International Journal of Infectious Diseases 14 (2010) e483–e488

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

A significant reduction in hepatitis B virus infection among the children of Shandong Province, China: the effect of 15 years of universal infant hepatitis B vaccination

Li Zhang [a,b], Aiqiang Xu [a], Bingyu Yan [a], Lizhi Song [a], Manshi Li [a], Zuokui Xiao [a], Qing Xu [a], Liming Li [c,*]

[a] Shandong Provincial Center for Disease Control and Prevention, Jinan, China
[b] School of Public Health, Shandong University, Jinan, China
[c] School of Public Health, Peking University, 38 Xue Yuan Road, Hai Dian District, Beijing, 100083, Beijing, China

ARTICLE INFO

Article history:
Received 8 January 2009
Received in revised form 17 July 2009
Accepted 1 August 2009

Corresponding Editor: William Cameron, Ottawa, Canada

Keywords:
Prevalence
Universal infant hepatitis B vaccination
Vaccination coverage

ABSTRACT

Objective: To evaluate the effect of the universal infant hepatitis B vaccination program on hepatitis B infection in China.
Methods: In 2006, a survey was conducted in Shandong Province, China, among children aged 1–14 years, 15 years after the introduction of universal infant hepatitis B vaccination. The subjects were selected by stratified, multi-stage sampling. Vaccination history was obtained by immunization certificate (when available) or parent recall. Hepatitis B surface antigen (HBsAg) and antibodies to HBsAg (anti-HBs) and core antigen (anti-HBc) were detected by ELISA. Hepatitis B infection was defined as the presence of HBsAg and/or anti-HBc. The prevalence rates of HBsAg, anti-HBs and hepatitis B infection obtained in this survey were compared with the results of a survey conducted in 1992 (prior to universal vaccination).
Results: A total of 3738 children aged 1–14 years were included in the final analysis. A vaccination coverage rate of 93% was achieved in 2006. The prevalence rates of HBsAg and hepatitis B infection decreased from 8% and 46% in the 1992 survey to 1% and 4%, respectively, in the 2006 survey.
Conclusions: Universal hepatitis B vaccination in infants can result in a 90.47% reduction in hepatitis B infection in children aged 1–14 years.

1. Introduction

Hepatitis B virus (HBV) infection, which was highly prevalent in China, is a main cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma.[1] In the first national hepatitis B serological survey in 1979, the prevalence rate of hepatitis B surface antigen (HBsAg) was found to be 8.75%,[2] and it was 9.8% in the second national survey in 1992.[3] The results of the third national survey in 2006 showed that the HBsAg carrier rate among population groups aged 1–59, 1–4, and 5–14 years had declined to 7.18%, 0.96%, and 2.42%, respectively.[4] In China, the hepatitis B vaccine (HepB) was first used in 1987 and was recommended for infants by the Ministry of Health in 1992. Since then, universal infant hepatitis B vaccination has been implemented in China. HepB was freely provided to infants (but with a user fee of about US$ 1.10) from 2002 and infants have been vaccinated without any charge since 2005. The vaccination records of elementary school entrants have been checked for evidence of vaccinations including HepB since 2005. Non- and incompletely vaccinated children are given catch-up vaccinations. Before 1997, 10 μg plasma-derived HepB were administered to vaccinate newborns delivered by HBsAg-negative mothers or mothers with no serological check record. A 30 μg–10 μg–10 μg plasma-derived HepB schedule was implemented in newborns delivered by HBsAg carriers. In 1997, the DNA recombinant vaccine was introduced into China, and the plasma-derived vaccine was withdrawn from the market in 2000. Today, 5 μg recombinant yeast vaccine is recommended for infants, and the HepB vaccination program consists of a first dose within 24 h after birth, followed by further doses at 1 and 6 months of age. Screening of pregnant women for HBsAg is not compulsory.

