Assessment of seroepidemic conditions of hepatitis B virus among people under 29 years of age and evaluation of the hepatitis B vaccine after 22 years in Jiangsu Province, China

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Abstract

Background This study aims to investigate the epidemiologic characteristics and variational trends following a hepatitis B vaccine (HepB) inoculation programme carried out in children over the last 22 years in Jiangsu province. It also aims to evaluate the effect of hepatitis B vaccine immunisation and to analyse the influential of HBsAg positive carriers. Finally, the study also provides reliable data and a baseline for adjusting future prevention and intervention strategies in Jiangsu province.

Methods The incidence rates of hepatitis B virus (HBV) in Jiangsu province from 2004 to 2014 were obtained from the National Notifiable Disease Reporting System (NNDRS). A stratified cluster random sampling method was used to select 3,002 subjects aged 1-29 years across 13 hepatitis B virus monitoring points throughout the province, which had been classified as either urban or rural. HBV was assessed from venous blood samples using Abbott microparticle enzyme immunoassay (MEIA) kits (Abbott Laboratories, Chicago, Illinois).

Results HBV incidence in the 1-29 age group showed a significant downward trend since 2004 (P<0.001). Serological assessments showed that the prevalence values of the hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) in the 1-29 age group were 1.20% and 5.33%, respectively. And 66.89% tested positive for the hepatitis B surface antibody (anti-HBs). The HBsAg positive rate among participants was significantly lower in subjects who had been vaccinated than in those who had not (0.46% vs 14.93%, p<0.0001). Among persons who had received the full three-dose vaccine regimen, 90.93% received the first dose of the HBV vaccine within 24 hours of the baby’s birth. In this same group, the prevalence rates of HBsAg and anti-HBc were 0.05% and 0.95%, respectively, and the HBV infection rate decreased significantly after 2006.

Conclusions The overall rate of Hepatitis B vaccinations and vaccinations administered
within 24 hours of the baby’s birth have continuously improved since the HepB vaccine was integrated into the immunisation programme in Jiangsu province. Hepatitis B prevention and control works in the target population has achieved remarkable results.

**Background**

Hepatitis B is an infectious disease that is caused by the hepatitis B virus in humans [1, 2]. Among the 6 billion people in the world, approximately 2 billion people have been infected with HBV, and more than 350 to 400 million have chronic HBV infections, accounting for approximately 6 percent of the global population. According to a global report from the World Health Organization (WHO), HBV remains a serious public health problem worldwide, resulting in approximately 1 million deaths from liver failure, liver cirrhosis and primary hepatocellular carcinoma each year [3–5].

The HepB vaccine (HepB) is the most economical and effective way to prevent HBV infection. Because HBV seriously harms people’s lives and health, the Chinese government integrated HepB into the routine immunisation management programme in 1992. Then, in 2002, HepB was integrated into the national expanded immunisation programme.

However, parents were still required to pay for the cost of the vaccination. As of 2005, the Chinese government has provided free vaccinations to all newborns, and the hepatitis B vaccine must be administered within 24 hours of the baby’s birth [6].

After 20 years of unremitting efforts, the prevalence of HBsAg in China has dropped drastically, especially among children under 5 years of age. According to the 1992 and 2014 national hepatitis B serological surveys, the prevalence of HBsAg in persons under 5 years of age decreased from 9.67% to 0.32% between survey years [6–8]. China has reached the goal for hepatitis B control proposed by the World Health Organization in the Western Pacific Region in September 2005, which states the prevalence of HBsAg among children under five in the western Pacific Region should be 1% or less.
2 Methods

2.1 Study design and participants

We conducted a cross-sectional serological study in Jiangsu Province, China. 13 monitoring sites (6 national-level and 8 provincial-level monitoring sites) [6] were selected from throughout the province according to their geographical locations. A stratified, two-stage cluster random sampling method was adopted. In the first stage, the village committee was selected and each county (district) where the monitoring points were to be selected was assigned to a layer (group). The village committees in each layer were the primary sampling units. A capacity ratio probability sampling method was adopted for each layer, and two village committees were randomly selected. In the second stage, the survey objects were selected, according to the sample size assigned by each village committee. A simple random sampling method was used to randomly select the indicated number of resident populations of 1 to 4, 5 to 14 and 15 to 29 year olds for the study. A return visit was made to initial non-responders (any person who did not respond to the first survey). Participants who did not respond after three consecutive visits were considered lost to follow-up, and the relevant information (reason for non-response, name, age, gender, etc.) was recorded in detail. The epidemiological investigation was conducted in residents of Jiangsu province (defined as residing in the province for >6 months). Blood samples were collected for HBV serological testing[9-11]. The target sample size was 3002 participants, based on the expected HBsAg prevalence rates among the different age groups in the study (0.8% for 1-4 years, 1.4% for 5-14 years, and 4.8% for 15-29 years. Specifically, the final sample size included 1,232 1- to 4-year-olds, 944 5- to 14-year-olds, and 826 15- to 29-year-olds.

