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The prevalence of hepatitis B core antibody in vaccinated Chinese children: A hospital-based study

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ABSTRACT

Background & aims: After nearly 30 years of immunization, there is little known about the prevalence of hepatitis B core antibody (anti-HBc) in Chinese children. The clinical significance of anti-HBc would be more and more important. In this study, we had tried to analyse the prevalence of anti-HBc in vaccinated Chinese children, exploring the post-immunization status based on a large sample sized investigation.
Methods: Proportions of anti-HBc were analysed among 215,627 hospitalized Chinese children immunized with HBV vaccination in this study.
Results: The proportions of anti-HBc were divided into 3 stages: 36.6% in 0-year-old group, followed by 1- to 10-year-old which stayed relatively stable (5.69 ± 0.40%, [4.86–6.28%]), and significant increasing within 11- to 16-year-old (7.80 ± 1.24%, [6.62–9.74%]), meanwhile, similar changes of HBsAg were showed in the corresponding ages, and significantly increased in children older than 9-year (1.40%, [1.00–2.04%]), comparing with 0.30% in 0-year-old, 0.55 ± 0.13% (0.30–0.64%) in 1- to 9-year-old. The average level of anti-HBc maintains 5.99% in children aged 1- to 16-year with 0.63% for HBsAg.
Conclusion: This is the first study of the prevalence of anti-HBc in vaccinated Chinese children: 36.6% of anti-HBc-positivity was found in 0-year-old group, which could be maternal in origin. Relatively high prevalence of anti-HBc may not be ignored in children aged 1- to 16-year-old. Strangely, our data also showed that HBV breakthrough infection would occur in immunized Chinese children older than 9-year-old, and more attention is needed on those children.

1. Introduction

The 2017 Word Health Organization (WHO) Global Hepatitis Report estimates that 3.5% (257 million) of the world population have chronic hepatitis B virus (HBV) infection, and the Western Pacific Region has the highest prevalence of hepatitis B surface antigen (HBsAg) (6.2%) [1,2]. China is HBV highly endemic country, and a nationwide vaccination program was launched in 1992 to reduce the burden of disease caused by HBV infection. According to two serosurveys conducted by Chinese Center for Disease Control and Prevention (China CDC) in 1992 and 2014, the overall number of "overt" HBV infection (HBsAg positive) among children <15 years of age declined 92.4% during 1992–2014 (from 10.5% to 0.8%) [3,4]. Although, positive rate of HBsAg has significant declined in children with the increasing use of vaccination, the age group with the highest HBsAg prevalence corresponds to the age groups with the highest fertility rate in China and in Asian countries, and most infections are transmitted from mother to child vertically/perinatally [5].

High titers of anti-HBc are produced in patients who have been exposed to HBV and the immunity usually lasting persistance. Occult HBV infection (OBI) is characterized by the persistence of HBV genomes in the liver tissue (with detectable or undetectable HBV DNA in the serum) of HBsAg-negative individuals [6]. Anti-HBc seropositivity associated with the risk of OBI has been

Abbreviations: anti-HBc, hepatitis B core antibody; WHO, Word Health Organization; HBV, hepatitis B virus; China CDC, Chinese Center for Disease Control and Prevention; HBsAg, hepatitis B surface antigen; OBI, occult HBV infection; CHCMU, Children's Hospital of Chongqing Medical University; anti-HBs, hepatitis B surface antibody; anti-HBe, hepatitis B e antibody; CMIA, chemiluminescent microparticle immunoassay; HCC, hepatocellular carcinoma.

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demonstrated extensively. HBV DNA is the primary test used for defining OBI, but the presence of anti-HBc response has been considered a surrogate marker, also recommended as a serological detection marker for the risk of HBV reactivation in patients undergo immunosuppressed [7–13].

Up to now, positive rate of HBsAg in immunized children has been significantly decreased with universal immunized program, but the data are scanty which analysed the changes of HBV serological markers in immunized Chinese children. Therefore, we tried to have a comprehensive study to investigate the proportion of anti-HBc in hepatitis B immunized Chinese children.

