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Epidemiological serosurvey of Hepatitis B in China—Declining HBV prevalence due to Hepatitis B vaccination☆

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ABSTRACT

Objective: To determine the prevalence of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core anti-body (anti-HBc) in a representative population in China 14 years after introduction of hepatitis B vaccination of infants.
Methods: National serosurvey, with participants selected by multi-stage random sampling. Demographics and hepatitis B vaccination history collected by questionnaire and review of vaccination records, and serum tested for HBsAg, antibody to anti-HBc and anti-HBs by ELISA.
Findings: The weighted prevalences of HBsAg, anti-HBs and anti-HBc for Chinese population aged 1–59 years were 7.2%, 50.1%, 34.1%, respectively. HBsAg prevalence was greatly diminished among those age <15 years compared to that found in the 1992 national serosurvey, and among children age <5 years was only 1.0% (90% reduction). Reduced HBsAg prevalence was strongly associated with vaccination among all age groups. HBsAg risk in adults was associated with male sex, Western region, and certain ethnic groups and occupations while risk in children included birth at home or smaller hospitals, older age, and certain ethnic groups (Zhuang and other).
Conclusions: China has already reached the national goal of reducing HBsAg prevalence to less than 1% among children under 5 years and has prevented an estimated 16–20 million HBV carriers through hepatitis B vaccination of infants. Immunization program should be further strengthened to reach those remaining at highest risk.

1. Background

In 1992, the China national hepatitis seroepidemiological survey found that the prevalence of HBsAg for population aged 1–59 years was 9.8%. Based on this survey, it has been estimated that in China, 120 million people carry HBsAg [1–3], 20 million suffer from chronic hepatitis B, and almost 300,000 die annually from chronic consequences of HBV infection. Both liver cancer and cirrhosis are among the 10 most common causes of mortality in China; for both, hepatitis B virus causes the majority of deaths [4–6].

To control hepatitis B, the Chinese government has implemented infant vaccination with hepatitis B vaccine as the highest priority. In 1992, the Ministry of Health recommended hepatitis B vaccine for routine immunization of infants but parents had to pay for the vaccine, therefore vaccine coverage was higher in urban and high socioeconomic areas and lower in rural and lower socioeconomic areas. In 1999, a National Expanded Programme on Immunization (EPI) review showed that, the immunization coverage with three doses of hepatitis B vaccine was 70.7%, but varied from 99% in Beijing to only 7.8% in Tibet [7]. A follow-up survey showed immunization coverage among children born in 2001 had reached 82.4 %, but with continued disparities in western provinces and rural counties [8]. In 2002, China integrated hepatitis B vaccine into EPI, with emphasis on providing a timely birth dose (within 24 h of birth). The cost of vaccine was paid by the government, but vaccine administration fees of up to $1.10 per dose were still allowed as a charge to parents. In addition, the

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China/Global Alliance on Vaccine and Immunization (GAVI) project provided $76 million funding to purchase hepatitis B vaccine and autodisable syringes for all children born in western provinces and poverty counties in middle provinces [9]. In May 2005, the government required that all infant vaccinations be given at no charge to parents.

To accelerate the control of hepatitis B, the Ministry of Health developed the "2006–2010 National guidelines for hepatitis B prevention and treatment", establishing national goals of achieving HBsAg prevalence less than 7% by 2010 for whole population and less than 1% for children under 5 years [10].

The vaccination program in China has been regarded as a success story in preventing hepatitis B through universal infant vaccination [11]. To measure the prevalence of hepatitis B markers among population aged 1–59 years, ongoing risk factors for hepatitis B infection, and to evaluate the impact of the hepatitis B vaccination programme since 1992, the China government conducted the national hepatitis serosurvey in 2006.

2. Methods

Planning for this study was started in December 2005 and data analysis completed in December 2007. All field work was conducted between September and October 2006.

2.1. Study population

The target population was local residents aged 1–59 years living in 160 disease surveillance points (DSP) in 31 provinces which have been selected by Chinese Center for Disease Control and Prevention (China CDC) to be representative of the population of China. Demographic, economic conditions and the situation of the population in these sites are not statistically different compared to whole country [12–14]. For the serosurvey, these sites were divided into six major regional groups – urban eastern, rural eastern, central urban, central rural, western urban and western rural – for further sampling[1]. Persons aged 1–59 years resident for more than 6 months at the survey visit were selected.

2.2. Sampling method

Using the expected HBsAg prevalences for different age groups in the study (1% for age 1–4 years, 4% for age 5–14 years, 9% for age 15–59 years), the desired sample size was 79129, and included 15,213 children <5 years and 23,416 children 5–14 years.

First, 369 townships were identified from 160 counties (1–4 per county) by simple random selection; secondly, one village was randomly selected from each township; third, the population aged 1–4, 5–14, and 15–59 years, respectively, were enumerated and selected based on the systematic interval from a list of village residents. Average sampling proportions for each age group at village were 1:1 for children <5 years, 1:7 for children 5–14 years, and 1:8 for population aged 15–59 years.