2.2 Investigation method
The centralized or house-to-house interviews were conducted by trained investigators. Investigators used a standardised questionnaire for the survey. Professional nurses and medical laboratory science officers collected and prepared biological samples. The survey mainly included basic participant characteristics, patient history of hepatitis, their vaccination history, and the detection of maternal HBsAg.

2.3 Specimen collection
After the face-to-face interview, 5 ml of venous blood was collected from participants 5 years or older, and 3 ml of venous blood was collected from children under 5. A bar code was pasted on each participant’s survey form and blood sample tube. All surveys and whole blood samples were then returned to the county-level CDC laboratory for serum separation. County-level CDC staff transported the interviews forms, the separated serum and the blood clot samples to the provincial CDC for testing.

2.4 Laboratory testing
All serum samples were tested for three HBV markers—HBsAg, anti-HBs and anti-HBc. These markers were detected using Abbott microparticle enzyme immunoassay (MEIA) kits (Abbott Laboratories, Chicago, Illinois). The sample was defined as positive if the S/N value of HBsAg was >2.0, the CO/S value of anti-HBc was <1.0, or the value of anti-HBs was >10 mIU/ml.

2.5 Statistical analysis
EpiData 3.1 was used to establish a case interview database. All data were entered into the database in duplicate. SPSS 22.0 (IBM, Armonk, New York, USA) was used for all statistical analyses. Descriptive studies were used for demographic characteristics and morbidity. Chi-square tests were used to compare rates. Statistical significance was defined as P<0.05.
3 Results

3.1 Incidence rates of HBV in Jiangsu province between 2004 and 2014

Figure 1 shows that the incidence of HBV in the 1-29 age group demonstrated a decreasing trend after 2004 (P<0.001). The incidence rate was 197.65/100,000 in 2004 and 56.44/100,000 in 2014, with average incidence rate of 99.10/100,000. The incidence of hepatitis B decreased by approximately 71.44% in Jiangsu province between 2004 and 2014. In the 0- to 4-year-old age group, the reported incidence was 17.00/100,000 in 2004 and 5.01/100,000 in 2014, a decrease of 70.53%. In the 5- to 14-year-old and the 15- to 29-year-old groups, the reported incidence of hepatitis B decreased 5.29 fold and 3.38 fold, respectively. The incidence of hepatitis B was significantly higher in the 15- to 29-year-old age group than in either the 1- to 4-year-old age group or the 5- to 14-year-old age group.

3.2 Demographic characteristics

A total of 3,002 subjects aged 1 to 29 years were investigated, among which there were 1,583 males (52.73%) and 99.00% were of the Han ethnicity. The group under 5 years old contained 1,232 subjects, the 5- to 15-year-old group contained 944 subjects, and the group between 15 and 29 years of age contained 826 subjects. There was a disproportionate number of participants under 5 years of age, accounting for 41.04% of the total number. Additionally, 269 participants (37.31%) had middle school education level or lower (Table 1).

3.3 Seroprevalence of HBV markers by sociodemographic characteristics

HBsAg indicates past or present infection with HBV. The overall prevalence of HBsAg in the 1 to 29 age group was 1.20% (95%CI:0.84–1.66). The prevalence of HBsAg was 0.41% in subjects under 5 years of age. HBsAg prevalence increased slowly to the age of 15 and
was the highest in the 25- to 29-year-old age group (5.83%). The positive rate of anti-HBc was maintained at a low level in the group under 15 years of age, with the highest rate (18.20%) being found in the 20-year-old group. The highest rate of anti-HBs was found in the 1-year-old group (95.00%), and this rate decreased with the age. The lowest rate (50.00%) was found in the 8-year-old group (Fig 2). The prevalence of HBV markers differed significantly by age group (p<0.0001). The anti-HBs rate was significantly higher for participants who lived in rural areas compared with those who lived in urban areas (p<0.0001, table 1). The prevalence of HBsAg was highest in participants with a junior high school education level (9.69%) and was lower in those with a university education (0.45%, p<0.0001). Anti-HBs seroprevalence was significantly higher in the northern regions than the southern and central regions (71.22% vs 64.39%/61.35%, p<0.0001). There was no significant difference in the seroprevalence of all HBV markers based on sex (Table 1).

