, especially for PTB infants who delayed injection of the birth dose.<sup>27</sup> Therefore, the immunization strategy of HepB for PTB infants is a matter of concern in China, especially for preterm PTB and LBW infants born to HBsAg-positive mothers. Consequently, the China ISIV-NIP-v2016 recommended a 4-dose HepB schedule (birth, 1, 2, and 7 months of age) for PTB and LBW infants (regardless of birth weight) born to HBsAg-positive mothers in 2016. Unfortunately, we observed that only four (1.22%) children completed the 4-dose of HepB schedule as ISIV-NIP-v2016 recommended, implying that recommendations for very special populations are likely to be ignored by vaccination clinic healthcare workers. It might be explained that the birth dose of HepB was given in the hospital's obstetric unit, while the subsequent two or three doses were administered in the vaccination clinics of community health service centers. However, the vaccination certificate usually does not record the information on the birth weight, gestational week, and maternal HBsAg status. As a result, vaccination clinic healthcare workers can't obtain that information, so it is difficult for them to judge which child is the special population that needs a special immunization schedule. It can be concluded that the implementation of the new recommendations of ISIV-NIP-v2021 in China is facing some gaps in the administration of the 4th dose of HepB vaccine to PTB and LBW that requires some strong public health intervention.

## Strengths and limitations

To the best of our knowledge, the implementation of the 4-dose HepB schedule for PTB and LBW infants born to HBsAg-positive

mothers recommended by ISIV-NIP-v2016 has never been evaluated in China. We aimed to address that gap and assess the annual number of such high-risk populations in China by baseline data from this study. Our findings are also subject to the following limitations. First, our investigation was only conducted in one city in China, so the findings may have limited generalizability. Therefore, multi-city field investigations should be carried out in the future to obtain more precise data in China. Second, this study was based on convenient sampling, so the number of PTB and LBW infants born to HBsAg-positive mothers may be underestimated. However, at least 80% of newborns were delivered in selected hospitals each year, which means that the results of this study can reflect the actual situation in Lu'an. Third, the prevalence of HBV infection among pregnant women was estimated only by the HBsAg marker, thus we may have underestimated the prevalence. Besides, the test instruments and kits for HBsAg detection may be different in each hospital which has a potential impact on the estimation of the prevalence of HBV infection among pregnant women. However, we consider the impact is limited as the detection method is mature and the sample size of this study is large enough.

## Conclusions

In conclusion, the prevalence of PTB, LBW, and HBV-infected pregnant women are at a medium level in Lu'an during 2016–2021. However, the 4-dose HepB schedule for PTB and LBW infants born to HBsAg-positive mothers recommended by ISIV-NIP-v2016 was not well implemented in Lu'an. A strong public health intervention should be taken to close the policy-practice gap in China in the future.

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## Author contributions

Wei Qin designed, conceptualized this study, and drafted the manuscript. Yao Wang, Fan Pan, and Xiaqing Zhang participated in the data clear and analysis. Haitian Sui revised the manuscript and polished the language. Shaoyu Xie critically reviewed and supervised the development of the paper. Yao Wang, Fan Pan, Wei Qin, and Kai Cheng participated in the immunization record review and quality control of the questionnaire. All the authors reviewed and edited the final manuscript.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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## Data availability statement

The raw data supporting the conclusion is with the first author and can be made available on reasonable request and prior approval.

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