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Association between timely initiation of hepatitis B vaccine and completion of the hepatitis B vaccine and national immunization program vaccine series

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SUMMARY

Background: Little is known about the association between the initiation of hepatitis B vaccine (HB vaccine) at birth and completion of the HB vaccine and the national immunization program vaccine (NIPV) series in Fujian, China.

Methods: A provincial survey, including children in the community and newborns in hospital, was conducted to evaluate coverage with a timely first dose of HB vaccine and the completion of three doses of HB vaccine and the NIPV series in 2013. A proportion of the samples was rechecked to investigate the relationship between the administration of a timely first dose of HB vaccine and completion of the HB vaccine series and the NIPV series (three doses of HB vaccine, one dose of Bacillus Calmette–Guérin vaccine, three doses of oral poliomyelitis vaccine, three doses of diphtheria–tetanus–pertussis vaccine, one dose of measles-containing vaccine, one dose of Japanese encephalitis attenuated live vaccine, and two doses of group A meningococcal polysaccharide vaccine).

Results: A total of 6589 subjects (including 3785 community children and 2804 hospital newborns) were included in this study; 97.34% of them received a timely first dose of HB vaccine (≤24 h after birth) and 99.10% and 88.27% completed the HB vaccine series and the NIPV series, respectively. Among the 1680 children from eight counties who were rechecked, those with a timely first dose of HB vaccine had higher completion rates of the HB vaccine series and the NIPV series than those with a delayed first dose of HB vaccine (99.69% and 88.90% vs. 83.05% and 79.66%, respectively; both $p < 0.001$). Compared to those with a delayed HB vaccine first dose, the odds ratios for completing the HB vaccine series and the NIPV series among children who received a timely first dose of HB vaccine were 65.96 (95% confidence interval (CI) 21.73–200.25) and 3.24 (95% CI 1.81–5.81), respectively.

Conclusions: Coverage with a timely first dose of HB vaccine is high in children in the community and newborns in hospital, and timely receipt of the first dose of HB vaccine is associated with an increased likelihood of completing the HB vaccine series and the NIPV series in Fujian, China.

1. Introduction

Infection with the hepatitis B virus (HBV) is highly prevalent in Fujian, China. The prevalence of positivity for hepatitis B surface antigen was estimated to be 10.2% in the population aged 1 to 59 years in 2006.[1] To control HBV infection, hepatitis B vaccine (HB vaccine) has been recommended for newborns and infants since 1992, and was included in the national immunization program vaccine (NIPV) series in 2002.[2] It is recommended that infants receive three doses of HB vaccine, to be given within 24 h after birth and at 1 month and 6 months of age.[1,2]

Many measures have been taken to improve coverage with a timely first dose of HB vaccine (within 24 h after birth) and completion of the HB vaccine series since 2002, such as the implementation of the free vaccine policy.[1] Correspondingly, the coverage rate for a timely HB vaccine first dose increased from

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40–60% in 1992–2002 to around 90% in 2003–2005 in Fujian.[1,3,4] However, previous studies have always evaluated coverage with a timely HB vaccine first dose in children in the community;[1,3,4] the level of vaccination among newborns in hospitals, and how different the coverage is between children in the community and newborns in hospital, remains unknown.

In addition, previous studies by the present investigators have revealed that infants who receive a timely first dose of HB vaccine are more likely to complete the HB vaccine, diphtheria–tetanus–pertussis (DTP), and measles-containing vaccine (MCV) series.[1,5] In the USA, administration of HB vaccine at birth was found to be associated with the timely receipt of three doses of HB vaccine and the 4:3:1 series (four doses of DTP vaccine, three doses of poliomyelitis vaccine, and one dose of MCV),[6] but not the 4:3:1:3 series (the 4:3:1 series plus three doses of *Haemophilus influenzae* type b vaccine).[7] However, the impact of timely initiation of the HB vaccine first dose on completion of the NIPV series in Fujian, China is still unclear.

Therefore, a provincial NIPV series survey, including community children and hospital infants, was conducted in 2013 to study coverage with a timely first dose of HB vaccine and to verify the association between timely administration of the first dose of HB vaccine and completion of the HB vaccine series and the NIPV series in Fujian, China, a region where HBV infection is highly endemic,[1] the immunization rate is high,[3] and the vaccine series and recommended vaccination schedules differ from those in the USA.[8,9]

2. Methods

2.1. Survey design and data collection

The survey was conducted in May 2013 to obtain coverage rates for the timely initiation of the HB vaccine first dose and completion of the HB vaccine and NIPV series among children in the community born between January 1, 2010 and December 31, 2011. The target population was selected by stratified random sampling. First, 18 random counties were selected from the nine cities of Fujian (two counties in each city), and 30 villages were identified in each selected county. Second, seven children who had resided in the village for at least 3 months at the time of the survey visit were selected by probability proportional to size sampling (PPS). Finally, a house-to-house investigation was completed by trained staff. Basic information, including date of birth, domicile, and immunization history, was extracted from the child's immunization certificate kept by the parents.