Shandong Province is located in the eastern part of China, covers an area of 156 700 km^2 (1.63% of the nation), and has a population of about 93 million (6.92% of the national population). It has 17 prefectures and 140 urban districts or rural counties. More than 1 million babies are born in the province each year. In addition to the national vaccination program, a massive HepB immunization campaign was carried out in Shandong Province in 2006, in which children aged 1–14 years with incomplete HepB

* Corresponding author. Tel.: +86 10 65105905; fax: +86 10 65592401.
E-mail address: lmlee@pumc.edu.cn (L. Li).

1201-9712/$36.00 – see front matter © 2009 International Society for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.ijid.2009.08.005

vaccination were required to obtain catch-up injections. About 1.9 million children received at least one dose of HepB during the campaign (data provided by Shandong Provincial Center for Disease Control and Prevention, unpublished). In 1992, the HBsAg prevalence rate among children aged 1–14 years was 8% in Shandong Province.[5] The next hepatitis B serological survey was conducted in April 2006, 15 years after the introduction of the universal infant HepB vaccination, and we performed a provincial hepatitis B serological survey in Shandong Province on the basis of this third national survey. Our survey aimed to determine HepB vaccination coverage and the prevalence rates of HBV markers among children born after universal hepatitis B vaccination was instituted, and to compare the results with those of 1992.

2. Materials and methods

2.1. Study population and sample design

In April 2006, we conducted a cross-sectional serological survey in Shandong Province, China. The target population was children aged 1–14 years, born after the launch of the universal hepatitis B vaccination program. The subjects were selected by stratified, multi-stage sampling. The 17 prefectures of Shandong Province were divided into three geographical areas: the eastern area (Qingdao, Yantai, Weifang, Weihai, and Rizhao prefectures), the middle area (Jinan, Zibo, Dongying, Laiwu, and Linyi prefectures), and the western area (Zaozhuang, Jining, Tai-an, Dezhou, Liaocheng, Binzhou, and Heze prefectures). Survey locations were selected by means of probability proportional to size (PPS) sampling techniques. Four survey locations (urban districts or rural counties) were obtained from each area, and these 12 survey locations were shown to have similar demographic compositions to the whole province (Table 1). Three sub-districts in each urban district, two towns in each rural county, and one resident commission (village) in each sub-district (town) were selected randomly. In the selected resident commission (village), all children aged 1–4 years were interviewed and participants aged 5–14 years were chosen by systematic sampling. If an interviewee was not contactable or the interview was not permitted by the parents, the child was replaced by another of the same age and gender living in the same resident commission (village).

Our survey required 1522 children aged 1–4 years and 2270 children aged 5–14 years to obtain an absolute precision of 0.5%, a significance level α of 0.05 ($Z_{\alpha/2} = 1.96$), and an estimated prevalence of HBsAg-positive children of 1% and 1.5%, respectively, in the two age groups. The design effects for the prevalence rate of HBsAg were 2.95 and 2.69 among children aged 1–4 and 5–14 years, respectively, obtained using PROC SURVEYFREQ in SAS 9.1.3.

Table 1
Demographic composition of the population in the sample locations and the whole of Shandong Province in China, 2006

	Sample locations (%)	Whole province[a] (%)
Age (years)		
1–4	4.62	4.61
5–9	5.42	5.79
10–14	11.96	12.23
15–19	8.92	9.47
20–24	7.36	7.63
25–29	9.98	9.80
30–34	12.10	12.02
35–39	10.81	10.49
40–44	8.86	8.15
45–49	9.10	8.85
50–54	6.31	6.45
55–59	4.57	4.50
	Chi-square = 0.156, $p > 0.05$	
Gender		
Male	50.75	50.62
Female	49.25	49.38
	Chi-square = 0.00068, $p > 0.05$	
Residential area		
Urban	31.26	24.55
Rural	68.74	75.45
	Chi-square = 2.43, $p > 0.05$	
Geographic location		
Eastern	29.96	31.02
Middle	25.19	25.65
Western	44.85	43.33
	Chi-square = 0.10, $p > 0.05$	

[a] Data source: Tabulation of the 2000 population census of Shandong Province.[6]

2.2. Data collection and laboratory procedures

Each survey team consisted of three interviewers from the local center for disease control and prevention. The interviews were carried out using a standard questionnaire. For a child with no immunization certificate, the HepB vaccination history was registered by parent description.

