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Article

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Abstract: Infant hepatitis B vaccine coverage in China is high, with over 95% of infants immunized; however, high vaccine coverage can often mask low timeliness. The vaccination interval between the second and third dose is not clearly defined by immunization guidelines in China. This retrospective cohort study assessed the time interval distribution of hepatitis B vaccination among a cohort of randomly selected live births from Centers for Disease Control and Prevention across four provinces or municipalities in China between January 2017 and December 2021. Among the infants analyzed, 163,224 received the first dose of hepatitis B vaccine with 146,905 (90.0%) and 135,757 (83.2%) infants receiving the second and third doses, respectively. A total of 132,577 (90.2%) infants received the second dose between 28–61 days after the first dose. Of the 119,437 (88.0%) infants that completed the hepatitis B series between 61–214 days after the second dose, 87,067 (64.1%) infants were vaccinated with the third dose between 151–180 days after the second dose. The time interval distribution for the three doses of hepatitis B vaccine varied across the four provinces or municipalities (P<0.001). Of the 58,077 infants who completed the hepatitis B vaccine series, 36,377 (62.6%) infants used the same type of hepatitis B vaccine for all three doses. Overall, the timeliness of hepatitis B vaccination for infants was lower than expected, with regional disparities observed. This highlights the need for improved timeliness through the introduction of a defined timeframe for the last two doses of vaccine, and training for obstetricians and related personnel.

Keywords: time interval; hepatitis B vaccination; infants; type of vaccine

1. Introduction

Perinatal transmission is a major mode of hepatitis B virus (HBV) transmission worldwide, with infection rate highest in China [1]. In response, China has implemented efforts to reduce transmission through universal infant immunization. In 2002, China integrated a hepatitis B vaccine into the

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Expanded Program on Immunization, and provided all neonates with free HBV immunization [2], resulting in high vaccine coverage, with over 95% of infants receiving three doses [3]. The schedule recommended in the 2021 immunization program of the National Health Commission of People's Republic of China [4] involves administration of the first dose within 24 hours after birth, and administration of subsequent doses at 1 and 6 months of age, respectively, and it's the birth dose that's really impactful on MTCT, the subsequent doses are to establish longer term protection for other modes of transmission [2,5].

Preventing perinatal and early childhood infections by providing hepatitis B vaccine for infants beginning from birth has proven to be a safe, effective, and important component of the comprehensive strategy to eliminate HBV transmission worldwide [5–10]. The Global Alliance for Vaccines and Immunization (GAVI), created in the early 2000s, has played an important role in promoting the implementation of universal hepatitis B vaccination in low- and middle-income countries, with children from 73 countries vaccinated between 2011–2020 [11]. This resulted in a dramatic increase in vaccine coverage in infants from 1% in 1990 to 84% in 2015 [12]. By the end of 2021, 190 countries adopted a universal hepatitis B vaccination policy, with global coverage of three doses of hepatitis B vaccine estimated at 85% [13].

Studies measuring vaccine timeliness have become more frequent in recent years, and suggest that the first dose of hepatitis B vaccine should be administered within 24 hours of birth regardless of the mother's HBV status [6,14–18], as recommend by the World Health Organization (WHO) [6]. The United States Advisory Committee on Immunization Practices (ACIP) proposed a 3-dose series at ages 0, 1–2, and 6–18 months [19]. In addition, 111 member states introduced a "birth dose" of hepatitis B vaccine to newborns within the first 24 h after birth [13]. Moreover, infants who received the first dose of hepatitis B vaccine at birth were more likely to complete the 3-dose series along with other recommended vaccinations in a timely manner [20].

Multiple factors influence coverage and timely administration of hepatitis B vaccines, including immigrant populations [2], region [21], location of birth [5,21], parental attitudes to vaccination [22–24], health care providers [25], and restricted medical resources or limited health consciousness [26]. A nationwide study from China demonstrated that 3-dose vaccine coverage was lower in those born before 2001, residing in western provinces or rural locations, home-birthed, or with Tibetan or Uigur ethnicity [2]. Vaccination coverage and timeliness of vaccine administration are related; however, high coverage can sometimes mask low timeliness. In 2012, the WHO verified that China achieved the hepatitis B surface antigen 1% prevalence control goal among children <5 years of age through universal hepatitis B immunization of newborns [27]. As such, it is important for future research to focus on further enhancing the effectiveness and economic benefits related to hepatitis B immunization.

