



Chronic and occult hepatitis B virus infections in the vaccinated Chinese population

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Abstract: In China, the prevalence of chronic hepatitis B virus (HBV) carriers declined from 9.5% to 7.2% in general population aged 1–59 years between 1992 when universal infant vaccination program was implemented nationwide and 2006. Approximately 75% to 90% reduction in hepatitis B surface antigen (HBsAg)-positivity was achieved in children, the HBsAg prevalence being reduced to 3% or less than 1% in children aged 5–14 years or <5 years, respectively. However, the non-responders with anti-HBs <10 IU/L and those with anti-HBs declining below the 100 IU/L protective level remain susceptible to breakthrough or occult HBV infections (OBI). Approximately 3–4% of HBV DNA carriers among the vaccinated population aged between 18 and 25 years, are HBV infected either vertically or horizontally from mothers, family contacts or sexual partners with high HBV viral load. The immunoprophylaxis efficacy of hepatitis B vaccine produced from an HBV genotype A2 strain may not be fully protective from HBV infection of genotype non-A2 strains, for instance, against HBV genotype B and C strains. An HBV vaccine boost between age 15 and 17 years might prevent asymptomatic infections acquired through sexual activity or other routes. Boosting at age 18–24 might induce an anamnestic response providing >100 IU/L of sero-protective anti-HBs level in college students. The implementation of a systematic hepatitis B boosting vaccination program for non- and low-responder children and adolescents at age 15–17 is suggested in China. Such strategy might be cost-saving and a significant health benefit for the Chinese population.

Keywords: Hepatitis B vaccinated population; hepatitis B virus (HBV) prevalence; chronic infection; occult infection; vaccination program

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Introduction

In China, approximately 120 million people are hepatitis B virus (HBV) carriers, accounting for nearly one-third of the people infected with HBV worldwide (1). Approximately 60% of the Chinese population has been in contact with HBV. However, prevalence of hepatitis B surface antigen (HBsAg) in the Chinese population aged 1–59 years has

declined from 9.5% in 1992 to 7.2% in 2006, in particular to only 1.0% of children <5 years in relation with universal hepatitis B vaccination program at birth implemented in China since 1992 (2,3).

Screening for HBsAg in collected blood units massively decreased the risk of blood-related HBV transmission, but could not detect the pre-seroconversion window period (WP) or occult HBV infection (OBI) (4). Anti-HBc

screening that could largely eliminate OBIs but not WP infections (5), is not suitable for screening blood donations in China as it would reduce the blood supply by over 50% (6). The availability of nucleic acid testing (NAT) for detection of HBV DNA in blood donations enabled the identification of HBV DNA positive but HBsAg negative (HBV DNA+/HBsAg-) carriers (7). However, there are a small number of individuals with low-level viral DNA who could not be identified even by individual donation HBV NAT due to insufficient sensitivity (8). In China, the NAT of blood donations as a mandatory testing for HBV DNA and HCV and HIV RNAs has been progressively implemented nationwide for improving blood transfusion safety.

HBV universal vaccination program of infants started in 1992 in China. The population of vaccinated blood donor has been increasing since 2010, positively impacting HBV blood safety although little data is available to evidence this assumption. HBV infection, mostly OBIs with genotype B or C have been identified in 18–21 years old vaccinated individuals who received HBV vaccine derived from genotype A2 recombinant protein (9). A previous report on HBV DNA blood donors from the American Red-Cross blood services suggested that genotype A2 HBV vaccine might not be fully protective of individuals sexually exposed to highly viremic non-A2 HBV strains (10). This article intends to discuss the occurrence of HBV breakthrough and occult infections and the potential causes of HBV vaccine failure in vaccinated Chinese populations.

HBV vaccines and vaccination programs

Since the discovery of HBV in the late 1960s, 50 years have elapsed (11). The first-generation vaccines were plasma-derived HBsAg, which were initially developed in France in 1981 and in the USA in 1982 (12,13). These vaccines are still produced and used in some Asian countries. The safety of these plasma-derived vaccines was a matter of concern particularly in connection with HIV infection risk and second-generation recombinant DNA hepatitis B vaccines were produced by expressing the envelope S protein of HBV genotype A2 in yeasts (i.e., *Saccharomyces cerevisiae*) (12,14). These vaccines were commercialized in 1986, and were used in the worldwide, in particular as part of the routine immunization programs for infants and children or adolescents. In contrast to yeasts, the third-generation hepatitis B vaccines were developed during the 1990s in mammalian cells, including a Pre-S2/S vaccine developed in France (15), and two Pre-S1/Pre-S2/S vaccines developed

in Israel (16) and Germany (17). These cell-derived Pre-S/S vaccines have already been introduced in France, Israel, and several countries of East Asia (18,19), where they appeared highly immunogenic, especially when compared to yeast-derived S protein vaccine non-responders.