Blood samples were collected and HBsAg, antibody to hepatitis B surface antigen (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc) were detected using ELISA by the laboratory of the National and Provincial Centers for Disease Control and Prevention. The kits were provided by Xiamen Xin Chuang Biotechnology Co., Ltd and Shanghai Ke Hua Biotechnology Co., Ltd.

2.3. Statistical analysis

We calculated the weighted complete vaccination coverage rate of HepB and the weighted prevalence rate of HBV markers in children of different ages, genders, and residential areas. The complete vaccination coverage rate of HepB was defined as the percentage of persons receiving three or more doses of HepB, and HBV infection was defined as the presence of HBsAg and/or anti-HBc. Weights were created to account for the different selection probabilities of persons across the sub-districts (towns), resident commissions (villages), and age groups, and the data were adjusted by the age and gender composition of the whole provincial population.[6] The numbers of sub-districts (towns) and resident commissions (villages) were obtained from the local statistics bureau and the demographic information for each sub-district (town) was obtained from the local domiciliary register. In order to compare the prevalence rates of HBV markers in our study with those of 1992,[5] the children were divided into five age groups: $\geq$1 year and $<$ 2 years, $\geq$2 years and $<$4 years, $\geq$4 years and $<$6 years, $\geq$6 years and $<$10 years, and 10–14 years. PROC SURVEYFREQ in SAS 9.1.3 was used for all calculations.

2.4. Ethical considerations

The study protocol was approved by the Ethics Committee of the Medical School of Shandong University and consent documents were signed by the children's parents.

3. Results

3.1. Demographic characteristics

A total of 3738 children participated in the survey: 1503 children aged 1–4 years and 2235 children aged 5–14 years. The gender and geographical distributions were as follows: 1945 males (52.03%) and 1793 females (47.97%); 1198 (32.05%) from urban areas and 2540 (67.95%) from rural areas; 1238 (33.12%), 1262 (33.76%), and 1238 (33.12%) from the eastern, middle, and western areas, respectively. Among the children selected, 15.14% were replaced by the method mentioned in the Materials and methods.

Table 2
History and coverage of HepB vaccination among children aged 1–14 years by age, gender, and residential area in Shandong Province, China, 2006

	Sample size	No. of children with different HepB doses			Complete coverage rate	
		Unknown	<3	≥3	%	95% CI
Overall	3738	48	119	3571	92.67	90.91–94.43
Age (years)						
1	355	0	7	348	98.87	97.05–100
2	415	0	1	414	99.93	99.81–100
3	391	0	1	390	99.83	99.48–100
4	342	1	0	341	99.92	99.79–100
5	262	0	1	261	99.69	99.10–100
6	243	1	1	241	99.27	98.15–100
7	219	0	2	217	99.36	98.25–100
8	246	2	4	240	98.56	96.31–100
9	283	4	7	272	96.75	93.19–100
10	243	1	6	236	94.93	90.20–99.66
11	201	4	16	181	86.68[a]	76.90–96.46
12	174	8	20	146	73.69[b]	61.81–85.56
13	185	12	23	150	72.95[b]	65.03–80.87
14	179	15	30	134	71.00[b]	63.26–78.73
Gender						
Male	1945	28	59	1858	92.31	89.80–94.81
Female	1793	20	60	1713	93.09	91.60–94.57
Residential area						
Urban	1198	32	35	1131	91.94	88.33–95.54
Rural	2540	16	84	2440	92.79	90.66–94.92
Geographic location						
Eastern	1238	5	15	1218	97.30	94.43–100
Middle	1262	5	61	1196	89.62[c]	86.06–93.17
Western	1238	38	43	1157	94.56	91.06–98.07

CI, confidence interval.
[a] $p < 0.05$ comparing results for children aged 11 years vs. those younger than 8 years.
[b] $p < 0.05$ comparing results for children older than 11 years vs. those younger than 11 years.
[c] $p < .05$ comparing results for children in the middle area vs. those in the eastern area.