2.3. Investigation

House to house investigation was completed by trained staff based on the sampled name list. A standard questionnaire was used to compile the basic information including gender, birth date, education, occupation, ethnicity, place of birth, and immunization history through face to face interview with the study subject or parent (if child <15 years). For children under 15 years, immunization status was recorded from the child's immunization certificate kept by the parents or by review of the child's immunization card kept at the township hospital immunization clinic; if neither were available, the village doctor's registry was reviewed. If none of these sources were available, the vaccination status was recorded as unvaccinated (if parent denied vaccination) or as unknown. Because there are no personal immunization records for adults, the immunization information for adults was based on memory (vaccinated, unvaccinated, unknown). Definitions of education and occupation are according to the Chinese social classification criteria, and only applicable to population aged 15–59 years. Occupation of public service worker is defined as a person who works in hotel, hospital, barber, transportation center, etc, and who has high frequency of contact with the public.

2.4. Specimen collection

Blood samples collected for each study participant included 4 ml for population above 2 years, and 2 ml for children age 2 years or less. Serum was separated in county laboratories, transported and stored at −20 °C at provincial laboratories, and submitted to National Hepatitis laboratory of Institute for Viral Disease Control and Prevention (IVDC) at China CDC in Beijing.

2.5. Laboratory testing

All serum specimens were tested in the National Hepatitis laboratory at IVDC, China CDC. A detailed laboratory testing protocol was established before testing, including retesting of specimens with inconsistent results. Testing reagents were selected based on evaluation of available ELISA kits from five companies in China compared to Abbott EIA reagents using a panel of 153 standard reference sera. ELISA reagents for HBsAg, anti-HBs, HBeAg and anti-HBe testing were purchased from Xiamen Xinchuang Production Company, utilizing a single lot of each test kit for all specimens[2]. Anti-HBc detection reagents were purchased from the Shanghai Kehua company. For specimens with inconsistent results, Abbott EIA reagents were used for reconfirmation testing, with neutralization method for final confirmation of HBsAg.

2.6. Statistical analysis

All data was double inputted into an EPI Data 3.02 software database, and checked for consistency with provinces. After verifying accuracy, the data was analyzed at China CDC, with SAS 9.13 software.

Appropriate sampling weights were constructed for national sample data set. The weight components computed for this design, which involves 160 county strata, 369 township and village clusters and 81,775 persons, consisted of factors reflecting township selection probability, village selection probability within the selected township, age-specific person selection probability within the selected village and post-stratification adjustments to adjust to the sex and age of the entire Chinese population. The weight for each person i can be expressed as follows:

$$w_{kji} = w_k \times w_{j|k} \times w_{i|k,j} \times w_{adj},$$

[1] Western provinces include: Chongqing, Gansu, Guangxi, Guizhou, Inner Mongolia, Ningxia, Qinghai, Shaanxi, Sichuan, Tibet, Yunnan, and Xinjiang. Central provinces include: Anhui, Hainan, Hebei, Heilongjiang, Henan, Hubei, Hunan, Jiangxi, Jilin, and Shanxi. Eastern provinces include: Beijing, Fujian, Guangdong, Jiangsu, Liaoning, Shandong, Shanghai, Tianjin, and Zhejiang. Urban counties are defined as that counties which are capital in prefecture; rural counties are those counties which are not capital of the prefecture.

[2] Batch number 2006071301 for HBsAg, 2006071401 for anti-HBs, 2006095312 for HBeAg, 2006071801 for anti-HBe; anti-HBc batch number 20060705.

where, w_k is the reciprocal of the inclusion probability of township k; $w_{j|k}$ is the reciprocal of the conditional inclusion probability of village j within the selected township k; $w_{i|k,j}$ is the reciprocal of the conditional inclusion probability of person i within the selected village j; w_{adj} is an adjustment factor for person i such that the sum of the weights equals the actual size of the Chinese population.

The Taylor series linearization methods were applied for variance estimation. The prevalence rates of HBV seromarkers include the point estimates and their estimated 95% CIs [15–20]. 95% confidence intervals (95% CI) were compared for HBV marker prevalence of each variable; 95% CI which did not overlap were considered as statistically significant. Multivariate analysis (forward multinomial logistic regression analysis) of weighted data was used to identify the predictors for high risk of prevalence of HBsAg among the study population.

2.7. Comparison with 1992 national serosurvey

The prevalence of HBsAg found in the 2006 national survey was compared with that of the 1992 national serosurvey, standardized to national census data in 2000. The target population of the 1992 serosurvey was persons aged 1 to 59 years residing in the same disease surveillance points (counties) in 31 provinces [1]. Based on the desired sample sizes, first, three villages were identified from each county by systematic random selection; secondly, families were randomly selected according the sample size for each village; thirdly, all family members in selected families were investigated and blood were taken for testing for hepatitis B markers.

The mathematical model developed by Goldstein [21] was used to estimate hepatitis B disease outcomes in China, and HBV carriers and deaths prevented by vaccination, using data from the 1992 and 2006 national serosurveys. Key data inputs included birth cohorts (from China national census data and projections), HBsAg and HBeAg prevalence among women of childbearing age, anti-HBc prevalence at 5 and 30 years of age, and proportions of children completing the three-dose vaccination series.