The world's first HBV universal vaccination program for infants was launched in Taiwan in July 1984 (20,21). All infants received plasma-derived HBV vaccines according to a mandatory schedule. The infants born to hepatitis B e antigen (HBeAg) positive mothers additionally received hepatitis B immunoglobulin (HBIG) 24 h after birth (22). In China, HBV vaccine was available in 1982 and the domestically produced hepatitis B vaccines were introduced on the market in 1985. The first pilot study of the universal HBV vaccination program started in 1986 in Long An county, Guangxi province (23–25). In 1992, China initiated universal hepatitis B vaccination of infants with yeast-derived vaccines (26), and hepatitis B vaccination was integrated into the national expanded program of immunization (EPI) in 2002 (27). A free nationwide catchup vaccination program was implemented in 2007 for unvaccinated children and adolescents aged 1–19 years (28,29). Since 2010 Hepatitis B vaccination was recommended to six high-risk populations, including health care workers, intravenous drug users, persons who are closely in contact with HBsAg-positive carriers, persons with high-risk sexual behavior, transfusion recipients, and hemodialysis patients (29).

In China, plasma-derived hepatitis B vaccines (5 mg/dose) were used for the first 10 years (from 1986 to 1996), and then were replaced by recombinant yeast-derived vaccine (5 mg/dose) (25). A three-dose vaccination program (0-1-6) was adopted with the first injection at any given time, and the other two at first and sixth months after the initial dose. Routine immunization was administered to all infants within 24 h of birth and subsequent doses at 1 and 6 months, respectively (2,26,28). According to the data obtained from the Global Alliance on Vaccine and Immunization project (GAVI) in China, the compliance rate of universal infant vaccination with the timely at-birth dose (TBD) increased from 20% to 91%, and the completion coverage of three-dose series of hepatitis B vaccines (HepB3) increased from 30% to 95% between 1992 and 2009 (Figure 1) (3,30). Coverage variations were found between different regions of China during two periods of 1992–2002 and 2003–2009 (Table 1) (3), in which the coverage for both TBD and HepB3 were relatively lower in the western part of China compared to those in the middle and eastern areas (30–32).

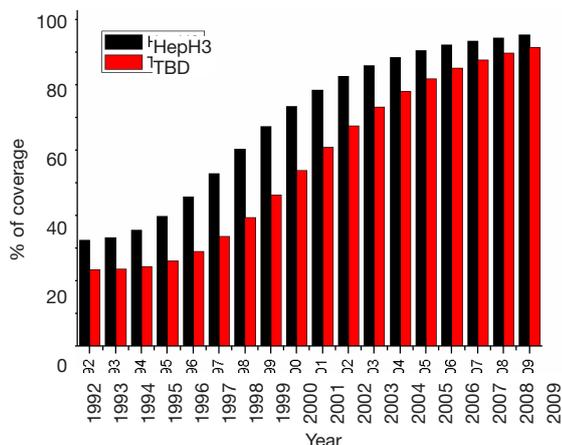


Figure 1 Coverage of universal infant vaccination of the hepatitis B vaccines between 1992 and 2009. Data were obtained from the GAVI China project (3). HepB3, three-dose series completion; TBD, timely birth dose.

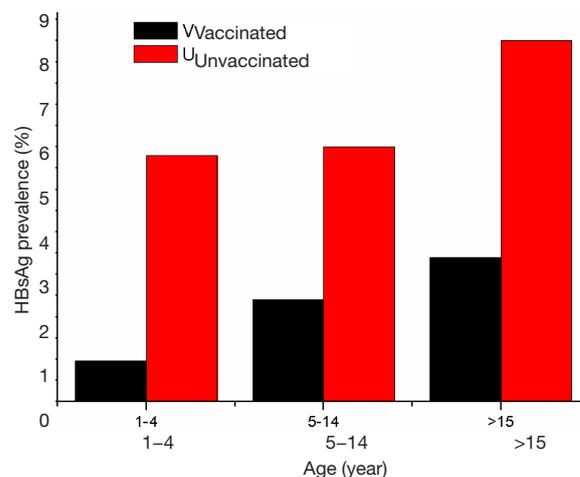


Figure 2 Prevalence of HBsAg between the vaccinated and unvaccinated Chinese population in various age groups. Data were obtained from the national surveys of universal infant vaccination program with the hepatitis B vaccines in 1992 and 2009 (2,42). HBsAg, hepatitis B surface antigen.