Currently, the vaccination interval between the second and third doses of hepatitis B vaccine is not clearly defined in the Chinese immunization guidelines, nor is the timely vaccine series completion defined in China. The aim of this study was to analyze the time interval distribution of three doses of hepatitis b vaccine administration across four provinces of China to further optimize the immunization schedule and the vaccine-type used.

2. Materials and Methods

2.1. Study design and study setting

We conducted a retrospective cohort study to assess vaccination status among randomly sampled live births with immunization records across four provinces or municipalities (Beijing, Anhui, Guizhou, and Inner Mongolia) between 1 January 2017 and 31 December 2021. A total of 3% of infants from at least three counties were randomly selected from each province or city.

2.2. Study population and data sources

The study population included all infants born from 1 January 2017 to 30 June 2021, that had immunization records between 1 January 2017 and 31 December 2021, allowing infants born at the

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end of June sufficient time to complete the 3-dose hepatitis B vaccination program. Notably, data may not have been complete for internal migrants (e.g., those who have moved from one county or province to another) due to electronic medical records not having been transferred. Exclusion criteria included incomplete or inconsistent data, such as missing or incorrect birth dates (such as birth after vaccination), vaccination time (or inconsistent vaccination sequence, such as the date of the third dose being earlier than the first dose), or vaccination dose (data only available for the first or third dose, but no information for the second dose).

2.3. Variables of interest

The primary endpoint was the proportion of infants who received three doses of hepatitis B vaccine at different intervals and was derived from two variables: date of birth and date of receiving hepatitis B vaccination. For the first dose of vaccine, timely vaccination was limited to 24 hours after birth, following international recommendations. Any vaccination after 24 hours of birth was considered delayed.

For the second and the third dose, guidelines recommend vaccination at 1 and 6 months of age, respectively, but a specific time interval is not defined. The time interval between the first and second dose was divided into three groups: 28–42 days, 43–61 days, and ≥62 days after the first dose. The time interval between the second and third dose was divided into seven groups: <60 days, 61–90 days, 91–120 days, 121–150 days, 151–180 days, 181–214 days, and ≥215 days after the second dose.

Sampled data from Beijing and Anhui was used to analyze the usage of three types of vaccines, coded as A, B, and C, differentiated by the technological platform used in their production, including the percentage of infants using the same or different type of vaccine between the various doses of the 3-dose schedule. Data for the other provinces was not available due to data privacy restrictions. Floating population defined as residing in an area for less than 6 months.

2.4. Statistical analysis

The total number of infants for each dose and the corresponding time interval between doses were presented as numbers and percentages. Chi-squared test/Fisher exact tests were used to compare the percentages of infants with different vaccination schedules and different types of vaccines. The level of statistical significance was set at 0.05 and Stata 16.0 (Stata Corp LP, College Station, TX) was used for all statistical analyses.

2.5. Ethical approval

The study was approved by the Ethics Committee of Peking University Health Science Center (IRB00001052-23084) and Guizhou Center for Disease and Prevention and Control (Q2023-10).

3. Results

3.1. Dose uptake

Description of the sociodemographic characteristics stratified by province are presented in Table 1. Among the infants analyzed, 163,224 received the first dose of hepatitis B vaccine. Vaccination uptake decreased for the subsequent two doses, with 146,905 (90.0%) and 135,757 (83.2%) infants receiving the second and third dose, respectively.

Table 1. Doses of vaccines administered within the pre-defined timeframe.

Provinces or province-level municipality	Doses	Total N	Administered within the custom time interval n (%)	Administered after the custom time interval n (%)
Beijing*	1	32,532	30,518 (93.8)	2014 (6.2)