2.8. Quality control

National specialist groups were convened to guide statistical design, epidemiological investigation, laboratory testing, training and analysis. Two field pilots were conducted before the survey. All the villages were selected at the national level. Appropriate visiting time was considered to ensure high response rate. Trained County CDC staffs were responsible for administering the questionnaire, collecting the blood specimens, and separating, storing and transporting the serum specimens. 227 of 378 inconsistent laboratory results were confirmed by testing with Abbott reagents, and 151 were tested by neutralization method for final confirmation.

2.9. Ethical Issues

The survey was approved by the China CDC Ethics Committee, and all study components done according the national ethics regulations. Study participants were informed of the study purpose and the right to keep information confidential.

3. Results

Overall, the survey investigated 82,078 persons, from whom 82,008 blood samples were collected, and 81,963 with both investigation and blood sample available. Among houses visited, in 93.5% the occupants participated in the survey. Among these, 81,775 (99.6%) were eligible for data analysis; 178 persons were excluded due to being outside the study age range, and for 10 persons serum samples were insufficient.

Table 1
Characteristics of study population.

Category		Frequency	Proportion (%)
Age (years)	1–4	16376	20.0
	5–14	23753	29.1
	15–59	41646	50.9
Gender	Male	38895	47.6
	Female	42880	52.4
Education (15–59 years)	Illiterate	3993	9.6
	Primary school	10125	24.3
	Middle school	16615	39.9
	High school	7581	18.2
	Junior college	2248	5.4
	Undergraduate degree	1068	2.6
Occupation (15–59 years)	Student	2232	5.4
	Farmer	24144	58.0
	Worker	5352	12.9
	Cadre	2443	5.9
	Health care worker	640	1.5
	Public place	1336	3.2
	Others	5499	13.2
Ethnicity	Han	70815	86.6
	Mongolian	566	0.7
	Tibetan	1211	1.5
	Uigur	1165	1.4
	Zhuang	525	0.6
	Hui	2441	3.0
	Others	5052	6.2
Urban/Rural	Urban	40840	49.9
	Rural	40935	50.1
Region	Eastern	27457	33.6
	Central	27218	33.3
	Western	27100	33.1
Immunization Status	Yes	5744	13.8
5–59 years	No	28642	68.8
	Unknown	7260	17.4
5–14 years	Yes	17257	72.7
	No	3274	13.8
	Unknown	3222	13.6
1–4 years	Yes	15475	94.5
	No	481	2.9
	Unknown	420	2.6

3.1. Characteristics of study population

The characteristics of study population are shown in Table 1. Among the study population, 20.0% were age 1–4 years, 29.1% age 5–14 years and 50.9% age 15–59 years. The male to female ratio is 0.91:1, and 86.6% were Han ethnicity. The proportions of persons reporting any hepatitis B vaccination were 13.8% among persons age 15–59 years; 72.7% among children age 5–14 years, and 94.5% among children <5 years old (Table 1).

3.2. Results of HBV testing and distribution of HBV serological markers by age

Among the eligible study population, 4150 persons were positive for HBsAg (5.1%); 44,928 positive for anti-HBs (54.9%) and 20,163 positive for anti-HBc (24.7%). The weighted prevalences adjusted to represent the Chinese population age 1–59 years were HBsAg 7.2%; anti-HBs 50.1%, and anti-HBc 34.1%. The major differences between unweighted and weighted prevalences were due to age standardization.

Table 2
Age Distribution of HBV markers among population aged 1–59 years.

Age goup (year)	Sample tested	HBsAg		Anti-HBs		Anti-HBc	
		Prevalence* (%)	95% CI	Prevalence* (%)	95% CI	Prevalence* (%)	95% CI
1–	16376	1.0	0.8–1.2	71.2	69.8–72.7	4.1	3.5–4.7
5–	11909	1.4	1.2–1.7	55.5	52.4–58.5	5.5	4.7–6.3
10–	11844	3.2	2.6–3.8	57.5	55.4–59.5	10.7	9.7–11.7
15–	2942	5.4	4.4–6.4	50.3	44.4–56.2	25.0	22.3–27.7
20–	6778	10.5	8.2–12.7	45.6	42.9–48.4	38.9	36.6–41.3
30–	13164	8.6	7.5–9.6	46.4	44.1–48.7	41.8	39.3–44.3
40–	10477	8.5	7.4–9.6	46.0	43.5–48.5	45.1	42.7–47.5
50–59	8285	8.9	7.1–10.7	50.3	47.2–53.5	50.0	46.6–53.4
Total	81775	7.2	6.7–7.7	50.1	48.8–51.3	34.1	32.8–35.5

* Weighted prevalence – see text.

Table 3
Prevalence of HBsAg by gender, occupation, education, nationality, geographic, vaccine status.