3.4 Seroprevalence of HBV markers and immunization history

Table 1 shows that the HBsAg positive rate was significantly lower among participants who were vaccinated than among those who not (0.46%, 95% CI: 0.24–0.81 vs 14.93%, 95% CI: 7.40–25.74, respectively, p<0.0001). Similarly, the prevalence of anti-HBc was lower among vaccinated participants (3.16%) than among unvaccinated participants (38.81%). The prevalence of anti-HBs in vaccinated people was 68.95% (95% CI: 67.13–70.73), which was significantly different from the prevalence in unvaccinated participants (p<0.0001). The proportion of the first dose of HBV vaccine that was administered in time was 90.93% among those participants who received the full three-dose immunisation series. The prevalence rates of HBsAg and anti-HBc were 0.05% and 0.95%, respectively. The prevalences of HBsAg and anti-HBc were much higher in those subjects who received the first dose more than 24 h after birth compared with those who were vaccinated within 24
3.5 Comparison with the results of the survey, 2006 vs 2014

Interviews were conducted only in persons between 1 and 29 years of age, though the 2006 survey included people between the ages of 1 and 59. The prevalence rates of HBsAg in the study sample were 1.20% and 2.52% in 2014 and 2006, respectively. While 13.47% of the participants in the 2014 survey were still unvaccinated or had an unknown vaccination status, the HBsAg positive rate still showed a significant decline in the 10- to 29-year-old age group compared to the 2006 survey. The two surveys both showed that 75% of subjects had anti-HBs positive antibodies within one year of receiving the HepB after birth. The rate decreased slowly thereafter. The positive rate of anti-HBs was higher in 2014 than it was in 2006 and increased in the 1- to 4-year-old age group between 2006 and 2014 (72.60% vs 76.38%, respectively) (Fig 3).

4 Discussion

Three national HBV serological epidemiology surveys were conducted in China in 1992, 2006 and 2014. Over this time period, the Chinese government took great measures to promote HBV vaccination among the population and effectively improved prevention and treatment of hepatitis B. These steps resulted in a significant decline in the positive rate of HBsAg in the population, especially for children under five, whose positive rate decreased from 9.67% to 0.32%. As hepatitis B had seriously endangered the lives and health of its people, the Chinese government integrated the hepatitis B vaccine into its routine immunisation management programme in 1992, and the hepatitis B vaccine was included in the national expanded immunisation programme in 2002. With these steps, the prevention and control of HBV entered a new era. With the widespread usage of HepB, the epidemiological characteristics of HBV in China changed greatly. The incidences of acute
and chronic HBV dropped significantly with the implementation of the hepatitis B vaccine immunisation programmes in Jiangsu province. However, our province has a large population and has seen increases in life expectancy; therefore, many people who had already been infected with HBV prior to the government efforts are still living, influencing prevalence rates in the short term. It will take several generations to contain hepatitis B at a low epidemic level. Therefore, we cannot slacken our efforts in the slightest with regards to the prevention and control of HBV.

The survey found that the prevalence rate of HBsAg was 0.41% in people aged 1 to 4 years, while the rate was 3.39% in the >15 years age group. Similarly, the positive rate of anti-HBc increased with age, indicating that new infections were still emerging. One reason is that the coverage rate of HepB is relatively low in the older age group, indicating that horizontal transmission of HBV plays an important role in adults. Another reason is that many people in the >15 years age group did not have vaccination certificates when they participated in the survey, and many did not know their immunisation history. Anti-HBs is a type of protective antibody that effectively protect the human body from infection. Anti-HBs can be obtained via inoculation with HepB or through natural infection with HBV. The survey showed that the prevalence rates of anti-HBs in Jiangsu province for people ages 1 to 4, 5 to 15, and 15 to 29 years were 76.38% (95% CI: 73.91–78.73%), 61.97% (95% CI: 58.79–65.08%), and 58.35% (95% CI: 54.91–61.74%), respectively. The proportion of patients who were infected with HBV differed by age.

Children infected within 1 year of birth had an 80–90% chance of developing a chronic infection. Children infected by 6 years of age had a 30–50% chance, while less than 5% of adolescents and adults developed a chronic infection. Therefore, the high level of anti-HBs in children under 6 years old plays an important role in controlling HBV. In this study, the lowest anti-HBs levels were found in the 15- to 29-year-old group, and the attenuation of
antibodies over time was relatively obvious. Therefore, revaccination of such populations is recommended.