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	2	32,515	27,798 (85.5)	4717 (14.5)
	3	29,955	21,736 (72.6)	8163 (27.3)
	1 to 3	29,955	17,617 (58.8)	12,338 (41.2)
Anhui*	1	29,533	23,990 (81.2)	5543 (18.8)
	2	29,230	26,858 (91.9)	2372 (8.1)
	3	28,122	25,989 (92.4)	2085 (7.4)
	1 to 3	28,122	19,533 (69.5)	10,000 (30.5)
Inner Mongolia*	1	39,650	34,255 (86.4)	5395 (13.6)
	2	29,516	28,126 (95.3)	1390 (4.7)
	3	28,449	28,393 (99.8)	8 (0.03)
	1 to 3	28,449	25,049 (88.0)	14,601 (12.0)
Guizhou*	1	61,509	56,491 (91.8)	5018 (8.2)
	2	55,644	49,795 (89.5)	5849 (10.5)
	3	49,231	43,319 (88.0)	5563 (11.3)
	1 to 3	49,231	38,235 (77.7)	23,274 (22.3)
Total	1	163,224	145,254 (89.0)	17,970 (11.0)
	2	146,905	132,577 (90.3)	14,328 (9.8)
	3	135,757	119,437 (88.08)	15,819 (11.7)
	1 to 3	135,757	100,434 (74.0)	60,213 (26.0)

The custom time interval for the first dose was within 24 h after birth, for the second dose was 28–61 days after the first dose, and the third dose was 61–214 days after the second dose; Administered after than the custom time interval for the first dose was >24 hours after birth, for the second dose was ≥62 days after the first dose, and the third dose was ≥215 days after the second dose. *: P<0.001, comparison the proportion between different doses in the same provinces or province-level municipality.

3.2. Time interval distribution of the three doses of vaccine

Of the 135,757 infants who completed the three doses hepatitis B vaccination schedule, a total of 100,434 (74.0%) infants received the first dose within 24 hours, the second dose 28–61 days after the first dose, and the third dose 61– 214 days after the second dose.

For the first dose of hepatitis B vaccine, 145,254 (89.0%) received within 24 hours after birth.

The time interval distribution for the second dose of hepatitis B vaccine across the four regions is shown in Table 2. Among the 146,905 infants who received two doses of hepatitis B vaccine, 132,577 (90.2%) received the second dose between 28–61 days after the first dose. The proportion of infants

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who received the second dose between 28–42 days after the first dose was the highest in Anhui (n=22,940, 78.5%), and lowest in Beijing (n=22,180, 68.2%; P<0.001); however, the proportion of infants who received the second dose between 43–61 days after the first dose was higher in Inner Mongolia (n=7032, 21.0%) compared to the other three regions (Beijing n=5618, 17.3%; Anhui n=3918, 13.4%; Guizhou n=11,659, 21.0%) (Table 2). The proportion of infants vaccinated between 43–61 days after the first dose was higher than those vaccinated ≥62 days after the first dose (19.2% vs. 9.8%, respectively).

Table 2. Distribution of time intervals of the second dose vaccination.

Provinces or province-level municipality	Total N	Between 28–42 days after the first dose n (%)	Between 43–61 days after the first dose n (%)	≥62 days after the first dose n (%)
Beijing*	32,515	22,180 (68.2)	5618 (17.3)	4717 (14.5)
Anhui*	29,230	22,940 (78.5)	3918 (13.4)	2372 (8.1)
Inner Mongolia*	29,516	21,094 (71.5)	7032 (23.8)	1390 (4.7)
Guizhou*	55,644	38,136 (68.5)	11,659 (21.0)	5849 (10.5)
Total	146,905	104,350 (71.0)	28,227 (19.2)	14,328 (9.8)

*: P<0.001, comparison the proportion between different doses in the same provinces or province-level municipality.

Of the 135,757 infants who received the third dose of hepatitis B vaccine, 119,437 (88.0%) completed the full series between 61–214 days after the second dose. 87,067 (64.1%) were vaccinated between 151–180 days after the second dose, and 17,210 (12.7%) were vaccinated between 181–214 days after the second dose (Table 3). Only around 1% (n=1,386) of infants were immunized ≤91 days after the second dose. Furthermore, proportionally more infants in Inner Mongolia (n=25,290, 88.9%) received the third dose of hepatitis B vaccine between 151–180 days after the second dose compared with Beijing (n=14,393, 48.1%), Anhui (n=17,935, 63.8%), or Guizhou (n=29,449, 59.8%; Table 3). The proportion of infants who received the third dose of hepatitis B vaccine between 121–214 days after the second dose reached 85.6% (n=116,266; Table 3).

Table 3. Distribution of time intervals for the third dose.