		Investigated	Prevalence* %	95% CI
Gender	Male	38895	8.6	7.8–9.4
	Female	42880	5.7	4.9–6.6
Education (15–59)	Illiterate	3993	9.7	7.6–11.7
	Primary school	10125	8.8	7.9–9.7
	Middle school	16615	9.1	8.1–10.1
	High school	7581	8.3	7.2–9.3
	Junior college	2248	5.9	4.2–7.7
	Undergraduate	1068	3.1	1.4–4.9
Occupation (15–59)	Student	2232	4.0	3.0–5.0
	Farmer	24144	8.5	7.8–9.3
	Worker	5352	8.9	7.7–10.1
	Cadre	2443	6.5	2.2––10.8
	Health care worker	640	2.7	1.2–4.2
	Public worker	1336	22.9	17.4–28.4
	Others	5499	10.0	8.1–12.0
Ethnicity	Han	70815	7.2	6.9–7.8
	Mongolian	566	2.1	0.8–3.3
	Tibetan	1211	5.0	4.1–6.0
	Uigur	1165	8.2	6.0–10.5
	Zhuang	525	13.4	7.4–19.4
	Hui	2441	3.1	1.2–5.1
	Others	5052	7.0	5.6–8.4
Region	Eastern	27457	6.5	5.7–7.3
	Middle	27218	6.7	5.6–7.8
	Western	27100	8.3	7.6–8.9
Urban/Rural	Urban	40840	6.8	5.8–7.8
	Rural	40935	7.3	6.7–7.9
Vaccinated	Yes	38476	2.1	1.8–2.4
	No	32397	9.4	8.4–10.3
	Unknown	10902	7.8	5.0–10.6

* Weighted prevalence – see text.

Prevalence of HBsAg varied markedly by age group, increasing steadily from 0.96% among children age 1–4 years, to 8–12% among persons age 20 years and older (Table 2). Differences in prevalence were highly significant for each 5 years age group through age 20 years, after which they did not vary significantly. The trend of prevalence of anti-HBc was similar to that of HBsAg, but continued to increase among adults to reach 50.0% among those age 50–59 years. The prevalence of anti-HBs was inverse to that of HBsAg, decreasing with increasing age from 72% among children age <5 years, to 45–50% among 15–59 year olds (Table 2).

3.3. Prevalence of HBsAg by other demographic characteristics

HBsAg prevalence was significantly higher for males (8.6%) than females (5.7%, $p < 0.01$) (Table 3). Persons of the Zhuang minority had the highest weighted HBsAg prevalence (13.4%), followed by Uigur (8.2%) and Han (7.2%) ethnic groups. HBsAg prevalence was significantly lower among Mongolian (2.1%), Hui (3.1%) and Tibetan (5.0%) ethnic groups. Among persons >15 years, the HBsAg prevalence decreased with increasing education level. The highest prevalence was in the illiterate population (9.7%), and was signifi-

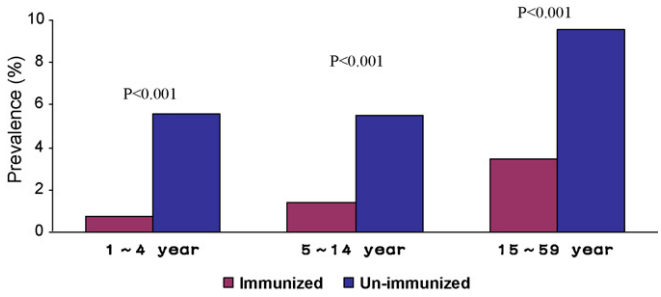

Fig. 1. Relationship between immunization and prevalence of HBsAg, by age.

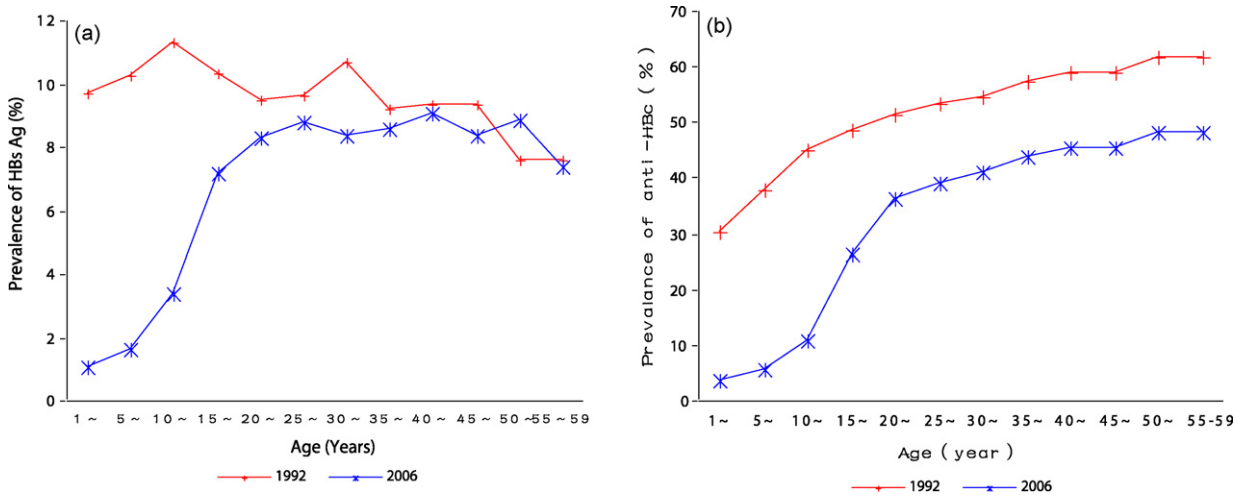

Fig. 2. (a) Comparison of Prevalence of HBsAg in 1992 and 2006. (b) Comparison of Prevalence of anti-HBc in 1992 and 2006.

cantly lower in persons with undergraduate degrees (3.1%). Among occupation groups, HBsAg prevalence was lowest in health care workers and students, and highest in public service workers (22.9%) (Table 3).