2. Materials and methods

2.1. Characteristics of the study population

A total of 215,627 subjects aged 0- to 16-year were involved in this retrospective study ("0" means that the age is ≤6 months, "1" means 7- to 18 months, and so on); 133,996 (62.1%) were male, and 81,631 (37.9%) were female, most children (78.5%) were aged within 6 years old. All participants were the inpatients of Children's Hospital of Chongqing Medical University (CHCMU) between August 2012 and December 2017, and had been received 3-doses vaccination against hepatitis B as infants according to the Chinese hepatitis B vaccination programme since 1992. Chongqing is a municipality located in the southwest China, which has a population of 30.17 million in 2015 according to the results of the National Bureau of Statistics. The participants basic information (patients ID, age, gender), results for HBV seromarkers (HBsAg, anti-HBs [hepatitis B surface antibody], anti-HBe [hepatitis B e antibody], anti-HBc) were getting from the Information Centre.

The study was approved by the Ethics Review Committee of Children's Hospital of Chongqing Medical University.

2.2. Serological testing

All specimens were tested HBV markers (HBsAg, anti-HBs, anti-HBe and anti-HBc) by chemiluminescent microparticle immunoassay (CMIA) using the Architect i system (Abbott Laboratories, Chicago, USA) in the outpatient and inpatient diagnostic laboratory. HBsAg was considered positive if the concentration was >0.05 IU/mL. Subjects with anti-HBs levels ≥10 mIU/mL were considered positive and had seroprotection. Anti-HBe, anti-HBc of the sample were detected by rate/cut-off rate (s/co) values which anti-HBe ≤ 1.0 and anti-HBc ≥ 1.0 were considered positive.

2.3. Data analysis

All data were analysed by using SigmaPlot (version10.0), SPSS (version 20.0). Continuous variables were calculated as the median (interquartile range), and categorical variables were determined as percentage and analysed using the Chi-squared test. All statistical tests were 2-tailed, and a p-value <0.05 was considered to be

Table 1
Demographic data and HBV serological markers on the population.

Age (year)	N (total)	Anti-HBc	Anti-HBe	Anti-HBs		HBsAg
		Positive rate (%)	Positive rate (%)	Median (mIU/mL)	Positive rate (%)	Positive rate (%)
	M/F	M/F	M/F		M/F	M/F
0	81 484	36.6	20.0	66.99	70.1	0.16
	49 904/31 580	36.2/37.2	19.8/20.2		70.2/69.9	0.15/0.18
1	16 428	6.28	2.77	243.51	93.6	0.30
	10 640/5 788	6.33/6.17	2.74/2.81		93.7/93.4	0.31/0.28
2	19 736	5.78	2.38	71.92	84.7	0.30
	12 559/7 177	5.60/6.10	2.29/2.54		84.8/84.7	0.29/0.31
3	15 435	5.55	2.03	30.4	72.1	0.39
	9 366/6 069	5.07/6.28	1.99/2.13		71.2/73.6	0.43/0.33
4	13 396	5.98	1.80	19.55	62.5	0.61
	8 203/5 193	5.17/7.26	1.51/2.25		61.4/64.3	0.44/0.89
5	12 067	5.91	1.71	14.21	56.6	0.60
	7 413/4 654	5.58/6.42	1.56/1.93		55.4/58.6	0.58/0.64
6	10 617	5.27	1.71	10.03	50.0	0.57
	6 613/4 004	5.02/5.67	1.54/2.00		48.4/52.7	0.51/0.67
7	8 627	4.86	1.43	7.78	45.7	0.64
	5 271/3 356	4.88/4.83	1.40/1.46		45.6/45.9	0.57/0.74
8	7 532	5.46	1.79	6.46	43.4	0.53
	4 647/2 885	4.91/6.34	1.61/2.08		42.2/45.4	0.54/0.52
9	6 529	5.58	1.79	5.52	42.3	0.52
	4 145/2 384	5.31/6.04	1.62/2.10		42.3/42.1	0.55/0.46
10	5 826	5.53	1.58	5.78	42.7	1.00
	3 618/2 208	5.39/5.75	1.71/1.36		42.2/43.5	1.00/1.00
11	5 042	6.62	2.36	6.18	44.1	1.37
	3 215/1 827	6.38/7.06	2.15/2.74		44.1/44.0	1.71/0.77
12	4 460	7.91	2.80	10.08	50.1	1.32
	2 793/1 667	6.80/9.78	2.65/3.06		49.4/51.3	1.18/1.56
13	3 844	7.44	2.84	14.42	53.6	1.56
	2 537/1 307	6.78/8.72	2.60/3.29		54.4/52.1	1.22/2.22
14	2 612	9.07	3.48	15.56	54.2	1.84
	1 720/852	8.90/9.86	3.43/3.76		55.3/54.6	1.51/2.58
15	1324	9.44	4.31	22.68	57.9	2.04
	881/443	9.00/10.4	3.52/5.87		56.9/60.0	2.04/2.03
16	688	9.74	3.78	22.92	58.7	1.60
	477/211	9.64/9.95	3.77/3.79		60.2/55.5	1.68/1.42
Total	134 163	5.99	2.13	26.00	63.6	0.63
(1–16Y)	84 098/50 025	5.67/6.54	2.02/2.32		63.3/64.2	0.60/0.67