An interesting finding was that there was no significant difference in the HBsAg positive rates between urban and rural areas. Other studies in China [6, 9, 12-14], have suggested that rural areas may have a higher positive rate, mainly due to the low coverage of the hepatitis B vaccine and differences in sanitary conditions. However, in recent years, more efforts have been made to strengthen basic immunisation in rural areas. The percentage of people receiving the full three-dose immunisation series and receiving the first dose according to the recommended timeline has been greatly improved. These improvements are conducive to the reduction of perinatal transmission[15-19]. Table 1 also shows that the higher rate of receiving the first dose according to the recommended time frame is closely related to lower positive rates of HBsAg and Anti-HBc. Previous studies have found that the infection rate of HBV in males is higher than that in female [14, 20-22], however, this study found no significant correlation between the positive rate of HBsAg and gender (male: 1.33% vs female: 1.06%, P > 0.05). This finding suggests that our long-term HBV vaccine strategy has changed the gender distribution of HBV. Our data also suggest that the positive rates of HBsAg and Anti-HBc are strongly related to educational level. Adults who had completed higher education were far less likely to be positive than those with a lower education level. This finding agrees with the results of many previous studies [6, 23, 24]. It is possible that people with higher education levels more efficiently utilise health services, such as health education, hospital resources and others.

The prevalence rates of HBsAg, Anti-HBc and Anti-HBs were significantly different between the subjects with and without an HBV immunisation history, which reflects the critical role of HepB in controlling HBV. As more research is published, most results have suggested that the protective effect of a routine full-course immunisation series can last 10-18 years.
The present study found that the level of anti-HBs increased significantly in 2014 compared with 2006, Figure 3. Other studies have suggested that a HepB booster immunisation should be given 18 years after the completion of the first vaccination series or earlier[29]. However, due to different types and immunisation procedures for HepB, as well as differences in the effectiveness and immunogenicity of HepB in different ethnic groups, the above result should be studied in China to determine whether it is appropriate in the Chinese population. Additionally, we found that 12 HBsAg-positive participants failed to respond to HepB. There are many factors influencing the effectiveness of the vaccination. One potential reason may be age[30, 31], previous studies have found that anti-HBs protection decreases with age. Other factors that may influence the effectiveness of the vaccine include smoking, obesity, HIV infection, genetic factors and other chronic diseases [32–36].

This study had three key limitations. First, this seroepidemiological survey used a cross-sectional design, so it is difficult to establish causal relationships between the various factors. Second, the participants were people who had lived in the surveillance points for six months. Many migrants or unregistered children outside of family planning were excluded, especially in some urban areas. HBsAg prevalence rates in these groups may be higher than those reported in this study, so we may have underestimated the overall prevalence in the province. Third, because the adults included in this study did not have their vaccination records, the acquisition of adult immunisation history was done by individual recall.

5 Conclusions

Overall, the epidemiological characteristics of hepatitis B have changed among the 1-29-year-old age group in Jiangsu Province, with the HBV infection rate decreasing significantly in the 10- to 29-year-old age group. The implementation of the hepatitis B
The vaccine immunisation strategy in Jiangsu Province over the last 22 years has been critical in improving the coverage rate of the hepatitis B vaccine, reducing the rate of HBV infection and protecting the susceptible population. While the vaccination programme has been especially effective in newborns, it is still necessary to continue to strengthen work on adult vaccinations.

**Abbreviations**

1. Hepatitis B vaccine (HepB)
2. Hepatitis B virus (HBV)
3. National Notifiable Disease Reporting System (NNDRS)
4. Hepatitis B surface antigen (HBsAg)
5. Hepatitis B core antibody (anti-HBc)
6. Hepatitis B surface antibody (anti-HBs)

**Declarations**

**Ethical issues**

This study was approved by the Medical Ethics Committee of the Chinese Provincial Center for Disease Control and Prevention (CDC) (NO: 201339). Participants and children’s guardians provided their written informed consent before the blood collection and interview.

**Competing interests**

The authors declared that no competing interests exist.

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Availability of data and materials
The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Illustrations:
Fig.1 The incidence rates of HBV in Jiangsu province between 2004 and 2014.
Fig.2 Seroprevalence of HBV markers among participants by age group.
Fig3. Comparison of Prevalence of HBsAg(a)and anti-HBs(b) in 2006 and 2014.