The HBsAg prevalence among persons living in western regions (8.3%) was higher than the eastern region (6.5%, $p < 0.05$). The prevalence of anti-HBs was slightly higher in urban (52.6%) than in rural areas (49.3%. $p < 0.05$), and in the western region (53.0%) than eastern region (46.8%. $p < 0.05$).

3.4. Relationship between hepatitis B immunization and prevalence of HBsAg

The prevalence of HBsAg among vaccinated persons was only 2.1%, compared to 9.4% among unvaccinated persons ($p < 0.001$). Similarly, prevalence of anti-HBc was lower among vaccinated (8.5%) than unvaccinated persons (41.1%), while the prevalence of anti-HBs was higher among vaccinated persons (68.2% vs. 42.6%, respectively). Among all age groups, the immunized population had a much lower prevalence of HBsAg than un-immunized population; this difference was proportionally greatest in children <5 years (Fig. 1).

3.5. Comparison with results of the 1992 national hepatitis serosurvey

Compared with the national serosurvey conducted in 1992, the prevalence of HBsAg among children age 1–14 years born after hepatitis B vaccine was recommended for routine childhood immunization was much lower than same age groups in 1992 (Fig. 2a). In particular, among children <5 years, prevalence was only 1.0%, 90% lower than in 1992 (9.7%). For person age 15–19 years, HBsAg prevalence was also moderately lower ($p < 0.05$), but for population aged 20–59 years, the prevalence of HBsAg was high in both surveys. In the 2006 survey, the prevalence of anti-HBc was consistently lower than in the 1992 survey, especially in younger age groups (Fig. 2b).

Among children age 1–14 years, assuming that the force of infection remained the same as in 1992, and using the mathematical model to estimate hepatitis B disease outcomes, an estimated 16–20 million HBV carriers and 2.8–3.5 million future HBV related deaths have been prevented [21].

3.6. HBeAg status among HBsAg positive persons

Among HBsAg positive children <15 years, the proportion positive for HBeAg was high (>68%). HBeAg decreased with age to 15% among persons age 40–59 years. The prevalence of HBeAg among HBsAg positive childbearing women was 30.0%, similar to that measured in 1992 (Table 4).

3.7. Multivariable analysis of HBsAg status for adults and children

To identify factors that affected the prevalence of HBsAg for population aged 15–59 years, a multivariable logistic regression was used, the dependent variable being the weighted prevalence of HBsAg; independent variables included gender, location of community (urban vs. rural), region, ethnicity, occupation, education, and immunization history. Results show that male sex (O.R. = 1.7), living in the western region (O.R. 1.2), and unvaccinated persons or with vaccination status unknown (O.R. = 2.5, 2.3) had higher likelihood of HBsAg positivity than females, persons living in Eastern region and vaccinated populations, respectively ($p < 0.01$) (Table 5a). Among the different ethnic groups, Inner Mongolian, Tibetan and Hui had lower HBsAg prevalence than Han ($p < 0.05$), while Zhuang had borderline significantly higher prevalence. Public workers and others were found to have higher HBsAg prevalence than farm-

Table 4
Proportion of HBeAg among HBsAg positive person by gender.

Age goups (yr)	Male			Female		
	HBsAg psitive	Prevalence* (%)	95% CI	HBsAg psitive	Prevalence* (%)	95% CI
1–4	106	76.4	65.5–87.2	71	74.1	58.9–89.3
5–14	341	69.4	61.4–77.4	249	67.6	56.4–78.7
15–39	962	38.4	29.6–47.2	874	30.0	25.9–34.1
40–59	814	15.7	11.8–19.6	733	15.0	11.4–18.5

* Weighted prevalence – see text.

Table 5a
Multinomial logistic re gression analysis of HBsAg prevalenceamong population aged 15–9 years.