Coverage of timely HB vaccine first dose initiation was also evaluated in hospital newborns. In each of the 18 counties, one county-level hospital and two township hospitals were selected randomly. At least 100 infants born between February 1 and February 28, 2012 in each county hospital, as well as all infants born between January 1 and December 31, 2012 in each of the 36 township hospitals, were investigated to calculate the coverage rate of a timely administration of the first dose of HB vaccine in newborns. Information on the HB vaccine first dose was obtained from the immunization certificate kept by the parents, or the immunization registry records kept by the hospitals. The nine cities (and 18 counties) surveyed were Fuzhou (Minqing, Taijiang), Xiamen (Huli, Haicang), Putian (Chengxiang, Xianyou), Sanming (Shaxian, Mingxi), Quanzhou (Yongchun, Shishi), Zhangzhou (Xiangcheng, Nanjing), Longyan (Xinluo, Yongding), Nanping (Jianyang, Songxi), and Ningde (Fu'an, Zherong).

To further study the relationship between timely initiation of the HB vaccine first dose and completion of the HB vaccine and the NIPV series, the immunization information of 1680 community children from eight counties (Minqing, Huli, Xianyou, Shaxian, Yongchun, Xiangcheng, Xinluo, and Jianyang) were rechecked with the vaccination records in the immunization surveillance system in immunization clinics, and were summarized by initiation time of the HB vaccine first dose ($\leq$ 24 vs. >24 h after birth) and completion of the three-dose HB vaccine and the NIPV series (yes vs. no).

2.2. Outcome definitions

Three outcomes were assessed in this analysis: timely initiation of the first dose of HB vaccine, completion of the HB vaccine series, and completion of the NIPV series. In accordance with the recommended vaccination schedule of the China Center for Disease Control and Prevention,[3] timely initiation of the first dose of HB vaccine was defined as receipt of the first dose of HB vaccine within 24 h after birth. Completion of the HB vaccine series was defined as the receipt of three doses of HB vaccine at the correct/appropriate intervals (i.e., >1 month between doses 1 and 2, >2 months between doses 2 and 3, and >4 months between doses 1 and 3) by 12 months of age, regardless of the time at receipt of the first HB vaccine dose.

The NIPV series refers to three doses of HB vaccine, one dose of Bacillus Calmette–Guérin vaccine (BCG), three doses of oral poliomyelitis vaccine (OPV), three doses of DTP vaccine, one dose of MCV, one dose of Japanese encephalitis attenuated live vaccine (JEV-L), and two doses of group A meningococcal polysaccharide vaccine (MPSV). Completion of the NIPV series was defined as the receipt of the NIPV series at the correct/appropriate intervals for the different vaccines and/or doses, in which the child should have completed the HB vaccine, BCG, OPV, DTP, MCV, and JEV-L series and the first dose of MPSV by 12 months of age, and have completed the second dose of MPSV by 18 months of age (with an interval of at least 3 months between the first and second dose). Community children aged less than 18 months at the time of the survey were deemed to have completed the NIPV series if they had received all NIPV series vaccines except the second dose of MPSV. Any violation of the requirement was defined as delayed initiation of the HB vaccine first dose, incompletion of the HB vaccine series, and incompletion of the NIPV series, respectively.

2.3. Statistical analysis

Individual vaccination data were checked and classified according to the definitions. The coverage rate of timely administration of the HB vaccine first dose was counted by city. The Chi-square test or Fisher's exact test was used to compare the rates of timely HB vaccine first dose between local children and floating children, and between community children and hospital infants. Local children were defined as children with a permanent local Hukou, while floating children were defined as those living without residence registration in the survey location.

The percentages of children who had completed the HB vaccine series and the NIPV series were calculated by initiation time of the HB vaccine first dose ($\leq$24 h and >24 h after birth). Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. A subgroup analysis was done by urbanicity (rural area vs. urban area). According to the distance between the area of residence and the central city, and the economic development of the region, three counties were classified as urban areas (Huli, Xiangcheng, and Xinluo) and five counties were classified as rural areas (Minqing, Xianyou, Shaxian, Yongchun, and Jianyang). Given the small sample of the control group, details of the delay in HB vaccine first dose were described, and the proportion of children with a delayed HB vaccine first dose was compared between the two subgroups (rural children vs. urban children; local children vs. floating children).