3.2. HepB vaccination coverage rate

HepB vaccination history was unknown in 48 (1.28%) children. Of the other 3690 children, 119 (3.18%) had received none or fewer than three doses of HepB, and 3571 (95.53%) had received three or more doses. The weighted complete vaccination rate was 92.67% (95% confidence interval (CI) = 90.91–94.43%) among children aged 1–14 years in 2006. It was significantly lower among children aged 10–14 years (81.22%, 95% CI = 77.85–84.60%) compared to those aged 1–9 years (99.10%, 95% CI = 97.96–100.00%). The rates were not significantly different when subjects were grouped according to gender or residential area (urban or rural area). However, a significantly higher vaccination rate was found among children from the eastern area compared to those from the middle area (Table 2).

3.3. Seroprevalence of HBV markers

The weighted prevalence rates of HBsAg, anti-HBc, anti-HBs, and HBV infection were 1.36% (95% CI = 0.60–2.13%), 4.24% (95% CI = 2.58–5.91%), 68.23% (95% CI = 65.68–70.78%), and 4.35% (95% CI = 2.82–5.88%), respectively, among children aged 1–14 years (Table 3). The HBsAg prevalence rate was lowest in 1-year-old children (0.73%, 95% CI = 0–1.70%) and highest among those aged 10–14 years (1.93%, 95% CI = 0.78–3.07%), but the difference was not significant. The anti-HBs prevalence rate in 1-year-olds was significantly higher than that for the other age groups. The highest prevalence rates of anti-HBc and HBV infection were observed in children aged 10–14 years. There was no significant difference in the prevalence rates of these markers for different genders and living conditions (urban or rural area). However, the children from the western area had a significantly higher HBsAg rate than those from the eastern area (2.17% vs. 0.62%) (Table 3). Even among children who had received three or more doses of HepB during infancy, the anti-HBc prevalence rate was still significantly higher in the 10–14 years age group than in the other age groups (Table 4).

In comparison with the 1992 survey,[5] the HBsAg prevalence rate among children aged 1–14 years decreased by 83.00% (from 8% to 1.36%), the HBV infection rate decreased by 90.47% (from 45.63% to 4.35%), and the anti-HBs rate increased by 257.04% (from 19.11% to 68.23%). Such trends were observed across all age groups (Figures 1–3).

4. Discussion

HBV was considered to be highly endemic in China. As HBV infection usually occurs during infancy or early childhood when it is most likely to become chronic, the vaccination of infants beginning at birth is the key strategy in preventing chronic HBV infection. Universal infant hepatitis B vaccination was launched in China in 1992 and, since then, great efforts have been made to achieve a high HepB coverage among children. Shandong Province has the second largest population in China, with more than 1 million babies born every year. Our study showed that the complete HepB vaccination coverage rate among children aged 1–14 years in Shandong Province in 2006 had reached 92.67%, similar to the average HepB coverage reported in eastern China.[7] Only 10 of 2008 preschool interviewees had incomplete HepB vaccination, while the complete vaccination coverage rate among children aged 10–14 years was very low (81.22%). This suggests that immunization certificate checks and catch-up vaccinations should be extended to junior middle school children. A lower complete hepatitis B vaccination rate was observed among children from the middle area of the province, which should be further investigated. Since immunization records were not well kept during the 1990 s,

Table 3
Prevalence rate of HBV markers among children aged 1–14 years by age, gender, and residential areas in Shandong Province, China, 2006

