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Epidemiological serosurvey of hepatitis B virus among children aged 1–14 years in Guangdong Province, China

Qi Zhu[a], Xiaoping Shao[a], Shaoli Chen[b], Dingliang Li[c], Xiaohong Chen[d], Wenjin Liu[e], Xianghua Wu[f], Zengyong Jian[g], Shannon Rutherford[h], Huizhen Zheng[a,*]

[a] Guangdong Provincial Center for Disease Control and Prevention, Guangzhou, Guangdong, China
[b] Dongguan Center for Disease Control and Prevention, Dongguan, Guangdong, China
[c] Yangjiang Center for Disease Control and Prevention, Yangjiang, Guangdong,China
[d] Zhongshan Center for Disease Control and Prevention, Zhongshan, Guangdong,China
[e] Taishan Center for Disease Control and Prevention, Jiangmen, Guangdong, China
[f] Nanxiong Center for Disease Control and Prevention, Shaoguan, Guangdong, China
[g] Xinxing Center for Disease Control and Prevention, Yunfu, Guangdong, China
[h] Centre for Environment and Population Health, School of Medicine, Griffith University, Brisbane, Queensland, Australia

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ABSTRACT

Objective: A cross-sectional community prevalence survey was conducted to investigate the sero-epidemiological features of hepatitis B virus (HBV) infection among children aged 1–14 years in Guangdong Province in 2013, and to provide baseline data for the evaluation of HBV disease burden and the impacts of HBV control.
Methods: A total of 2765 children aged 1–14 years from 16 villages/streets of eight cities in Guangdong Province were recruited as subjects. A blood sample was obtained from each subject. A chemiluminescence microparticle immunoassay (CMIA) was used to detect hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (HBsAb), and antibody to hepatitis B core antigen (HBcAb).
Results: The prevalence rates of HBsAg, HBsAb, and HBcAb among children aged 1–14 years were 1.16%, 61.63%, and 2.35%, respectively. The prevalence of HBsAg and HBcAb increased with increasing age, and the prevalence was lowest in the 1–4 years age group (0.97% for HBsAg and 1.45% for HBcAb). In contrast, the prevalence of HBsAb decreased with increasing age; however the prevalence was also highest in the 1–4 years age group (76.48%). Eastern Guangdong had the highest prevalence of HBsAg and HBcAb, and the lowest prevalence of HBsAb. The prevalence of HBsAg was under 1% in the Pearl River Delta and western Guangdong regions. Children who had received three or more doses of vaccine had a lower prevalence of HBsAg and HBcAb and a higher prevalence of HBsAb compared to those who had received fewer than three doses of vaccine.
Conclusions: The prevalence of HBsAg among children aged 1–14 years in Guangdong in 2013 was 1.2%, showing a dramatic decrease compared to the 1992 provincial-level cross-sectional survey (19.9%). Children aged 1–4 years and children from the Pearl River Delta had the lowest prevalence of HBsAg positivity. High vaccination coverage among children and timely vaccination of newborns has played an important role in reducing the prevalence of HBsAg.

1. Introduction

Infection with the hepatitis B virus (HBV) is a major public health problem, especially in Sub-Saharan Africa and East Asia (MacLachlan et al., 2015). Recent studies have estimated that HBV infection caused 686 000 deaths in 2013, and it is in the top 20 causes of human mortality (Naghavi et al., 2015) . In China, a national serosurvey in 1992 revealed that the prevalence of hepatitis B surface antigen (HBsAg) was 9.75% in the general population, categorizing China as a high prevalence area for HBV (Dai and Qi, 1997). In the 2006 serosurvey, the prevalence of HBsAg had dropped to 7.18% in the population aged 1–59 years; this improvement changed China's status to a medium prevalence area for HBV (DDCPMHC and CCDCP, 2011).

* Corresponding author. Guangdong Provincial Center for Disease Control and Prevention, No. 160, Qunxian Road, Panyu District, Guangzhou, 511430, China. Tel.: +86 20 31051182; fax: +86 20 31051071.
E-mail address: zhzgdcdc@163.com (H. Zheng).