Age, "0" means that the age is ≤6 months, "1" means 7- to 18 months, and so on.
N, number of children with available results.
Median, according to the statistics of positive values.

statistically significant. Children with antibody concentrations of ≥10 mIU/ml were considered seroprotected. anti-HBs values ≥1000 mIU/ml were calculated as 1000 mIU/ml.

3. Results

3.1. Demographic data and HBV serological markers on the population (Table 1)

The detailed characteristics of 215,627 subjects who involved in this study were provided in Table 1. The percentages and medians of HBV seromarkers (anti-HBc, anti-HBe, anti-HBs, and HBsAg) changes were similar with each other, and not significantly difference were found between males and females.

3.2. The distribution of age related anti-HBc and anti-HBe (Fig. 1)

For the distribution of anti-HBc, there were 3 stages: 0-year-old group had the highest prevalence in 36.6%, followed by 1–10-year-old which stayed relatively stable (5.69 ± 0.40%, [4.86–6.28%]), and significant increasing within 11–16-year-old (7.80 ± 1.24%, [6.62–9.74%]) ($p < 0.05$). On the other hand, in the subjects, proportions of anti-HBc had obviously reduced among children aged 0- to -1-year (36.6% to 6.28%) ($p < 0.001$), but 5.55% prevalence existed among children in 3-year-old group. The percentage of anti-HBe had a similar pattern with anti-HBc in the corresponding age groups, which had the highest positive rate in 0-year-old group (20.0%), with average levels of 2.01% for 1- to 10-year-old subjects, and then increased in children aged 11- to 16-year (2.93%) ($p < 0.05$). The changes for interquartile distribution of anti-HBc, anti-HBe were similar with those for positive rates corresponded with age.

3.3. The prevalence of HBsAg (Fig. 2)

The average value of HBsAg positive rate was 0.63% (0.30–2.04%) in children aged 1- to 16-year-old. For the age groups, 0.16% in 0-year-old, 0.46% (0.30–0.64%) in 1- to 9-year-old, 1.40%