Pair-wise comparisons of heterogeneity were applied among the ORs for relationships between the timely initiation of HB

vaccine and completion of the HB vaccine series and completion of the NIPV series.[10] Heterogeneity in the ORs for the associations between rural and urban areas was assessed separately.[10]

The level of statistical significance was set at 0.05. All analyses were completed using IBM SPSS Statistics version 19.0 (IBM Corp., Armonk, NY, USA).

3. Results

Immunization data for 6589 subjects, including 3785 community children and 2804 hospital newborns, were included in this study. Overall, 97.34% of subjects received the HB vaccine first dose within 24 h after birth. The completion rates of the HB vaccine series and the NIPV series were 99.10% and 88.27%, respectively. The coverage rates of timely HB vaccine first dose among community children and hospital newborns were 96.22% and 98.86%, respectively. The proportion of timely HB vaccine first dose among hospital newborns was significantly higher than that among community children ($p < 0.001$). Among community children, local children had a slightly higher coverage rate of timely HB vaccine first dose than floating children; however, the difference was not statistically significant (96.41% vs. 94.44%; $p = 0.063$) (Table 1).

Among the 1680 children from the eight counties, 96.49% (1621/1680) had received a timely HB vaccine first dose. The percentages of children who had completed the HB vaccine series and the NIPV series among the children with a timely HB vaccine first dose were 99.69% and 88.90%, respectively, while these were 83.05% and 71.19%, respectively, among children with a delayed HB vaccine first dose (both $p < 0.001$ for Chi-square test or Fisher's exact test) (Table 2).

Timely initiation of the HB vaccine first dose was associated with an increased likelihood of completion of the vaccine series. Compared with children who received the first dose of HB vaccine at >24 h, the ORs for completing the HB vaccine series and the NIPV series among children with a timely HB vaccine first dose were 65.96 (95% CI 21.73–200.25) and 3.24 (95% CI 1.81–5.81), respectively (Table 2). Significant heterogeneity was found when comparing the OR for the association between receipt of a timely HB vaccine first dose and completion of the NIPV series, with that for the association between a timely initiation of the HB vaccine first dose and completion of the HB vaccine series ($p < 0.001$) (Table 2).

Children in the control group received the HB vaccine first dose at an average of 35 days of age (standard deviation 54.41 days), with a range of 2–362 days. The proportion of children with a delayed HB vaccine first dose among local children was lower than that among floating children (3.06% vs. 7.39%, $p = 0.003$). Similarly, the percentage of children with a delayed HB vaccine first dose in urban areas was lower than that for rural areas (2.29% vs. 5.56%, $p < 0.001$).

Sensitivity analyses indicated no significant difference in the associations between a timely initiation of HB vaccine first dose and completion of the HB vaccine series and the NIPV series among children living in urban areas and those living in rural areas. The corresponding ORs were 148.50 and 4.33 for urban children, and 29.17 and 3.27 for rural children, respectively (p-value for urbanicity difference: 0.22 and 0.64, respectively).

4. Discussion

The coverage with a timely first dose of HB vaccine in this study was higher than that in previous studies,[1,3,4] and higher than that in other provinces and in the Global Alliance for Vaccine and Immunization (GAVI) area of China.[11–13] Unlike previous studies in which the coverage with a timely HB vaccine first dose has been calculated based on community children alone, this study included both community children and hospital newborns. Hence, the sample in this study may be more representative than those included in previous studies, because more and more newborns are born in hospital rather than at home (about 99.7% of newborns have been born in hospital since 2013[14]). In addition, the difference might be attributed to the implementation of policies and approaches focusing on improving the coverage with a timely HB vaccine first dose since 2002, such as the provision of adequate

Table 1
Coverage rates of timely first dose of hepatitis B vaccine in Fujian, by city[a]

City	Community children born in 2010–2011						Hospital newborns born in 2012		Total	
	Local children		Floating children		Total					
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Fuzhou	358	98.04	62	98.39	420	98.10	300	100[c]	720	98.89
Xiamen	237	98.31	187	93.58[b]	424	96.23	163	98.16	587	96.76
Putian	418	99.28	2	100.00	420	99.29	500	100.00	920	99.67
Sanming	403	94.29	17	94.12	420	94.29	375	96.27	795	95.22
Quanzhou	381	98.43	39	94.87	420	98.10	542	99.08	962	98.65
Zhangzhou	407	94.59	13	92.31	420	94.52	224	100[c]	644	96.43
Longyan	403	94.79	17	94.12	420	94.76	200	100[c]	620	96.45
Nanping	404	95.05	16	93.75	420	95.00	300	97.00	720	95.83
Ningde	414	95.89	7	85.71	421	95.72	200	99.50[c]	621	96.94
Total	3425	96.41	360	94.44	3785	96.22	2804	98.86[c]	6589	97.34

[a] Percentage of timely hepatitis B vaccine first dose.
[b] $p < 0.05$ for the Chi-square test comparing the coverage rate of timely first dose among local children with that among floating children.
[c] $p < 0.05$ for the Chi-square test comparing the coverage rate of timely first dose among community children with that among hospital newborns.