	Sample size	HBsAg		Anti-HBs		Anti-HBc		HBV	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
Overall	3738	1.36	0.60–2.13	68.23	65.68–70.78	4.24	2.58–5.91	4.35	2.82–5.88
Age (years)									
1	355	0.73	0–1.70	81.92[a]	75.89–87.94	1.03	0–2.72	1.43	0–3.25
2–3	806	1.17	0–2.64	71.31	67.10–75.52	2.52	0–6.12	2.52	0–6.12
4–5	604	1.05	0–2.42	65.50	57.46–73.54	1.86	0–3.77	1.87	0–3.77
6–9	991	1.05	0.31–1.78	70.06	65.29–74.83	2.55	1.54–3.56	2.77	2.05–3.48
10–14	982	1.93	0.78–3.07	64.18	60.16–68.20	7.81[b]	5.34–10.28	7.86[b]	5.40–10.32
Gender									
Male	1945	1.61	0.67–2.55	67.16	64.06–70.26	4.46	3.05–5.87	4.50	3.09–5.91
Female	1793	1.08	0.36–1.8	69.47	65.45–73.49	4.00	1.45–6.54	4.18	1.92–6.45
Residential area									
Urban	1198	1.65	0.43–2.88	65.55	60.94–70.16	3.99	3.03–4.95	4.13	3.07–5.19
Rural	2540	1.31	0.36–2.26	68.68	65.53–71.83	4.29	2.19–6.39	4.39	2.45–6.32
Geographic location									
Eastern	1238	0.62	0.29–0.94	71.51	63.76–79.26	1.7	0–3.72	1.71	0–3.72
Middle	1262	1.02	0–2.67	69.13	64.73–73.53	3.61	2.69–4.53	3.66	2.84–4.48
Western	1238	2.17[c]	1.08–3.26	65.48	60.34–70.62	6.29	1.73–10.86	6.52	2.45–10.59

HBsAg, hepatitis B surface antigen; anti-HBs, antibodies to hepatitis B surface antigen; anti-HBc, antibodies to hepatitis B core antigen; HBV, hepatitis B virus; CI, confidence interval.
[a] $p < 0.05$ comparing results for children aged 1 year vs. those aged 2–14 years.
[b] $p < 0.05$ comparing results for children aged 10–14 years vs. those aged 1 year, 4–5 years and 6–9 years.
[c] $p < 0.05$ comparing results for children in the western area vs. those in the eastern area.

Table 4
Prevalence rate of HBV markers among children who received three doses of HepB during infancy in Shandong Province, China, 2006

Age (years)	Sample size	HBsAg			Anti-HBc			Anti-HBs		
		Positive number	%	95% CI	Positive number	%	95% CI	Positive number	%	95% CI
1	346	2	0.74	0–1.73	5	1.05	0–2.78	295	81.88[a]	75.64–88.12
2–3	796	6	1.19	0–2.68	13	2.56	0–6.21	594	71.45	67.47–75.42
4–5	592	4	1.07	0–2.45	11	1.9	0–3.82	414	65.45	57.33–73.56
6–9	912	6	1.14	0.38–1.89	17	2.56	1.29–3.84	646	69.98	65.12–74.84
10–14	735	19	2.38	0.79–3.97	48	8.72[b]	5.29–12.16	476	64.82	59.54–70.08
Total	3381	37	1.47	0.63–2.32	94	4.17	2.19–6.16	2425	68.82	66.23–71.4

HBsAg, hepatitis B surface antigen; anti-HBc, antibodies to hepatitis B core antigen; anti-HBs, antibodies to hepatitis B surface antigen; CI, confidence interval.
[a] $p < 0.05$ comparing results for children aged 1 year and the other four age groups.
[b] $p < 0.05$ comparing results for children aged 10–14 years vs. those aged 1 year, 4–5 years and 6–9 years.

the HepB vaccination history for those with no written records was obtained by interviewing the child's parents. Uncertain answers were classified as unknown immunization history, which might partly have contributed to the low HepB coverage among children aged >10 years. Recall bias was minimized by independent interviews with the parents.

In 1992, when HepB was first recommended in infants, an HBV serological survey was conducted in Shandong Province based on the second national survey. Our survey was conducted in 2006, 15 years after universal infant hepatitis B vaccination was instituted. There were some differences between the two surveys. One thousand two hundred and twenty-five children aged 1–14 years were selected by two-stage sampling from seven urban districts or rural counties in the 1992 survey, while 3738 children were selected by three-stage sampling from 12 districts or counties in the 2006 survey. Markers for HBsAg, anti-HBs, and anti-HBc were detected in both surveys, but they were detected by solid phase radioimmunoassay (SPRA) in the 1992 survey and by ELISA in the