Provinces or province-level municipality	Days after the second dose							
	Total N	≤60 n (%)	61–90 n (%)	91–120 n (%)	121–150 n (%)	151–180 n (%)	181–214 n (%)	≥215 n (%)
Beijing	29,955	56 (0.2)	321 (1.1)	749 (2.5)	3234 (10.8)	14,393 (48.1)	3039 (10.2)	8163 (27.3)
Anhui	28,122	48 (0.2)	128 (0.5)	638 (2.3)	4203 (15.0)	17,935 (63.8)	3085 (11.0)	2085 (7.4)
Inner Mongolia	28,449	48 (0.2)	51 (0.2)	162 (0.6)	1067 (3.8)	25,290 (88.9)	1823 (6.4)	8 (0.03)
Guizhou	49,231	349 (0.7)	385 (0.8)	737 (1.5)	3485 (7.1)	29,449 (59.8)	9263 (18.8)	5563 (11.3)
Total	135,757	501 (0.3)	885 (0.7)	2286 (1.7)	11,989 (8.8)	87,067 (64.1)	17,210 (12.7)	15,819 (11.7)

3.3. Dose uptake within the specific time interval by region

The proportion of infants receiving the first, second or third hepatitis B dose varied significantly across the four regions (Beijing, Anhui, Inner Mongolia, and Guizhou; P<0.001; Table 1). In Anhui and Inner Mongolia, 23,990 (81.2%) and 34,255 (86.4%) infants received the first dose of hepatitis B

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vaccine within 24 hours after birth, respectively, compared with 30,518 (93.8%) and 56,491 (91.8%) infants born in Beijing and Guizhou, respectively (Table 1). Conversely, the proportion of infants receiving the second dose of hepatitis B vaccine between 28–61 days after the first dose was 26,858 (91.9%) and 28,126 (95.3%) in Anhui and Inner Mongolia, respectively, compared with 27,798 (85.5%) and 49,795 (89.5%) of infants born in Beijing and Guizhou, respectively (Table 1). Similarly, those receiving the third dose of hepatitis B vaccine between 61–214 days after the second dose were higher in Anhui (n=25,989, 92.4%) and Inner Mongolia (n= 28,393, 99.8%), compared with Beijing (n=21,736, 72.6%) and Guizhou (n= 43,319, 88.0%) (Table 1). The proportion of infants who received the first dose of hepatitis B vaccine within 24 hours, the second dose between 28–61 days after the first dose, and the third dose between 61–214 days after the second dose, was higher in Inner Mongolia (n=25,049, 88.0%) and Guizhou (n=38,235, 77.7%), compared with Beijing (n=17,617, 58.8%) and Anhui (n=19,533, 69.5%) (Table 1).

3.4. Analysis of three doses of immunization using different types of hepatitis B vaccines

A total of 58,077 children from Beijing and Anhui who received all three doses of hepatitis B vaccine were analyzed to assess the type of vaccine used for each dose. Of those included, 36,377 (62.6%) infants used the same type of vaccine for all three doses, 21,613 (37.2%) infants used two different types of vaccines for the three doses, and only 87 (0.2%) infants used completely different types of vaccines for the three doses (Table 4). Furthermore, 12,590 (21.7%) infants used a different type of hepatitis B vaccine for the second dose than for the first dose.

Table 4. Use of different types of hepatitis B vaccines.

First dose			Second dose			Third dose			Using the same type of vaccine to complete the course	
Type	N	%	Type	N	%	Type	N	%	N	%
						A	83	65.4		
			A	127	40.6	B	13	10.2		
						C	31	24.4		
						A	1	1.8		
A	313	0.5	B	56	17.9	B	38	67.9	83	0.1
						C	17	30.4		
						A	3	2.3		
			C	130	41.5	B	14	10.8		
						C	113	86.9		
						A	24	44.4		
			A	54	0.2	B	20	37.0		
						C	10	18.5		
						A	54	0.3		
B	24,540	42.3	B	17,853	72.8	B	12,858	72.0	12,858	22.1
						C	4941	27.7		
						A	28	0.4		
			C	6633	27.0	B	1331	20.1		
						C	5274	79.5		
						A	35	53.0		
			A	66	0.2	B	12	18.2		
						C	19	28.8		
						A	6	0.1		
C	33,224	57.2	B	5651	17.0	B	3116	55.1	23,436	40.4
						C	2529	44.8		
						A	31	0.1		
			C	27,507	82.8	B	4040	14.7		
						C	23,436	85.2		

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Total	58,077		36,377	62.6

A, B and C represent three different types of hepatitis B vaccines.