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Guangdong is a province located in the southeast of China; the population of this province was 106 million in 2013 (Guangdong Provincial Bureau of Statistics, 2013). The 1992 serosurvey reported that 16.7% of the general population of Guangdong and 19.9% of children aged 1–15 years were HBV carriers, making it the most prevalent HBV area in China (Dai and Qi, 1997). The latest provincial-level HBV serosurvey in Guangdong was conducted in 2006 and it found that the prevalence of HBsAg was 11.1% in those aged 1–59 years and 4.9% in children aged 1–15 years (Xiao et al., 2012).

Vaccination is an effective measure in HBV control (Plotkin et al., 2011). Since 1992, Guangdong has made important investments in promoting vaccination for HBV (especially for newborns). For example, in 1992, Guangdong introduced the HBV vaccine from human plasma for the childhood immunization program. A genetically engineered HBV vaccine was introduced in 1996, and this had fully replaced the HBV vaccine from human plasma by 2000. In 2002, the HBV vaccine was fully integrated into the routine immunization program and a three-dose schedule (0, 1, and 6 months) was adopted for infants. In 2001 and 2008–2011, several provincial campaigns were undertaken to identify children (less than 15 years old) who had not completed their HBV vaccination schedule in order to catch up any missing dose(s). In 2013, the antigen content of the HBV vaccine was increased from 5 μg to 10 μg for newborns whose mothers were HBsAg-positive. In 2011, hepatitis B immune globulin (HBIG) was provided free for newborns whose mothers were HBsAg-positive in 87 districts/counties of Guangdong, and this policy was expanded to cover the whole province by 2015.

Given that the last provincial survey had been conducted 10 years earlier and that much activity had occurred since then, the Guangdong Provincial Center for Disease Control and Prevention (GDCDC) conducted a provincial-level serosurvey in 2013 to investigate the current prevalence of HBV. The results of this serosurvey provide baseline data on which to assess the HBV disease burden and the impacts of HBV control, as well as baseline information for future surveys.

2. Materials and methods

2.1. Study design

The main purpose of this study was to estimate the prevalence of HBsAg among children 1–14 years of age. The sample size was calculated based on Equation 1, in which p was the estimated prevalence of HBsAg (3.5% was used according to the 2006 serosurvey results (DDCPMHC and CCDCP, 2011)), δ was the permissible error (0.5%), and α was the significance level (5%).

$$n = \left(\frac{\mu_{\alpha/2}}{\delta}\right)^2 p(1-p) \quad (1)$$

After primary calculation, n was 2648. Considering that the sample size had to be divided equally into 14 age groups and eight sample cities, the total sample size was finally set to 2688.

Subjects were selected using a multi-stage sampling method. There are four geographical regions and 21 cities in Guangdong Province. Eight cities were randomly sampled according to the stratification by region (Dongguan, Zhongshan, and Jiangmen in the Pearl River Delta; Chaozhou and Shanwei in eastern Guangdong; Yangjiang and Yunfu in western Guangdong; Shaoguan in northern Guangdong). Two villages/streets were randomly selected in each city. Children aged 1–14 years from these villages/