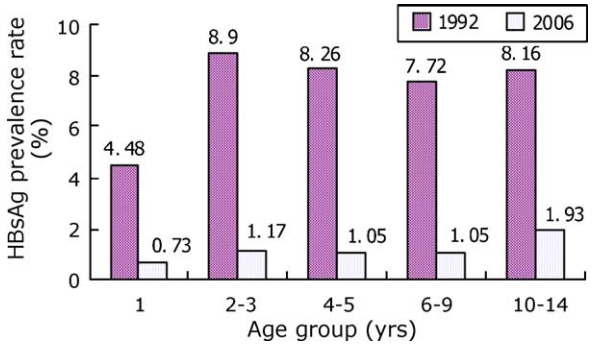

Figure 1. Comparison of the age-specific prevalence rate of HBsAg among children aged 1–14 years in 1992 and 2006.

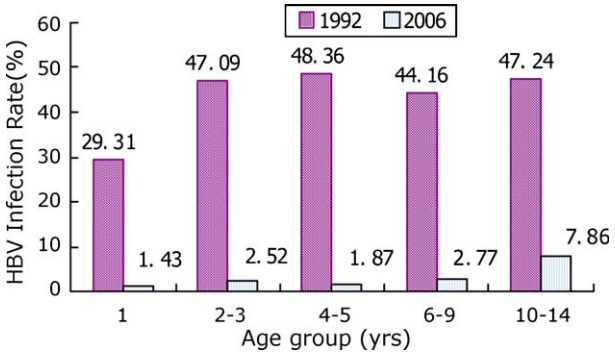

Figure 2. Comparison of the age-specific HBV infection rate among children aged 1–14 years in 1992 and 2006. In the 1992 survey,[5] HBV infection was defined as the presence of either HBsAg, anti-HBc, or anti-HBs.

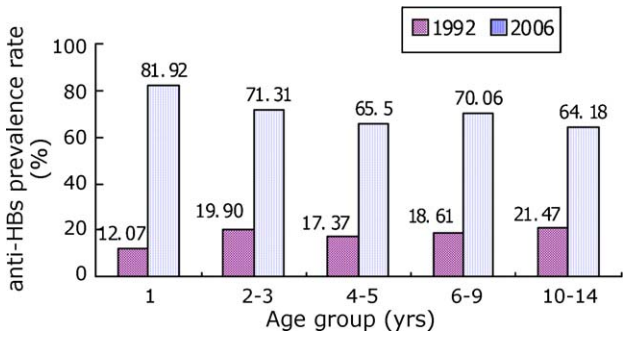

Figure 3. Comparison of the age-specific prevalence rate of anti-HBs among children aged 1–14 years in 1992 and 2006.

2006 survey. We could not compare the prevalence rates of anti-HBc for the two surveys because the rate was not reported in the 1992 survey. HBV infection was defined as the presence of HBsAg, anti-HBs, or anti-HBc in the 1992 survey, and subsequently as the presence of HBsAg or anti-HBc because of comprehensive vaccination with HepB after 1992. Despite these differences, the two surveys demonstrated a decline in the HBV infection rate after the implementation of universal infant hepatitis B vaccination, because the trends could not be explained by the differences in survey methods (Figures 1–3). Similar results have been reported in other countries and areas.[8–11] The incidence of hepatitis B reported by the National Notifiable Infectious Disease Reporting System also declined from 14.5/100 000 to 1.82/100 000 among children aged 0–4 years, and from 21.30/100 000 to 4.51/100 000 among those aged 5–14 years in Shandong Province during the same period. Other public health measures, such as the enforcement of blood screening and implementation of safe injection practices, were not investigated in our study, but may also have played some part in these achievements. However, the high HepB coverage undoubtedly played the most important role in the decrease in HBV infections among children, because maternal–neonatal transmission is the major route for chronic HBV infection in HBV endemic areas.