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### Tables

**Table 1 Seroprevalence of HBV markers by sociodemographic characteristics**

| Characteristics          | n/N(%) | HBsAg prevalence (%[95%CI]) | P value | Anti-HBs prevalence (%[95%CI]) | P value | Anti-HBc prevalence (%[95%CI]) |
|--------------------------|--------|-----------------------------|---------|-------------------------------|---------|-------------------------------|
| All participants         | 3002(100) | 1.20(0.84-1.66)            | 66.89(65.17-68.57) | 5.33( |
| Age                      |         |                             |         |                               |         |                               |
| 1-4 years                | 1232(41.04) | 0.41(0.13-0.94)            | 0.000   | 76.38(73.91-78.73)            | 0.000   | 1.38( |
| 5-14 years               | 944(31.45)  | 0.32(0.07-0.93)            | 0.000   | 61.97(58.79-65.08)            | 0.000   | 1.80( |
| 15-29 years              | 826(27.51)  | 3.39(2.26-4.86)            | 0.000   | 58.35(54.91-61.74)            | 0.000   | 15.2( |
| Residential area         |         |                             |         |                               |         |                               |
| Urban                    | 1544(51.43) | 0.91(0.50-1.52)            | 0.128   | 63.84(61.39-66.24)            | 0.000   | 4.79( |
| Rural                    | 1458(48.57) | 1.51(0.95-2.28)            | 0.000   | 70.12(67.70-72.47)            | 0.000   | 5.91( |
| Sex                      |         |                             |         |                               |         |                               |
| Male                     | 1583(52.73) | 1.33(0.82-2.02)            | 0.498   | 68.16(65.80-70.45)            | 0.118   | 5.44( |
| Female                   | 1419(47.27) | 1.06(0.59-1.74)            | 0.000   | 65.47(62.93-67.94)            | 0.000   | 5.21( |
| Region                   |         |                             |         |                               |         |                               |
| South                    | 872(29.05)  | 0.92(3.97-1.80)            | 0.216   | 61.35(58.03-64.60)            | 0.000   | 5.40( |
| Central                  | 643(21.42)  | 0.78(0.25-1.81)            | 0.000   | 64.39(60.55-68.09)            | 2.80(   |  |
| North                    | 1487(49.53) | 1.55(0.98-2.31)            | 0.000   | 71.22(68.84-73.51)            | 6.39(   |  |
| Ethnic origin            |         |                             |         |                               |         |                               |
| Han                      | 2972(99.00) | 1.18(0.82-1.63)            | 0.280   | 66.96(65.23-68.65)            | 0.420   | 5.25( |
| Others                   | 30(1.00)   | 3.33(0.08-17.22)           | 0.000   | 60.00(40.60-77.34)            | 13.3(   |  |
| Education(>18years)      |         |                             |         |                               |         |                               |
| Illiterate               | 19(2.64)   | 5.26(0.13-26.02)           | 0.038   | 42.11(20.25-66.50)            | 0.092   | 21.0( |
| Primary school           | 23(3.19)   | 4.35(0.11-21.95)           | 0.000   | 47.83(26.82-69.41)            | 30.4(   |  |
| Education Level | Cases | Incidence Rate (95% CI) | Prevalence Rate (95% CI) | Mortality Rate (95% CI) |
|-----------------|-------|-------------------------|-------------------------|------------------------|
| Middle school   | 227   | 9.69(6.17-14.31)        | 52.31(45.43-59.13)     | 23.61                  |
| High school     | 229   | 5.68(3.06-9.51)         | 59.39(52.72-65.81)     | 16.54                  |
| College         | 223   | 0.45(0.01-2.47)         | 62.78(56.08-69.14)     | 8.85                   |

| Immunization history of HBV | Cases | Incidence Rate (95% CI) | Prevalence Rate (95% CI) | Mortality Rate (95% CI) |
|-----------------------------|-------|-------------------------|-------------------------|------------------------|
| Yes                         | 2590  | 0.46(0.24-0.81)         | 68.95(67.13-70.73)      | 0.00                   |
| No                          | 67    | 14.93(7.40-25.74)       | 55.22(42.58-67.40)      | 38.81                  |
| Unknown                     | 336   | 4.17(2.30-6.89)         | 53.27(47.78-58.71)      | 15.43                  |

| Full immunization(<15years) | Cases | Incidence Rate (95% CI) | Prevalence Rate (95% CI) | Mortality Rate (95% CI) |
|------------------------------|-------|-------------------------|-------------------------|------------------------|
| Vaccinated within 24h after birth | 1904  | 0.05(1.49-7.44)         | 70.59(68.48-72.63)      | 0.126                  |
| Vaccinated more than 24h after birth | 190   | 3.68(1.49-7.44)         | 65.26(58.03-72.01)      | 6.32                   |

**Figures**

Figure 1

The incidence rates of HBV in Jiangsu province between 2004 and 2014.
Figure 2

Seroprevalence of HBV markers among participants by age group.

Figure 3

Comparison of Prevalence of HBsAg(a) and anti-HBs(b) in 2006 and 2014.