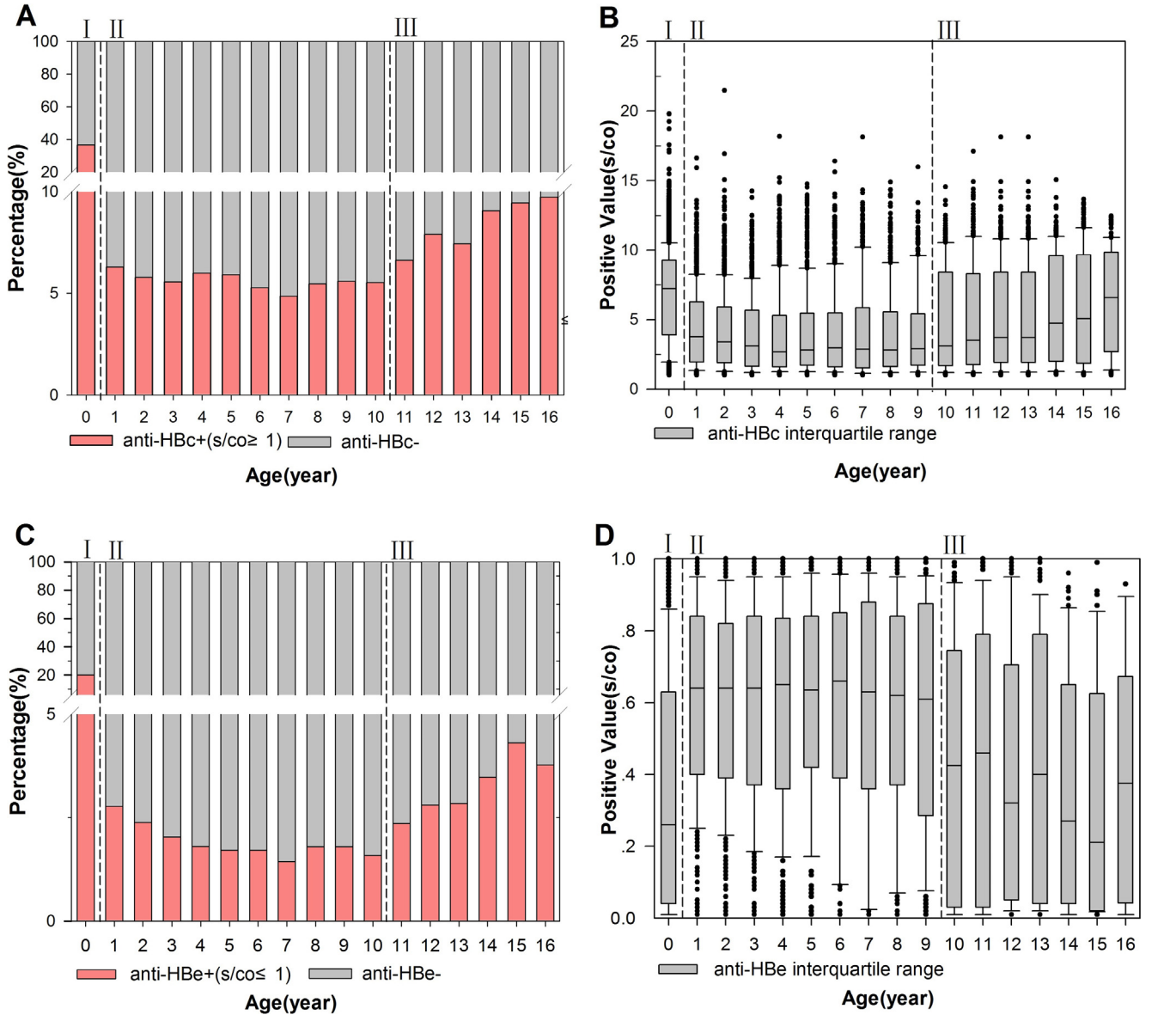

Fig. 1. The distribution of age related anti-HBc and anti-HBe. Proportions of anti-HBc (A), anti-HBe (C) and positive values interquartile distribution of anti-HBc (B), anti-HBe (D) were showed in 3 age stages (stage I: 0-year-old; stage II: 1- to 10-year-old; stage III: 11- to 16-year-old. (The "0" in X-axis means that the age is ≤6 months, age of >6 months were rounded up to the next year).