3.5. Univariate analysis of vaccination using different types of hepatitis B vaccines

A univariate analysis of the 58,077 infants who completed all three doses of hepatitis B vaccine showed that several factors influenced the number of different vaccine types used. The proportion of Han that received the same type of vaccine was higher than for other ethnic groups (64.9%vs. 53.9%), respectively. Additionally, in 2018 and 2019, 57.5 and 57.2%, respectively, received the same type of vaccine, which were lower compared with other years included in this analysis. However, the proportion of infants vaccinated with all doses at the same location was higher than those who received subsequent hepatitis B vaccines at an alternative location (79.2% vs. 62.1%). Furthermore, a higher proportion of second born children (64.6%) received the same type of vaccine compared with those born in any other birth order (Table 5, P<0.001).

Table 5. Characteristics of infants who received all three doses of hepatitis B vaccine.

Characteristics	Using the same type of hepatitis B vaccine	Using the different type of hepatitis B vaccine	OR	P Value
	N (%)	N (%)	95% CI	
Birth order				
1	25,493 (62.1)	15,577 (37.9)	Reference	
2	6103 (64.6)	3350 (35.4)	1.11 (1.09, 1.17)	<0.001
3 or more	4782 (63.3)	2772 (36.7)	1.05 (1.003, 1.11)	0.042
Ethnicity				
Han	29,872 (64.9)	16,133 (35.1)	Reference	
Other	6506 (53.9)	5566 (46.1)	0.63 (0.61, 0.63)	<0.001
Year of birth				
2017	9993 (66.2)	5106 (33.8)	Reference	<0.001
2018	7939 (57.5)	5877 (42.5)	0.69 (0.66, 0.69)	<0.001
2019	7174 (57.2)	5380 (42.9)	0.68 (0.65, 0.69)	<0.001
2020	7449 (70.4)	3128 (29.6)	1.22 (1.20, 1.28)	<0.001
2021	3823 (63.4)	2208 (36.6)	0.88 (0.83, 0.91)	<0.001
Vaccination at the same location				
Yes	1435 (79.2)	377 (20.8)	Reference	
No	34,961 (62.1)	21,322 (37.9)	0.43 (0.39, 0.44)	<0.001
Floating population				
Yes	8650 (63.3)	5015 (36.7)	Reference	
No	27,728 (62.4)	16,684 (37.6)	0.96 (0.92,1.01)	0.067
Total	36,378 (62.6)	21,699 (37.4)		

CI, confidence interval; OR, Odd ratio.

3.6. Vaccination coverage of other National Immunization Program vaccines

A total of 69,183 immunization records for infants from Anhui and Inner Mongolia who had received at least the first dose of hepatitis B vaccine were analyzed to determine the coverage rates of other vaccines, including the diphtheria, tetanus and pertussis vaccine (DTP), oral poliovirus vaccine (OPV), inactivated polio vaccine (IPV), meningococcal conjugate vaccines (MCV), and bacillus Calmette-Guerin vaccine (BCG). Vaccination coverage rates for DTP, MCV, and BCG all exceeded 90%; however, vaccine coverage rates were lower for subsequent doses. The coverage rates of the first and second dose of OPV also exceeded 90%; however, coverage for the third dose reached

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only 16.7%. Similarly, the coverage rate for the first dose of IPV was 82.1% but decreased to 56.3% for the second dose (Table 6).

Table 6. Vaccination coverage rate for other vaccines in Anhui and Inner Mongolia.

	Total number	Number of vaccinations	Coverage rate (%)
DTP			
DTP1	69,183	65,413	94.6
DTP2	69,183	64,958	93.9
DTP3	69,183	64,566	93.3
OPV			
OPV1	69,183	65,340	94.5
OPV2	69,183	65,076	94.1
OPV3	69,183	11,536	16.7
IPV			
IPV1	69,183	56,800	82.1
IPV2	69,183	38,972	56.3
MCV	69,183	66,697	96.4
BCG	69,183	66,295	95.8

BCG, Bacillus Calmette-Guerin Vaccine; DTP, diphtheria, tetanus, and pertussis mixed vaccine; IPV, inactivated polio vaccine; MCV, meningococcal vaccine; OPV, oral polio vaccine.