Variable	Category	Frequency	O.R.	95.0% C.I. for O.R.		*p* value
				Lower	Upper	
Gender	Female*	23637	1			
	Male	17883	1.7	1.5	2.02	<0.01
Urban/Rural	Urban*	20785	1			
	Rural	20735	1.0	0.8	1.2	0.96
Region	Eastern*	13887	1			
	Central	13833	1.1	0.8	1.31	0.70
	Western	13800	1.4	1.2	1.64	<0.01
Ethnicity	Han*	36041	1			
	Mongolian	230	0.3	0.2	0.6	<0.01
	Tibetan	1296	0.5	0.3	0.7	<0.01
	Uigur	608	0.7	0.3	1.6	0.38
	Zhuang	281	1.5	0.9	2.5	0.08
	Hui	580	0.4	0.2	0.7	<0.01
	Others	2480	0.9	0.7	1.1	0.32
Occupation	Student	2117	0.6	0.5	0.9	<0.01
	Farmer*	24136	1			
	Worker	5352	1.1	0.9	1.3	0.36
	Cadre	2442	1.2	0.4	3.7	0.71
	Health worker	639	0.5	0.2	1.2	0.12
	Public worker	1335	3.8	2.9	4.8	<0.001
	Others	5499	1.4	1.1	1.8	<0.01
Education	Illiterate	3972	2.8	0.9	8.7	0.07
	Primary school	10097	2.4	0.8	6.3	0.11
	Middle school	16574	2.4	0.9	5.6	0.08
Immunization History	High school	7564	2.2	0.9	4.6	0.76
	Junior college	2246	1.4	0.8	2.5	0.21
	undergraduate*	1067	1			
	Yes*	5730	1			
	No	28557	2.5	1.9	3.2	<0.01
	Unknown	7233	2.3	1.5	3.6	<0.01

* Reference category.

Table 5b
Multinomial logistic regression analysis of HBsAg prevalence among population aged 1 to 14 years.

Variable	Category	Frequency	O.R.	95% C.I.for O.R.		P value
				Lower	Upper	
Gender	Female*	19169	1			
	Male	20960	1.3	0.9	1.9	0.20
Urban/Rural	Urban*	19999	1			
	Rural	20130	1.1	0.8	1.4	0.65
Region	Eastern*	13530	1			
	Central	13336	1.0	0.7	1.3	0.23
	Western	13263	0.6	0.4	0.8	<0.01
Age group (yrs)	1–4*	16376	1			
	5-9	11909	1.1	0.9	1.4	0.41
	10-14	11844	1.9	1.3	2.7	<0.01
Ethnicity	Han*	34668	1			
	Inn Mongolia	336	0.2	0.0	1.2	0.08
	Tibetan	1138	1.0	0.6	1.7	0.98
	Uigur	599	1.9	0.5	7.4	0.35
	Zhuang	244	3.5	1.8	6.9	<0.01
	Hui	583	0.9	0.3	2.5	0.89
	Others	2561	1.5	0.9	2.4	0.08
Immunization History	Yes*	32732	1			
	No	3755	2.5	1.5	4.1	<0.01
	Unknown	3642	2.0	1.4	3.0	<0.01
Birth Place	County Hospital	19156	1			
	Township hospital	11266	2.1	1.5	3.5	<0.01
	Home	8631	4.0	2.7	6.0	<0.01
	Others	1076	3.5	2.0	6.3	<0.01

* Reference category.

ers, while students were found to have lower HBsAg prevalence ($p < 0.01$).

Among children aged 1–14 years, multivariate analysis showed the strongest predictors of HBsAg status were vaccination status (unvaccinated or vaccination status unknown, O.R. = 2.5, 2.0), and place of birth (Table 5b). Children born in hospital had the lowest prevalence, while those born in smaller township hospitals or at home had successively higher risk. Children aged 10–14 years have higher prevalence than children aged 1 to 4 years (O.R. = 1.9) ($p < 0.01$). Among the different ethnic groups, Zhuang (O.R. = 3.5, $p < 0.01$) have higher prevalence than Han ethnicity, and other ethnic groups (mainly from southern China) had borderline significant higher risk (O.R. = 1.5, $p = 0.08$).

4. Discussion

Hepatitis B is among the most important infectious diseases in China. Based on the national serosurvey in 1992, Chinese population's prevalence of HBsAg was about 10% for all age groups, including young children. The national serosurvey in 2006 shows that for population aged 1–59 years, the prevalence of HBsAg has decreased from 9.8% to 7.2%, and for children under 5 years is now only 1.0%. The findings from this survey indicate that the HBsAg prevalence in the whole population is now close to the national goal (less than 7% by 2010), and that the prevalence for children under 5 has already reached both the national goal of less than 1% by 2010, and the WHO Western Pacific Regional goal of less than 2% by 2012.

The most dramatic finding is the decrease in HBV infection risk and HBsAg prevalence among children born after hepatitis B vaccine was recommended for infant routine immunization in 1992, and especially for children born after hepatitis B vaccine was fully integrated into infant routine immunization in 2002. The HBsAg prevalence among children aged 1–4 years has decreased by 90%; in addition, HBsAg prevalence among children aged 5–9 and 10–14 years have decreased by 86% and 72%, respectively. In these cohorts, an estimated 16–20 million HBV carriers and 2.8–3.5 million future HBV related deaths have been prevented [21].

Conversely, the prevalence of anti-HBs for population aged 1–59 years has increased from 27.4% in 1992 before hepatitis B vaccine was recommended, to 50.1% in 2006, with a four fold increase among children 1–4 years (from 15.8% to 72.3%).