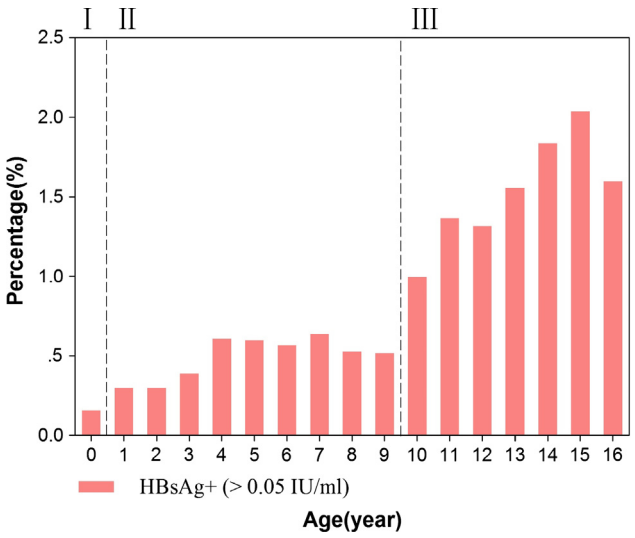

Fig. 2. The prevalence of HBsAg. The lowest in 0-year-old (0.16%); significantly increased was showed in 10- to 16-year-old groups (range, 1.00–2.04%), and with average level of 0.75% (range, 0.39–2.04%) in children aged 3- to 16-year-old.

(1.00–2.04%) in 10- to 16-year-old, and there were significant differences between them ($p < 0.001$).

3.4. The changes of anti-HBs levels in different age groups (Fig. 3)

After 3-dose HBV vaccination, the proportion of protective antibody level (titers ≥10 mIU/mL) had increased significantly, from 70.1% (0-year-old) to 93.7% (1-year-old), and statistical difference was found between them ($P < 0.001$), and the percentage of children with seroprotected antibody was 63.6% in children aged 1–16 years. Only, 6.3% of children did not seroconvert in the 1-year-old group, and the ratios of protected antibody decreased with age, to 42.3% in the 9-year-old group, then increased in children aged from 10- to 16-year-old (42.7% to 58.7%). For the distribution of anti-HBs interquartile range, it had same changes with the percentage of anti-HBs, the highest median value in the 1-year-old group, and decreased with age, then began to increase in children >9-year-old.

4. Discussion

Hepatitis B virus infection is a significant public healthy concern worldwide, and China has a relatively high epidemiology of HBV chronic infection. In China, the overall HBsAg prevalence has greatly diminished since a universal vaccination program for infants was launched in 1992. However, a significant reservoir of HBV infection is still existed with 97 million HBV carriers, and HBV infection is characterized by a significant family history that 23.2% of HBsAg-positive families contained more than two HBsAg carriers [14]. For children, the majority of HBV infection occurs at an early age, chronicity and viral persistence are more easily developed, which persist in 20–30% of young children and up to 90–95% of perinatally infected subjects [15].

A greater clinical significance in persons with OBI has been found, as OBI reactivation with an immunosuppressive status, transmission through blood transfusion, involving in hepatocellular carcinoma (HCC) development. Anti-HBc is traditionally recognized as an important serological marker in identifying patients infected or exposed to HBV, and important role of anti-HBc in OBIs has been explored widely. In this study, a detailed anti-HBc analysis was performed to explore the post-immunization status for Chinese vaccinated children with increasing age in Chongqing, China.

Relatively high sensitivity and specificity of anti-HBc to predict OBI was shown in previous studies [7,13]. There is no doubt that the analysis of liver DNA extracts is the gold standard for occult HBV infection. However, the availability of liver tissue specimen must be considered, as is obvious, cannot be performed in the great majority of the subjects. In fact, most of the researches on OBI with the analysis of blood samples. Notably, a negative HBV DNA result does not rule out OBI, as it cannot detect very low levels of cccDNA in the liver and may be influenced by the material tested, the limitations of OBI detection method available presently, and geographic differences [16]. Moreover, HBV DNA testing is expensive and is not always possible for underdevelopment areas. In this case, anti-HBc could be used as a surrogate marker. The 2017 Clinical Practice Guidelines clearly stated that prophylaxis drugs (entecavir [ETV], tenofovir disoproxil fumarate [TDF], tenofovir alafenamide [TAF]) must be considered in anti-HBc positive patients receiving immunosuppressive regimens [17]. Although false positive anti-HBc reactivity might exist.