Table 1 Coverage of universal infant vaccination of hepatitis B vaccines in different regions of China

Region and year	Birth cohort (million)	Vaccine coverage (%)	
		HepB3	TBD
Western			
1992–2002	65.4	17–68	14–49
2003–2009	31.2	73–89	57–85
1992–2009 total	96.6	17–89	14–85
Middle			
1992–2002	16.3	29–80	12–60
2003–2009	8.4	83–94	69–94
1992–2009 total	24.8	29–94	12–94

Data were estimated by the GAVI China project (3,31,32). HepB3, three-dose series completion; TBD, timely birth dose.

Impact of vaccination on HBV prevalence in the general population

Over the past 30 years, the effective implementation of vaccination has resulted in a substantial decrease of hepatitis B chronic carriage, in disease burden, and in hepatitis B-related morbidity and mortality (21,33-36). Universal vaccination has led to a 70–90% decrease in chronic HBV carrier rates worldwide (34), a 60% reduction in the incidence of hepatocellular carcinoma (HCC) in Taiwan (37,38). The remarkable efficacy of HBV

vaccination program was best demonstrated in Taiwan, where HBsAg carrier rates decreased from 8.2% to 0.9% in the populations 26–30 years old and ≤25 years born before or after the universal program was launched on July 1, 1984 (21). In other areas with high HBV prevalence, chronic HBV carriers also dropped significantly after implementation of vaccination programs during the past 2 decades. For instance, the HBsAg positivity went from 8% to 3.7% in the general population and 0.44% in teenagers in Korea (39), from >8% to 2.7% in Vietnamese children (40), and from 13.4% to 0.9% in Afragola of Southern Italy (41).

In China, approximately 2% of chronic HBV carriers reduction was observed from 9.5% to 7.2% in the general population aged 1–59 years between 1992 and 2006 since universal vaccination program was implemented nationwide (2). However, 75% to 90% reduction of HBsAg-positivity was achieved in children, whose HBsAg prevalence was reduced to 2.3% or ≤1% in children aged 5–14 or <5 years, respectively (2). HBsAg prevalence between the vaccinated and unvaccinated populations is presented in Figure 2 according to distribution in various age groups reported in 2006 (2,42). It shows the progressive decrease of chronic HBV prevalence in vaccinated Chinese population since universal infant hepatitis B immunization was launched in 1992 (43). A number of surveys also demonstrated that the great impact of hepatitis

B vaccination successfully prevented the vast majority of incident chronic HBV infection and disease over the past 20 years among Chinese people in all regions across the country (3,25,29,36,44-47).

Impact of vaccination on vertical transmission of HBV from HBsAg positive mothers to infants

In Taiwan, approximately 40% of infants perinatally exposed to HBV infection from HBsAg positive but HBeAg negative (HBsAg+/HBeAg-) mothers in the pre-vaccination era without any clinical intervention became HBV chronic carriers (48). Moreover, the incidence of HBV vertical transmission was as high as 70% to 90% in infants born to mothers carrying both HBsAg and HBeAg (HBsAg+/HBeAg+) (48,49). Immunization with Hepatitis B vaccine alone or plus HBIG of the exposed newborns born to HBsAg+/HBeAg+ or HBsAg+/HBeAg- mothers could prevent 75% to 95% of chronic HBV infection (50,51). A study was carried out in 2,356 pairs of maternally exposed Taiwanese children age 6 months to 10 years between 2008 and 2009, indicating that active/passive immunization prevented 90.7% and 99.77% HBV transmission in children and overall 97.58% children were prevented from HBV vertical infection (52). Similarly, HBV vaccine efficacy was observed in a study of 1,202 pairs of Chinese infants born to HBsAg+ mothers between 2008 and 2013, which showed 100% protection for infants born to HBsAg+/HBeAg- mothers, but 90.3% protection for infants born to HBsAg+/HBeAg+ mothers whose HBV-DNA load was less than 10^6 copies/mL, and 96.7% vaccination efficacy in general (53).

HBV infection in the vaccinated Chinese populations

As above described, the successful introduction of universal infant hepatitis B vaccination programs had a major impact on the prevalence of HBsAg in the Chinese population. However, a small proportion of vaccinated individuals were nevertheless infected with HBV through vertical or horizontal transmission in children, adolescents and adults (2,9,21,25,54,55).