Our data showed that children aged 1 year had a significantly higher prevalence of anti-HBs than those older than 1 year. No significant difference in HBsAg prevalence was found between age groups, while anti-HBc prevalence in the group aged 10–14 years was significantly higher than that in children aged <10 years (Table 3). This could potentially be explained by lower HepB coverage and waning anti-HBs among older children.[12–16] Even among children who received three doses of HepB during infancy, a significantly higher anti-HBc prevalence and similar HBsAg prevalence were found in the group aged 10–14 years, which is comparable to the previous observation.[12,16]

In recent years, many researchers have focused on the need for HepB booster injections. The majority of results have indicated that the protection induced by HepB primary immunization may persist for 10–18 years,[13,17–19] and some results have suggested that a booster dose, given 18 years after the first injection or even earlier, is necessary to retain immunity.[20] Although a number of studies have identified the persistence of anti-HBs, the results were not well accepted because different vaccine products and different immunization schedules were used.[17–20] Moreover, some researchers noted geographic and ethnic variations in the long-term efficacy and immunogenicity of HepB.[18] It is necessary to initiate a nationwide and well-controlled epidemiological investigation in China.

In our study, 37 children with complete hepatitis B vaccination in infancy were HBsAg-positive. Among them, only one child described a history of an HBsAg carrier mother in the questionnaire. This is quite different from observations in Taiwan[8] and Uzbekistan,[21] where most HBsAg-positive children were born to HBV-infected mothers. One reason may be that the screening of pregnant women for HBsAg is not compulsory in China, so that some of them were not aware of their HBV infection until clinical diagnosis. Another explanation is that parents may deny their HBV carrier status to avoid potential discrimination in the community. A third possibility is immuno-tolerance towards the HBV vaccine or infection with vaccine escape variants.[8,12,22]

In the 2006 study, we selected subjects from a population register provided by the local government. During the investigational period, some children moved to other locations or traveled with their parents. This was the main reason for the high non-responder rate (15%) in our study. Very few parents refused to permit interviews or to provide blood samples. To ensure a sufficient sample size, we replaced children lost to follow-up with children of the same age and gender living in the same resident commission (village). We were not able to compare the characteristics of the children lost to follow-up with those of the children who replaced them. Considering the main reason for non-response was the floating population rather than refusal to participate in the investigation, we believe that the replacement of subjects would have had very little impact on our results.

In conclusion, our study demonstrates a high complete hepatitis B vaccination rate among children born after the introduction of universal infant vaccination in Shandong Province. The HBV infection rate among children declined by about 90% following 15 years of universal HepB vaccination in infancy. An interesting finding is that the risk of HBV infection, but not the risk of being an HBsAg carrier, increased 10 or more years after HepB primary immunization. Further research should be carried out on the long-term efficacy and immunogenicity of HepB vaccination in China.

Acknowledgements

We thank our colleagues in the province, prefectures, and counties for help with blood sample collection and Dr Jian-hua Liu of the China Center for Disease Control and Prevention for his support in the statistical analysis.

Conflict of interest: No conflict of interest to declare.

References

1. Beasley RP, Hwang LY, Lin CC. Hepatocellular carcinoma and hepatitis B virus: a prospective study of 22,707 men in Taiwan. *Lancet* 1981;**2**:1129–33.
2. Li Yu. An epidemiological study on viral hepatitis in China. Zhonghua Weishengwuxue He Mianyixue Zhazhi 1986;(Suppl):1–15.
3. Dai ZC, Qi GM. [Viral hepatitis seroepidemiological survey in Chinese population, 1992–1995 (part one)] (in Chinese). Beijing, China: Science and Technical Documents Publishing House; 1997, p. 39–59.
4. Chinese Center for Disease Control and Prevention. Results from a nationwide hepatitis B seroepidemiological survey in China, 2006. Available at: http://www.chinacdc.net.cn/n272442/n272530/n3246177/23316.html (accessed April 2008).
5. Dai ZC, Qi GM. [Viral hepatitis seroepidemiological survey in Chinese population, 1992–1995 (part two)] (in Chinese). Beijing, China: Science and Technical Documents Publishing House; 1997. p. 105–14.
6. Population Census Office of Shandong Province. [Tabulation on the 2000 population census of Shandong Province] (in Chinese). Beijing, China: China Statistics Press; 2002. p. 1041–4.
7. Centers for Disease Control and Prevention (CDC). Progress in hepatitis B prevention through universal infant vaccination—China, 1997–2006. *MMWR Morb Mortal Wkly Rep* 2007;**56**:441–5.
8. Ni YH, Huang LM, Chang MH, Yen CJ, Lu CY, You SL, et al. Two decades of universal hepatitis B vaccination in Taiwan: impact and implication for future strategies. *Gastroenterology* 2007;**132**:1287–93.
9. Hayashi J, Kajiyama W, Noguchi A, Ikematsu H, Nomura H, Nakashima K, et al. Marked decrease of hepatitis B virus infection among children in Okinawa, Japan. *Int J Epidemiol* 1990;**19**:1083–5.
10. Hsu HM, Lu CF, Lee SC, Liu SR, Chen DS. Seroepidemiologic survey for hepatitis B virus infection in Taiwan: the effect of hepatitis B mass immunization. *J Infect Dis* 1999;**179**:367–70.