4. Discussion

This retrospective cohort study conducted in the four provinces or municipalities in China, (Anhui, Inner Mongolia, and Guizhou, and one province-level municipality Beijing), China, we found that vaccine coverage and timeliness of hepatitis B vaccination differed among the four regions analyzed (Anhui Inner Mongolia, Guizhou and Beijing); however, approximately 70% of infants received all three doses of hepatitis B vaccine within the specific time interval defined as vaccinating first dose within 24 hours after birth, the second dose between 28 and 61 days after the first dose, and the third dose between 61 and 214 days after the second dose. The proportion of infants vaccinated between 28–42 days after the first dose was higher than those vaccinated between 43–61 days and ≥62 days after the first dose. For the third dose, more than half of the infants were vaccinated between 151–180 days after the second dose.

These data showed that the proportion of infants who received all three doses hepatitis B vaccine within the pre-defined time intervals did not reach 95%. These findings are similar to a previous study conducted in Hohhot, China, which found that timely vaccination with the first dose of hepatitis B vaccine was achieved in only 90% of newborns in 2019 and 2021 [28]. Conversely, a study in Guangxi. China, found that the timely vaccination was achieved in 94.88% of newborns, with delayed vaccination attributed to low birth weight, preterm delivery, and dystocia [29]. This suggests that newborns from rural areas may not receive their first dose of vaccine in a timely manner.

Under- or delayed-vaccination is a significant, avoidable public health risk, and contributes to the low overall vaccine coverage (40–60%) observed in some population subgroups [30,31]. As low vaccine coverage increases the overall susceptibility of the population to outbreaks of vaccine preventable diseases, it is important that medical resources are readily accessible across all areas. Local health departments should be encouraged to assess vaccination coverage so that they can use it as a baseline for designing and implementing interventions in the region, with the aim of increasing vaccination rates. Although a previous study on hepatitis B vaccine coverage rate in the central and western regions of China showed that timely full and complete coverage increased from 46.6% in 2011 to 59.3% in 2016, this study was conducted earlier and may underestimate the full coverage rate [32]. Overall, our data show that the majority of infants who received both the second and third doses of hepatitis B vaccine were clustered between 28–61 days (90.3%) after the first dose and between 121–214 days (85.6%) after the second dose, respectively. This indicates that setting a clear vaccination schedule would further improve vaccination uptake and timely vaccination rate.

In terms of the different types of vaccines used, we found that the majority of infants were immunized with the same type of vaccine. However, although the vaccination procedure for all three doses of hepatitis B vaccine is not clearly stipulated by the Chinese hepatitis B vaccination procedure, our study also revealed that 21.7% of infants received a different type of hepatitis B vaccine for their first two doses, and 37.2% of infants received two types of hepatitis B vaccine for over the three doses; this may due to convenience and availability of vaccines. This reflects real-world clinical practice, whether for newborns or other populations, as an individual may receive two different vaccines for sequential immunizations due to issues with vaccine procurement and supply. However, it is important to note that multiple studies have shown that different types of hepatitis B vaccines display comparable effects in terms of safety and immunogenicity [33,34], with no significant difference in immunization of effect noted between schedules using the same of different hepatitis B vaccines for the 3-dose schedule[34,35]. Notably, our data also revealed that infants were more likely to receive the same type of vaccine if they were of Han nationality, vaccinated in the same location, or second born children or later. This is likely related to the accessibility of hepatitis B vaccine, parents' knowledge, and previous experience of the hepatitis B vaccine.

Lastly, our data also showed that infants vaccinated with hepatitis B vaccines were more than 90% likely to receive the DTP, OPV, MCV, and BCG vaccines. However, the proportion of those who received OPV3 was lower because China implemented an updated immunization program incorporating bivalent IPV and bivalent OPV on 1 May 2016 [36].

This study had multiple limitations that warrant discussion. Firstly, those who did not receive the second and third dose or received the third dose outside of the specified timeframe (1 January 2017 and 31 December 2021), were not included in the analysis, which may have led to an overestimation of the timely vaccination rate. However, according to previous research, the proportion of infants receiving three doses within the pre-defined time interval did not reach 95%, therefore highlighting the need for improved timely vaccination rates and implementation of vaccination time intervals for both the second and third hepatitis B vaccine doses. Secondly, the factors affecting timely vaccination were not analyzed as this was beyond the scope of this study.