These data are consistent with many studies globally and in China which show that after introduction of hepatitis B vaccination programs, the prevalence of HBsAg has declined significantly [22–29]. The decline of HBsAg among children in China can be attributed primarily to impact of hepatitis B vaccination [30], and will not only bring the decreased prevalence of HBsAg, but will decrease the future incidence of cirrhosis and hepatocellular carcinoma [31]. Other factors such as the single child policy which reduces horizontal (child to child) transmission in the home, and possibly safer injection practices that reduce nosocomial transmission may have also contributed to this decline, but their precise impact cannot be evaluated in this survey.

The multivariate analysis provided useful insights into risk factors for HBsAg positivity among both the adult and child population, in addition to showing the clear effect of hepatitis B immunization. Among adults, risk factors included male sex, living in Western provinces, belonging to specific ethnic groups (Zhuang), and certain work professions. We found a relatively low HBsAg prevalence among health care workers, but also that public service workers had a high prevalence of HBsAg. Health care workers are in high socio-economic status, have better access to public health services, and some are already protected by vaccination, but high prevalence of HBsAg for social workers in public places is of concern, particularly for risk of long term disease and of discrimination. On detailed review, the high prevalence for public service workers was found in a single cluster of workers with high prevalence of HBsAg in one large community; outside of this community prevalence among public workers was similar to that of other workers.

Among children, the main risk factors for HBsAg positivity, in addition to lack of vaccination, included birthplace – a predictor of health care and immunization access; age, region and ethnicity. Infants born in hospitals are much more likely to receive a birth dose of HepB than those born at home; in addition, in larger hospitals mothers may be screened for HBsAg, and infants of those found positive may also be given HBIG (1.9% of infants born in larger hospitals between 2002 and 2005 were given HBIG). The reason for low risk in the western region may be greater recent improvement in vaccination status. While certain northern China groups (Mongolian, Hui) consistently have lower risk, risk is consistently elevated in the Zhuang and others mainly in southern China [1]. For these groups, particularly the Zhuang, the risk of developing chronic HBV infection remains high among children, in part due to lower accessibility to hepatitis B vaccine before incorporation in routine EPI and removal of financial barriers to infant immunization.

Despite the substantial progress in preventing hepatitis B infection in children, this study confirms the ongoing high prevalence of active HBV infection among adults, and its consequent high risks of HBV transmission and chronic sequelae. The continued high prevalence of HBsAg and HBeAg positive women of child bearing age – who have a 90% chance of infecting their newborns unless the newborns are treated with vaccine or vaccine plus HBIG soon after birth – reaffirms the need to further strengthen infant immunization programs, including assuring timely birth doses are given to all children in the poorest areas and to underserved ethnic groups. In addition, expanded vaccination is needed to prevent HBV infection in older children and adults, among whom 40–50% remain susceptible to HBV infection. Catch-up vaccination is now planned for children under 15 years, and immunization is recommended for adults at high risk. Finally, programs to prevent the long-term consequences of HBV infection, through screening and antiviral drug treatment, need to be developed and expanded to reach those at risk of developing cirrhosis and liver cancer. The China government has greatly expanded funding to evaluate strategies for prevention of hepatitis B, and for identifying and treating those persons at highest risk for developing cirrhosis and liver cancer [10].

One study limitation is that study participation was limited to persons resident in the villages for 6 months or more, and excluded the short-term floating population, who are estimated to comprise 3% of the total population in China (higher in some urban areas) [8], and unregistered children born outside of family planning. As the majority of these persons come from poorer, rural areas, they may have a relatively high prevalence of HBsAg and lower likelihood of hepatitis B vaccination, therefore, underestimating overall HBsAg prevalence. In addition, 6.5% of the interviewees were not present during the visits.

In conclusion, China has successfully integrated hepatitis B vaccine into routine immunization programs and has achieved very significant impact on decreasing the HBsAg carrier rate among children born after 1992. The national goal of reducing HBsAg prevalence to less than 1% by 2010 among children less than 5 years old will certainly be reached if current immunization programs can be sustained. To achieve the national goal for whole population in decreasing the prevalence of HBsAg to less than 7%, free immunization of infants should be maintained and timely birth dose should be targeted to reach all newborn infants in the coming years. In addition, expanded vaccination is needed to prevent HBV infection in older children and adults.

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Conflict of interest statement: All authors agree with results presented in this paper and none of the authors has conflicts of interest.