11. Zanetti AR, Romano L, Zappa A, Velati C. Changing patterns of hepatitis B infection in Italy and NAT testing for improving the safety of blood supply. *J Clin Virol* 2006;**36**(Suppl 1):S51–5.
12. Dentinger CM, McMahon BJ, Butler JC, Dunaway CE, Zanis CL, Bulkow LR, et al. Persistence of antibody to hepatitis B and protection from disease among Alaska natives immunized at birth. *Pediatr Infect Dis J* 2005;**24**: 786–92.
13. Yuen MF, Lim WL, Chan AO, Wong DK, Sum SS, Lai CL. 18-year following-up study of a prospective randomized trial of hepatitis B vaccinations without booster doses in children. *Clin Gastroenterol Hepatol* 2004;**2**:941–95.
14. Liao SS, Li RC, Li H, Yang JY, Zenf XJ, Gong J, et al. Long-term efficacy of plasma-derived hepatitis B vaccine: a 15-year following-up study among Chinese children. *Vaccine* 1999;**17**:2661–6.
15. El Sawy IH, Mohamed ON. Long-term immunogenicity and efficacy of a recombinant hepatitis B vaccine in Egyptian children. *East Mediterr Health J* 1999;**5**:922–32.
16. Goh KT, Oon CJ, Heng BH, Lim GK. Long-term immunogenicity and efficacy of a reduced dose of plasma-based hepatitis B vaccine in young adults. *Bull World Health Organ* 1995;**73**:523–7.
17. Zanetti AR, Mariano A, Romano L, D'Amelio R, Chironna M, Coppola RC, et al. Long-term immunogenicity of hepatitis B vaccination and policy for booster: an Italian multicentre study. *Lancet* 2005;**366**:1379–84.
18. Gabbuti A, Romano L, Blanc P, Meacci F, Amendola A, Mele A, et al. Long-term immunogenicity of hepatitis B vaccination in a cohort of Italian healthy adolescents. *Vaccine* 2007;**25**:3129–32.
19. Lin YC, Chang MH, Ni YH, Hsu HY, Chen DS. Long-term immunogenicity and efficacy of universal hepatitis B virus vaccination in Taiwan. *J Infect Dis* 2003;**187**:134–8.
20. Su FH, Chen JD, Cheng SH, Sung KY, Jeng JJ, Chu FY. Waning-off effect of serum hepatitis B surface antibody amongst Taiwanese university students: 18 years post-implementation of Taiwan's national hepatitis B vaccination programme. *J Viral Hepat* 2008;**15**:14–9.
21. Avazova D, Kurbanov F, Tanaka Y, Sugiyama M, Radchenko I, Ruziev D, et al. Hepatitis B virus transmission pattern and vaccination efficiency in Uzbekistan. *J Med Virol* 2008;**80**:217–24.
22. Hsu HY, Chang MH, Ni YH, Chen HL. Survey of hepatitis B surface variant infection in children 15 years after nationwide vaccination program in Taiwan. *Gut* 2004;**53**:1499–503.