Table 2
Relationship between receipt of a timely first dose of the HB vaccine and completion of the HB vaccine series and the NIPV series

Time of initiation of HB vaccine first dose	No. surveyed	Completion of HB vaccine series		Completion of the NIPV series	
		%	OR (95% CI)	%	OR (95% CI)
After 24 h	59	83.05	Reference	71.19	Reference
Within 24 h	1621	99.69	65.96 (21.73–200.25)	88.90	3.24 (1.81–5.81)[a]

HB vaccine, hepatitis B vaccine; NIPV, national immunization program vaccine; OR, odds ratio; CI, confidence interval.
[a] $p < 0.001$ for the heterogeneity test comparing the OR with that for the association between a timely first dose and completion of the HB vaccine series.

free HB vaccine, the increased collaboration between maternal child health and Expanded Program on Immunization (EPI) departments, and the setting of assessment indicators for the coverage with a timely HB vaccine first dose for county-level health bureaus.[1,15,16]

pt?>Similar to the results of the previous study by this study group, timely HB vaccine first dose administration was found to be associated with an increased likelihood of completing the HB vaccine series.[5] Generally, parents in high HBV endemic provinces maintain positive attitudes towards HB vaccine immunization and are more concerned about their children receiving prophylaxis against HBV infection. Receiving a timely first dose of HB vaccine might help emphasize the importance of this vaccine to parents who may be motivated to have their child complete subsequent doses.[1,6,7,17,18]

This appears to be the first study to explore the association between the receipt of a timely first dose of HB vaccine and completion of the NIPV series in Fujian, China. It was found that children who received a timely HB vaccine first dose were more likely to complete the NIPV series, which is similar to findings in the USA.[6] The accomplishment of a timely HB vaccine first dose might prompt an educational intervention for the parents and improve their compliance with vaccination. Further, it was found that local and urban children were more likely to receive a timely HB vaccine first dose, which may reflect they have greater access to medical care and/or come from families with a higher income;[19,20] these advantages factors may make it more convenient and affordable to complete the NIPV series. Alternatively, the HB vaccine first dose is often delayed as a result of false contra-indications (e.g., low birth weight, prematurity),[15,16] or for those born at home,[13,15] and the delay might affect appropriate catch-up regimens for these children,[21] resulting in them being less likely to complete the HB vaccine and NIPV series.

Significant heterogeneity in the ORs between completion of the HB vaccine series and the NIPV series might reflect different schedule durations for these vaccine series. Besides, other factors, such as self-paid vaccine immunization, might influence the completion of the NIPV series,[22–24] but not affect the completion of the HB vaccine series.

This study has several limitations. First, this was a rapid evaluation of inoculation rates in children; only vaccination data were collected, without other information such as the child's sex, age, and place of birth. Therefore, it was not possible to control for confounders when examining the independent association between timely initiation of the HB vaccine and completion of the HB vaccine series and NIPV series. Second, due to the interests of the investigators, immunization data of community children from only eight counties were included in the examination of the association between timely initiation of the HB vaccine first dose and completion of the HB vaccine series and NIPV series, which might somewhat affect the interpretation of the results. Finally, children with a delayed birth dose of HB vaccine were set as the control group; however, the sample size of this group was small and the information collected was not sufficient to have a good description of these 59 children, e.g., why the vaccination was delayed.

In this quality assessment study including community children and hospital newborns, it was found that coverage with a timely HB vaccine first dose was high in Fujian in 2013. A positive impact of the timely initiation of the HB vaccine first dose on completion of the HB vaccine series and the NIPV series was also found. Policy and related approaches should be continued and strengthened to ensure that newborns receive their first dose of HB vaccine on time. Staff at EPI clinics should pay more attention to those with a delayed HB vaccine first dose to promote their completion of the HB vaccine and NIPV series. Further studies should be conducted to identify the reasons for the delay in the HB vaccine first dose and to draw up more comprehensive guidelines for newborns.

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Conflict of interest: The authors declare that they have no competing interests.

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