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References

[1] Xia GL, Liu CB, Cao HL, Bi SL, Zhan MY, Su CA, et al. Prevalence of hepatitis B and C virus infections in the general Chinese population. Results from a nationwide cross-sectional seroepidemiologic study of hepatitis A, B, C, D and E virus infections in China, 1992. Int Hepatol Commun 1996;5:62–73.
[2] Dai ZC, Qi GM. Seroepidemiological Survey in Chinese population (part one), 1992–1995. Beijing. Sci Tech Exp 1996:39–59.
[3] Zhuang H. Epidemiology of hepatitis. Chin J Vaccines Immun 2004;10(3):180–1.
[4] He J, Gu DF, Wu XG, Kristi R, Duan XF, Yao CH, et al. Major causes of death among men and women in China. N Engl J Med 2005;353:1124–34.
[5] Perz JF, Armstrong GL, Farrington LA, Hutin YJF, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006;45:529–38.
[6] Evans AA, Chen G, Ross EA, Shen FM, Lin WY, Thomas LW, et al. Eight-year follow-up of the 90,000-person Haimen City cohort: I. Hepatocellular carcinoma mortality, risk factors, and gender differences. Cancer Epidemiol, Biomarkers Prev 2002;(11):369–76.
[7] Zhu X, Zhang X, Wang L. National EPI vaccination and hepatitis B vaccine coverage rate and the related factors: Results from the 1999 nationwide survey. Chin J Vacc Immun 2000;6(4):193–7.
[8] Ministry of Health, National EPI review in 2004. Beijing, Chinese people's health express; 2005. p. 24.
[9] Cui FQ, Wang XJ, Cao L, Liang XF, Lu Y, Hu YS, et al. Progress in hepatitis B prevention through universal infant immunization – China, 1997-2006. MMWR 2007;56(18):441–5.
[10] Ministry of Health, China. 2006–2010 National guidelines for hepatitis B prevention and treatment; January 28, 2006.
[11] CDC. Global progress toward universal childhood hepatitis B vaccination, 2003. MMWR 2003;52:868–70.
[12] Yang GH, Zhou MG, Huang ZJ, et al. Study on the trend and disease burden of Injury deaths in Chinese population, 1991–2000. Chin J Epidemiol 2004;25(3):192–8.
[13] Yang GH. Disease surveillance system selection in second stage and its representative. Chin J Epidemiol 1992;1(13):197–201.
[14] Chinese Center for Disease Control and Prevention. Guideline for chronic disease and high risk factors surveillance in China; August 2007.
[15] Sun Z, Xu Y. Medical statistics (second edition), Beijing. Chin People's Health Exp 2006:579–80.
[16] Korn E, Graubard B. Examples of differing weighted and unweighted estimates from a sample survey. Am Statistician 1995;49(August (3)):291.
[17] Hyattsville, 2003 National Health Interview Survey (NHIS) Public Use Data Release, Division of Health Interview Statistics, National Center for Health Statistics, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; December, 2004. p. 8–9.
[18] Chantala K, Blanchette D, Suchindran CM. Software to compute sampling weights for multilevel analysis. Carolina Population Center, UNC at Chapel Hill, Last Update; January 17, 2006.
[19] Lohr SL. Sampling: Design and analysis, Beijing. China Statistical Exp 2002:245.
[20] Euler GL, Wooten KG, Baughman AL, Williams WW. Hepatitis B surface antigen prevalence among pregnant women in urban areas: Implications for testing, reporting, and preventing perinatal transmission. Pediatrics 2003;111:1192–7.
[21] Goldstein ST, Zhou FJ, Hadler S, Bell BB, Mast EE, Margolis HS, et al. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. Int J Epidemiol 2005;34:1329–39.
[22] Davaalkham D, Ojima T, Uehara R, Watanabe M, Oki I, Wiersma S, et al. Impact of the universal hepatitis B immunization program in Mongolia: achievements and challenges. J Epidemiol 2008;17(3):69–75.
[23] Ni YH, Huang LM, Chang MH, Yen CJ, Lu CY, Kao SL, et al. Two decades of universal hepatitis B vaccination in Taiwan: impact and implication for future strategies. Gastroenterology 2007;132(4):1287–93.
[24] Da Villa G, Romano L, Sepe A, Iorio R, Paribello N, Zappa A, et al. Impact of hepatitis B vaccination in a highly endemic area of south Italy and long-term duration of anti-HBs antibody in two cohorts of vaccinated individuals. Vaccine 2007;25(16):3133–6.
[25] Madani TA. Trend in incidence of hepatitis B virus infection during a decade of universal childhood hepatitis B vaccination in Saudi Arabia. Trans R Soc Trop Med Hyg 2007;101(3):278–83.
[26] Ng KP, Saw TL, Baki A. Impact of the expanded program of immunization against Hepatitis B infection in school children in Malaysia. Med Microbiol Immunol 2005;194(3):163–8.
[27] Gong J, Li RC, Yang JY, Li YP, Chen XR, Xu ZY, et al. Long-term efficacy of infant hepatitis B immunization program. Chin J Hepatol 2003;11:203–5.
[28] Gong XH, Wang FZ, Li H, Liu LR, Li YH, Wang BL, et al. Observation on effects of hepatitis B vaccine immunization for 12 years in children in Beijing. Zhonghua Yu Fang Yi Xue Za Zhi 2005;39:265–8.
[29] Wu WS, Sun CM, Jiang MB. Long-term effect of plasma derived vaccine in prevention of hepatitis B (Eigthteen years followup study). Chin J Vacc Immunization 2005;11:204–7.
[30] Liang XF, Bi Sl, Yang WZ, Wang LD, Cui G, Cui FQ, et al. Evaluation of the impact of Hepatitis B vaccination among Children born between 1992 and 2005 in China. J infect Dis 2009;200(1):39–47.
[31] Chang MH, Chen JC, Lei MS, Hsu HM, Wu TC, Kong MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. N Engl J Med 1997;336:1855–9.