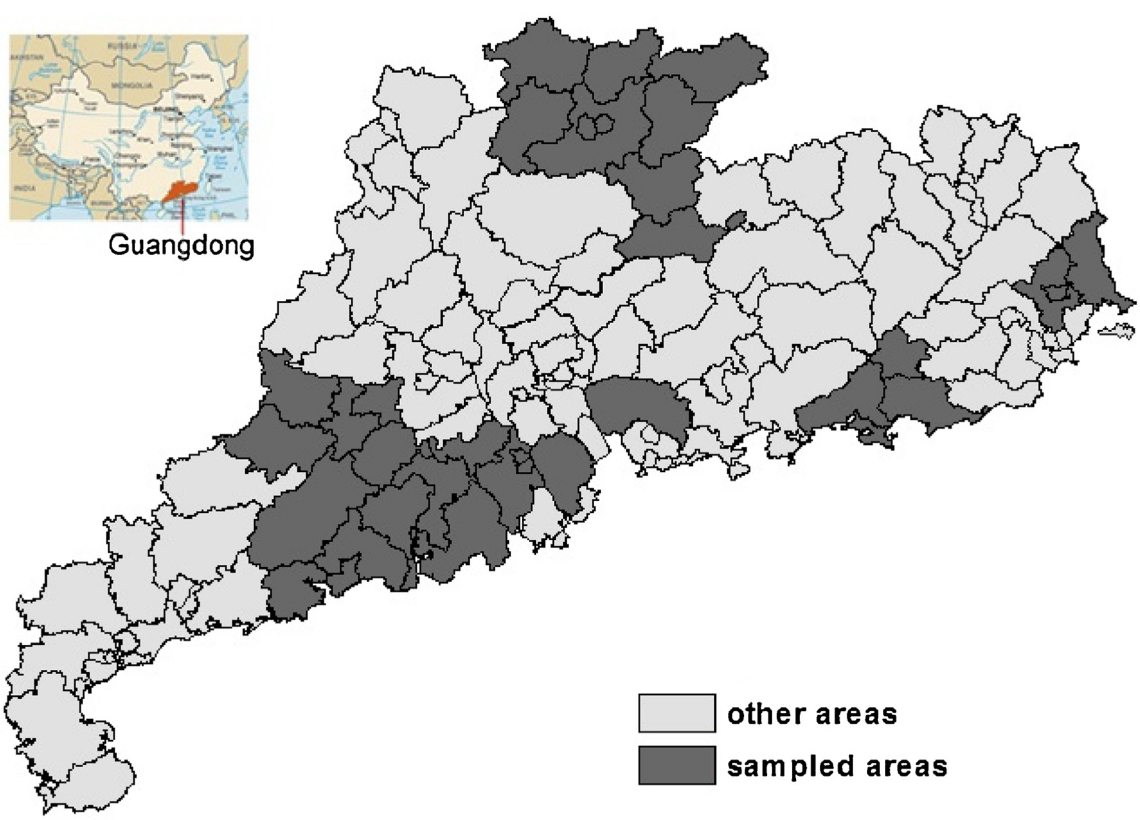

Figure 1. Areas sampled in this study.

streets were recruited as subjects in this study. The sample size for each age group in each city was 24, such that there was a sample size of 336 for each city and 2688 for the whole province. The survey began in August 2013 and was conducted by Guangdong Provincial Center for Disease Control and Prevention (GDCDC). The areas sampled in the study are shown in Figure 1.

2.2. Investigation

Subjects were recruited through local vaccination clinics. A face to face investigation was completed by trained staff of the local CDC. Information on sex, birth, residence, and HBV immunization history was collected using a standard questionnaire.

2.3. Specimen collection and laboratory testing

A 4–5-ml blood sample was obtained from each subject; 2 ml of serum was separated from each blood sample in the local laboratories. All serum specimens were delivered to the provincial laboratory. The temperature was maintained below 8 °C during storage and transportation. A chemiluminescence microparticle immunoassay (CMIA) was used to detect hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (HBsAb), and antibody to hepatitis B core antigen (HBcAb).

2.4. Ethical approval and informed consent

Approval to conduct this study was granted by the relevant departments of the GDCDC (approval number 2013005). Written informed consent was acquired from a parent of each participant. All specimens and information was collected only after permission was granted.

2.5. Data analysis

Data were entered into Epidata 3.1 software. Double entry was used to ensure the quality of the data during the input process. SPSS 16.0 software (SPSS Inc., Chicago, IL, USA) was used for the data analysis. The prevalence rates of HBsAg, HBsAb, and HBcAb across the different regions and age groups were calculated. The Chi-square test was used to determine whether the differences between groups were statistically significant.

3. Results

3.1. Characteristics of the study population

A total of 2765 subjects aged 1–14 years were included in this study; 1435 (51.9%) were male and 1330 (48.1%) were female. Two thousand six hundred and twenty-one (94.8%) were local residents of Guangdong and 133 (4.8%) were from other provinces. The proportions of children aged 1–4, 5–9, and 9–14 years were 29.8%, 37.0%, and 33.1%, respectively.

3.2. Distribution of HBV serological markers by age

Table 1 shows the distribution of HBV serological markers by age group. The prevalence of HBsAg and HBcAb increased with increasing age, and the prevalence was lowest in the 1–4 years age group (0.97% for HBsAg and 1.45% for HBcAb). The difference across age groups was not statistically significant for HBsAg (Chi-square = 0.443, $p = 0.801$), but was statistically significant for HBcAb (Chi-square = 6.345, $p = 0.042$). The prevalence of HBsAb decreased with increasing age and the prevalence was highest in the 1–4 years age group (76.48%). The difference in HBsAb positivity across age groups was statistically significant (Chi-square = 111.154, $p < 0.001$).