HBcAg is the most immunogenic HBV component during infection [18], and the immunity usually lasting persistence. The highest prevalence of anti-HBc (36.6%) was found in 0-year-old group, which would be material origin [19,20]. A relatively high prevalence of anti-HBc was shown in Chinese women of reproductive age with 57.16% in a cross-sectional HBV serological survey conducted in 2013 [21]. Some previous researches showed that anti-HBc in new-born babies obtained from their mothers usually fell gradually with age, and became almost undetectable in all infants after the first 3 years of life [19,20]. In this study, although, the positive rates of anti-HBc had dropped significantly in children aged from 0- to 1-year (36.6% to 6.28%) ($p < 0.001$), persistent anti-HBc-positive was still existed in children older than 3-year, maintaining relatively stable in children aged 1- to 10-year (4.86% to 6.28%). Notably, the prevalence of anti-HBc was with an average value of 5.99% (range, 4.86% to 9.74%) in children aged 1- to 16-year, however, for the positive rate of HBsAg, there was only 0.63% (range, 0.30–2.04%) in this age group. How about the another 5.36% of anti-HBc-positive individuals, there might be existed a persistent seropositive occult HBV infection.

Persistent antibody reaction (anti-HBc positive with or without anti-HBs) may be caused by the OBI (low viremia levels). A very-low-level viral replication and HBsAg expression may be the main mechanism underlying occult HBV infection in the postvaccination era [13]. The most important and extensive studies to identify OBI is the liver tissue detection: a true OBI status of 52–90% in subjects for anti-HBc-positive with liver tissue samples was reported [22,23]. A previous review article revealed that more than 20% of occult carriers are negative for all serum markers of HBV infection (seronegative-OBI) [24]. So, we speculate the existence of occult HBV infection in HBsAg-negative children might be more than 3.35–6.03% with a formula "[Anti-HBc (%) × 52–90%]/(1 − 20%)". Therefore, taking prospective follow-up studies to detect and clarify the HBV infection status in anti-HBc-positive children with active immunization would be so important for the development of HBV-related prevention and control measures. This group might be at a higher risk of OBI, and HBsAg reappearance later on in life—for example, when these children become adolescents and become sexually active, a known risk factor to transmit hepatitis B infection [25].

It is worth noting that the positive rate of anti-HBc had significantly increased in children aged ≥10-year, which was similar to our previous study of anti-HBs titers in the corresponding ages. In previous, we had speculated the improved protective antibody titers was due to revaccination, with questionnaires about 168 patients' history of hepatitis B revaccination [26]. However, HBV