5. Conclusions

As there are currently large regional disparities in the timeliness of infant hepatitis B vaccination, it is necessary to precisely define the time of vaccination for the last two doses of hepatitis B vaccine, to further investigate the factors affecting timely vaccination, and strengthen training for obstetricians and related personnel. Additionally, our study showed the interchangeability of hepatitis B vaccine that exists in real-world clinical practice, with different types of hepatitis B vaccine used for immune prophylaxis, which may also help improve full vaccination coverage and timeliness of hepatitis B vaccination.

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References

1. Liu D., Y. Liu, J.Q. Ni, et al., Hepatitis B Infection Among Pregnant Women in China: A Systematic Review and Meta-Analysis. Frontiers in Public Health, 2022. 10.
2. Liang X., S. Bi, W. Yang, et al., Evaluation of the impact of hepatitis B vaccination among children born during 1992-2005 in China. J Infect Dis, 2009. 200(1): p. 39-47.
3. Hennessey K., J. Mendoza-Aldana, B. Bayutas, et al., Hepatitis B control in the World Health Organization's Western Pacific Region: targets, strategies, status. Vaccine, 2013. 31 Suppl 9: p. J85-92.
4. National Health Commission of People's Republic of China, Immunization schedules and instructions for vaccines of the national immunization program Chinese Journal of Viruses, 2021. 11(04): p. 241-245.
5. Centers for Disease C.,Prevention, Progress in hepatitis B prevention through universal infant vaccination--China, 1997-2006. MMWR Morb Mortal Wkly Rep, 2007. 56(18): p. 441-445.
6. in *Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection*. 2015: Geneva.
7. Luman E.T., A.E. Fiore, T.W. Strine, et al., Impact of thimerosal-related changes in hepatitis B vaccine birth-dose recommendations on childhood vaccination coverage. JAMA, 2004. 291(19): p. 2351-2358.
8. Goldstein S.T., F. Zhou, S.C. Hadler, et al., A mathematical model to estimate global hepatitis B disease burden and vaccination impact. Int J Epidemiol, 2005. 34(6): p. 1329-1339.
9. Masters N.B., A.L. Wagner,M.L. Boulton, Vaccination timeliness and delay in low- and middle-income countries: a systematic review of the literature, 2007-2017. Hum Vaccin Immunother, 2019. 15(12): p. 2790-2805.
10. Xu B., C. Xu, J. Feng, et al., Reduced mother-to-child transmission of hepatitis B after implementation of completely charge-free active-passive immunoprophylaxis: an observational cohort study. Expert Rev Vaccines, 2021. 20(7): p. 899-905.
11. Lee L.A., L. Franzel, J. Atwell, et al., The estimated mortality impact of vaccinations forecast to be administered during 2011-2020 in 73 countries supported by the GAVI Alliance. Vaccine, 2013. 31 Suppl 2: p. B61-72.
12. WHO . Global Hepatitis Report. 2017.
13. WHO . Immunization coverage. Fact sheet. Updated 2023. July 18.
14. Schillie S., C. Vellozzi, A. Reingold, et al., Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep, 2018. 67(1): p. 1-31.
15. Dhouib W., M. Kacem, C. Bennasrallah, et al., Hepatitis B birth vaccination, cohort study, Tunisia 2000-2017. Libyan J Med, 2020. 15(1): p. 1809223.
16. E B., K. Ko, R. Kim, et al., Residual risk of mother-to-child transmission of HBV despite timely Hepatitis B vaccination: a major challenge to eliminate hepatitis B infection in Cambodia. BMC Infect Dis, 2023. 23(1): p. 261.
17. Segeral O., B. Dim, C. Durier, et al., Immunoglobulin-free strategy to prevent HBV mother-to-child transmission in Cambodia (TA-PROHM): a single-arm, multicentre, phase 4 trial. Lancet Infect Dis, 2022. 22(8): p. 1181-1190.
18. Lei D., T. Miller, J. Carr, et al., Timing of the First Dose of the Hepatitis B Vaccine in Preterm Infants. Vaccines (Basel), 2022. 10(10).
19. Advisory Committee on Immunization Practices (ACIP). Recommendations for Ages 18 Years or Younger, United States, 2023.
20. Yusuf H.R., D. Daniels, P. Smith, et al., Association between administration of hepatitis B vaccine at birth and completion of the hepatitis B and 4:3:1:3 vaccine series. JAMA, 2000. 284(8): p. 978-983.
21. Kyuregyan K.K., V.S. Kichatova, O.V. Isaeva, et al., Coverage with Timely Administered Vaccination against Hepatitis B Virus and Its Influence on the Prevalence of HBV Infection in the Regions of Different Endemicity. Vaccines (Basel), 2021. 9(2).
22. Okenwa U.J., M.D. Dairo, B. Uba, et al., Maternal reasons for non-receipt of valid Hepatitis B birth dose among mother-infant pairs attending routine immunization clinics, South-east, Nigeria. Vaccine, 2019. 37(46): p. 6894-6899.