3.3. Distribution of HBV serological markers by region

Table 2 shows the distribution of HBV serological markers by region. Eastern Guangdong had the highest prevalence of HBsAg and HBcAb, and the lowest prevalence of HBsAb. The prevalence of HBsAg was under 1% in both Pearl River Delta and western Guangdong. The difference was statistically significant for HBsAb (Chi-square = 90.363, $p < 0.001$), but not for HBsAg (Chi-square = 5.094, $p = 0.165$) or HBcAb (Chi-square = 5.658, $p = 0.129$).

3.4. Distribution of HBV serological markers by immunization history

Table 3 shows the distribution of HBV serological markers by immunization history. It was found that 93.2% of the subjects had received more than three doses of HBV vaccine. Subjects who had received three or more doses of vaccine had a lower prevalence of HBsAg and HBcAb and higher prevalence of HBsAb compared to those who had received fewer than three doses of vaccine. The difference was statistically significant for HBsAb ($p < 0.001$), but not for HBsAg ($p = 0.514$) or HBcAb ($p = 0.064$).

The distribution of HBV immunization history by region is shown in Table 4. The proportion of children who had received three or more doses of vaccine was highest in northern Guangdong (98.9%) and lowest in eastern Guangdong (88.5%). This result may explain the higher HBsAg prevalence in eastern Guangdong.

4. Discussion

This was a cross-sectional community prevalence study. Sampled areas were randomly selected from four stratified geographic regions and participants were randomly recruited based on age categories. Selection bias must be acknowledged in this study. Participants were recruited through vaccination clinics, and hence they may have had better knowledge, attitude, and practice (KAP) on vaccination and other health-related issues. Vaccination was the main factor influencing seromarkers of HBV. The HBV vaccine coverage rate for the total population of Guangdong aged 1–14 years was over 90% (collected by the national surveillance system for vaccine coverage rates (Chinese

Table 1
Distribution of HBV serological markers by age group

Age group, years	HBsAg		HBsAb		HBcAb	
	Positive (%)	Negative (%)	Positive (%)	Negative (%)	Positive (%)	Negative (%)
1–4	8 (0.97)	817 (99.03)	631 (76.48)	194 (23.52)	12 (1.45)	813 (98.55)
5–9	12 (1.17)	1012 (98.83)	579 (56.54)	445 (43.46)	23 (2.25)	1001 (97.75)
10–14	12 (1.31)	904 (98.69)	494 (53.93)	422 (46.07)	30 (3.28)	886 (96.72)
Total	32 (1.16)	2733 (98.84)	1704 (61.63)	1061 (38.37)	65 (2.35)	2700 (97.65)

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBsAb, antibody to hepatitis B surface antigen; HBcAb, antibody to hepatitis B core antigen.

Table 2
Distribution of HBV serological markers by region

Region	HBsAg		HBsAb		HBcAb	
	Positive (%)	Negative (%)	Positive (%)	Negative (%)	Positive (%)	Negative (%)
Pearl River Delta	8 (0.77)	1029 (99.23)	735 (70.88)	302 (29.12)	20 (1.93)	1017 (98.07)
Eastern Guangdong	12 (1.77)	666 (98.23)	327 (48.23)	351 (51.77)	23 (3.39)	655 (96.61)
Western Guangdong	6 (0.86)	695 (99.14)	437 (62.34)	264 (37.66)	12 (1.71)	689 (98.29)
Northern Guangdong	6 (1.72)	343 (98.28)	205 (58.74)	144 (41.26)	10 (2.87)	339 (97.13)
Total	32 (1.16)	2733 (98.84)	1704 (61.63)	1061 (38.37)	65 (2.35)	2700 (97.65)

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBsAb, antibody to hepatitis B surface antigen; HBcAb, antibody to hepatitis B core antigen.

Table 3
Distribution of HBV serological markers by immunization history

Immunization history (doses)	HBsAg		HBsAb		HBcAb	
	Positive (%)	Negative (%)	Positive (%)	Negative (%)	Positive (%)	Negative (%)
<3	1 (1.52)	65 (98.48)	21 (31.82)	45 (68.18)	4 (6.06)	62 (93.94)
≥3	27 (1.05)	2551 (98.95)	1623 (62.96)	955 (37.04)	57 (2.21)	2521 (97.79)
Unknown	4 (3.31)	117 (96.69)	60 (49.59)	61 (50.41)	4 (3.31)	117 (96.69)
Total	32 (1.16)	2733 (98.84)	1704 (61.63)	1061 (38.37)	65 (2.35)	2700 (97.65)

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBsAb, antibody to hepatitis B surface antigen; HBcAb, antibody to hepatitis B core antigen.