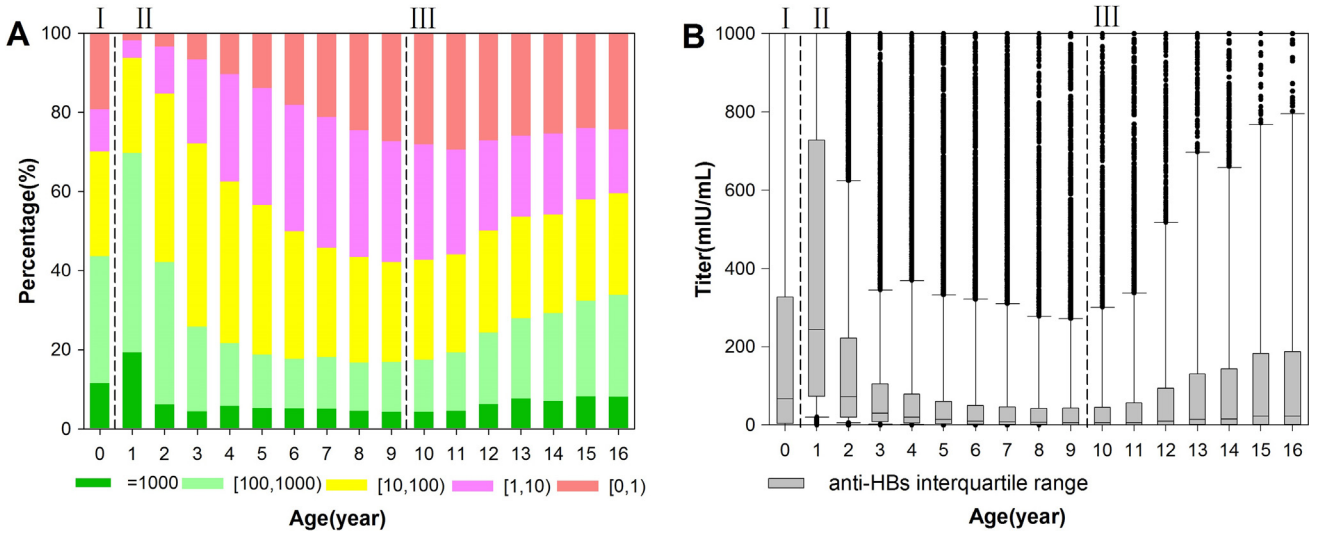

Fig. 3. The changes of anti-HBs levels in different age groups. Stacked bars (A) and box-plot (B) showed protective anti-HBs reached the highest in 1-year-old group after 3 doses of HBV vaccine vaccinated, then decreased with age, whereas it began to rise in children aged >9-year.

vaccine is a yeast-derived recombinant vaccine that include HBsAg, and the presence of anti-HBs is the only HBV marker detected in people who have acquired immunity through vaccination [27]. With analysing the distribution of HBsAg in children aged 0- to 16-year-old, there was also a significant increasing in children older than 9-year-old. Therefore, there must be HBV breakthrough infection in children aged ≥9-year, the positive rates of anti-HBc, anti-HBe, anti-HBs, HBsAg had significantly increased after it. It is unknown why the significantly increased positive rate of active HBV infection in children older than 9-year-old, may be the breakthrough of OBI caused by increasing activity of HBV which had already existed in the body that may also be caused by horizontal transmission. In China, children aged 6–12-year are in primary school, their lifestyles and habits often do not change much, thus, the possibility of occult HBV breakthrough infection is more likely.

Occult HBV infection should not be ignored in immunized children lived in HBV highly endemic areas, even with undetected HBV-DNA. In our study, after completing the 3-dose HBV immunization schedule, the positive rate of protective antibody had up to 93.6%, and the proportion of active HBV infection was only about 0.30% in children aged 1-year-old. Comparing with the 1992 pre-recombinant vaccine survey, the effect of anti-HBs which developed in response to HBV vaccines to prevent perinatal infection of neonates is clearly, but the levels of protective antibody decrease with age, the efficiency to prevent the occurrence of OBI and breakthrough infection in children is still not clear so far. Although, results of some studies shown that infants born to HBsAg-positive mothers be diagnosed with OBI might be a transient phenomenon with the production of protected antibody [28–30]. But with insufficient follow-up time and the intermittent nature of virus, it cannot be certainty that the HBV DNA in children is completely removed, there may be an inactive state or a silent infection at earlier age.

This study still has some limitations: firstly, all the analyse results are based on the special population of hospitalized children, and the test result of HBV markers may be affected by the child's illness; secondly, this study is a retrospected analysis, so data from the mother was scanty, more detail may be not reflected.

In conclusion, this is the first study to have analysed the prevalence of anti-HBc in vaccinated Chinese children: 36.6% of anti-HBc-positivity was found in 0-year-old group, which could be maternal in origin; relatively high prevalence of anti-HBc may not be ignored in children aged 1- to 16-year-old, and occult HBV infection might be more common in anti-HBc-positive population. Strangely, our data also showed that HBV breakthrough infection would occur in immunized Chinese children older than 9-year-old, therefore, more attention is needed to pay on 9–16-year-old children. In addition, the universal HBV vaccination program must be sustained for decades to come, and augmented strategies will be needed to control the occult HBV infection and breakthrough infection in children.

Conflict of interest

We declare no competing interests.

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