23. Jiles R.B., D. Daniels, H.R. Yusuf, et al., Undervaccination with hepatitis B vaccine: missed opportunities or choice? Am J Prev Med, 2001. 20(4 Suppl): p. 75-83.
24. Thanh Thi Le X., A. Ishizumi, H. Thi Thu Nguyen, et al., Social and behavioral determinants of attitudes towards and practices of hepatitis B vaccine birth dose in Vietnam. Vaccine, 2020. 38(52): p. 8343-8350.
25. Smith P.J., A.M. Kennedy, K. Wooten, et al., Association between health care providers' influence on parents who have concerns about vaccine safety and vaccination coverage. Pediatrics, 2006. 118(5): p. e1287-1292.
26. Miyakawa M., L.M. Yoshida, H.T. Nguyen, et al., Hepatitis B virus infection among pregnant mothers and children after the introduction of the universal vaccination program in Central Vietnam. Sci Rep, 2021. 11(1): p. 8676.
27. Cui F., J. Drobeniuc, S.C. Hadler, et al., Review of hepatitis B surveillance in China: improving information to frame future directions in prevention and control. Vaccine, 2013. 31 Suppl 9(Suppl 9): p. J79-84.
28. Ren Xianyun K.H., Liu Zhirui, Yang Shuang, Wu Yunsang, Zhang Yao, Yu Longfei, Wang Zhiping, Jin Xin, Bao Qianjun, , Analysis on the first hepatitis B vaccine coverage rate of newborns in Hohhot from 2019 to 2021 [J] Disease Monitoring and Control, 2023,17 (01): 11-13.
29. Huang H.,R. Wei, Analysis on the first hepatitis B vaccination of newborns in Yizhou District, Hechi City from 2015 to 2018 [J]. China Contemporary Medicine, 2020,27 (13): 177-179.
30. Cai J., Investigation and Analysis on the Clinical Characteristics and Vaccination of H1N1 Among Preschool Children in Xiang'an District,Xiamen City from2018 to 2022. Port Health Control, 2023. 28(05): p. 18-21.
31. Fan L., C. Yang, H. Zhou, et al., Hepatitis B vaccine coverage rate and its influencing factors among rura residents, Harbin. Modern Preventive Medicine, 2021. 48(7): p. 1298-1301.
32. Liu X., C. Yang, Q. Song, et al., Fairness analysis on the timeliness of hepatitis B vaccination for children aged 12 to 35 months in western China [J]. China School Health, 2018,39 (08): 1128-1131.
33. Han B.F., W. Liu, J. Du, et al., Immunogenicity and safety of hepatitis B vaccination in patients with type 2 diabetes in China: An open-label randomized controlled trial. Vaccine, 2021. 39(25): p. 3365-3371.
34. Lian L., C. Li, H. Zhao, et al., Immune effect of different hepatitis B vaccines and sequential immunization in infants born to HBsAg negative mothers. Journal of Guangxi Medical University, 2019. 36(03): p. 428-430.
35. Cui L., Y. Zhang, Z. Zuo, et al., Feasibility study of sequential immunization of different kinds of hepatitis B vaccines. Occupation and Health, 2012. 28(4): p. 3103-3104.
36. Childhood Immunization Schedule for National Immunization Program Vaccines-China (Version 2021). China Cdc Weekly, 2021. 3(52): p. 1101-1108.