Table 4
Distribution of HBV immunization history by region

Region	Immunization history (doses)		
	<3 (%)	≥3 (%)	Unknown (%)
Pearl River Delta	29 (2.8)	953 (91.9)	55 (5.3)
Eastern Guangdong	12 (1.8)	600 (88.5)	66 (9.7)
Western Guangdong	21 (3.0)	680 (97.0)	0 (0)
Northern Guangdong	4 (1.1)	345 (98.9)	0 (0)
Total	66 (2.4)	2578 (93.2)	121 (4.4)

HBV, hepatitis B virus.

Center for Disease Control and Prevention, 2013)). The proportion of participants in this study who had completed three doses of vaccine was 93.2%. This study involved a representative sample. The total sample size reached 2700, making the estimated HBV prevalence rate sufficiently accurate.

According to the national serosurveys of 1992 and 2006 (Xiao et al., 2012), Guangdong was in the top three most prevalent HBV areas in China. However, many measures have been taken to reduce the disease burden of HBV, with vaccination (especially in newborns) being the most important one. Guangdong has made great efforts in its HBV immunization program, including full immunization of infants with three routine doses, improvement in the timeliness of the first dose (within 24 h after birth), combined injection with HBIG for newborns with an HBV carrier mother, and supplementary immunization for those who have not completed three routine doses (Zheng and Deng, 2012). As a result of these effective measures, the prevalence of HBsAg in Guangdong decreased dramatically between 1992 and 2013. The prevalence of HBsAg among children under 15 years of age was 19.9% in 1992, declining to 4.9% in 2006 and falling to 1.2% in 2013.

The prevalence of HBsAg and HBcAb were both shown to increase with age, indicating that the potential for infection with HBV is much lower for recent birth cohorts and suggesting that the measures taken in newborns have been highly effective. The prevalence of HBsAb reflects the level of immunity to HBV. Children under 5 years of age showed significantly higher levels of HBsAb. This may be attributed to the short time interval since vaccination. HBsAb concentrations decline with time after vaccination, and completion of vaccination probably confers lifelong protection (Publication, 2010).

From a spatial perspective, the Pearl River Delta had the lowest prevalence of HBsAg and the highest prevalence of HBsAb. This may be because the Pearl River Delta is the most developed area in Guangdong; people living there experience better socio-economic conditions and make use of the better medical services, including vaccination. High coverage of HBV vaccine in the Pearl River Delta was achieved earlier than in less developed areas.

In this study, the proportion of children who received the full vaccination schedule was 93.2% (2578/2765). The proportion may be slightly underestimated as 121 children with an unclear vaccination history were included in the denominator. Coverage with the three doses increased steadily over the 10-year period, from 86.1% in 2002, to 92.4% in 2006, and to 93.2% in 2013. Children who had received the full vaccination schedule (three or more doses) had significantly higher levels of HBsAb. The three-dose routine schedule has proven to be very effective in providing immunity against HBV infection.

This was a multi-stage sampling survey with a sample size of 2765. The results of this study are considered representative and sufficiently accurate to estimate the prevalence of HBV seromarkers in Guangdong Province. However, several limitations should also be mentioned: (1) although the sample areas were selected randomly based on four geographical regions of Guangdong, the sample areas appear not to be evenly distributed according to the map; (2) subjects were recruited from vaccination clinics, leading to concerns regarding representativeness.

Interventions to reduce the prevalence of HBsAg among adults are difficult. The key to reducing the prevalence of HBsAg in the entire population is to avoid HBV infection in childhood. Timely and full-course vaccination is the best way to prevent HBV infection during childhood. The government should continue to invest resources in HBV vaccination in order to maintain the high vaccination coverage among children and timely vaccination of newborns.

In conclusion, this study provides sero-epidemiological information on HBV for Guangdong, which indicates that the interventions implemented in the past 10 years have had a significant impact on reducing the risk of HBV.

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