Distribution of HBV serological markers in vaccinated population

The pattern of serological markers HBsAg, anti-HBc and anti-HBs in the vaccinated population has been considerably

modified since the implementation of systematic HBV vaccination program. In 1,734 new university freshmen aged around 18 years, who were vaccinated with the plasma-derived hepatitis B vaccine at birth in Taiwan, HBV markers were detected during the period September 2006 to October 2008 (54). The prevalence of serologic markers was 2.4% for HBsAg+, 5.2% (90/1734) for anti-HBc+ and 38.2% (662/1735) for anti-HBs+, respectively (*Table 2*). The rate of HBV-naïve subjects was 58.2%. Among HBsAg+ subjects, 1.8% were anti-HBc+ while 0.6% were anti-HBc-. Among HBsAg- subjects, 2.2% were positive for both anti-HBc+ and anti-HBs+, but 1.2% were anti-HBc only. In Qingdao, Northern China, young adults with neonatal HBV immunization were enrolled for an HBV serologic survey at age 19–21 years between 2007 and 2009 (55). Of 2,919 individuals, 2.1% were HBsAg+ and 43.9% (1281/2919) were anti-HBs+, while 14.6% (426/2919) were anti-HBc+, 4.3% of them were also anti-HBs+ but 8.3% were anti-HBc+ only. In this population, 45.8% were negative for all HBV markers. Another representative study was conducted in Shenzhen, Southern China, of 1,494 blood samples were collected between 2012 and 2013 from presumably HBV vaccinated blood donors aged 18–21 years (9). The donors were assumed to have received the systematic hepatitis B vaccines since January 1992 with the first injection at birth. The distribution of HBV serologic markers was 3.4% for HBsAg+, 65.8% (983/1494) for anti-HBs+, and 21.6% (322/1494) for anti-HBc+ including 16.5% anti-HBs+ and 1.7% anti-HBc+ only (*Table 2*). Approximately 31% (461/1494) of these young donors did not carry detectable anti-HBs, and 29% did not have any HBV serologic markers 18 to 21 years after vaccination. In the three regions of Taiwan, Qingdao and Shenzhen, an overall prevalence of HBsAg, anti-HBs, anti-HBc and no markers was 2.5%, 47.6%, 13.7% and 45.3%, respectively (*Table 2*).

The prevalence of HBV serologic markers presented in the Taiwanese and Chinese populations according to age groups of young individuals (2,9,21,47) indicated that the prevalence of HBsAg and anti-HBc increased with age, while the frequency of vaccinees with low anti-HBs and no markers progressively declined (*Figure 3A,B*). The anti-HBs rate declined to the low level in the vaccinated individuals between ages 11 and 17 years, but the anti-HBs prevalence rebounded after age 18 in likely relation with boosting after HBV new contact suggested by the occurrence of HBsAg and anti-HBc positivity, followed by secondary decrease after age 25.

Table 2 Distribution of HBV serologic markers in vaccinated Chinese populations from Taiwan and mainland China

Vaccinated population	Taiwan	Qingdao	Shenzhen	Overall
Age (years)	18	19–21	18–21	18–21
Sample collection time	2006–2008	2007–2009	2012–2013	2006–2013
Sample number	1,734	2,919	1,494	6,147
Serologic marker				
HBsAg+ [number (%)]	41 (2.4)	60 (2.1)	50 (3.4)	151 (2.5)
Anti-HBc+	30 (1.8)	60 (2.1)	50 (3.4)	140 (2.3)
Anti-HBc–	11 (0.6)	0	0	11 (0.2)
HBsAg– [number (%)]				
Anti-HBs+/anti-HBc+	39 (2.2)	124 (4.3)	247 (16.5)	410 (6.7)
Anti-HBs+/anti-HBc–	623 (35.9)	1,157 (39.6)	736 (49.3)	2,516 (40.9)
Anti-HBs–/anti-HBc+	21 (1.2)	242 (8.3)	25 (1.7)	288 (4.7)
Anti-HBs–/anti-HBc–	1,010 (58.2)	1,336 (45.8)	436 (29.2)	2,782 (45.3)

Data were obtained from previous studies (9,54,55). HBV, hepatitis B virus.

Breakthrough HBV infection in vaccinated individuals

In circumstances of universal infant vaccination, approximately 3% infants were vertically infected by HBsAg positive mothers, more frequently by HBeAg positive and high HBV-DNA load mothers (53,56). Among 432 HBsAg+/HBeAg+ mothers, 9.3% (40/432) infants presented with vertically transmitted HBV breakthrough infection, whose mothers all carried serum HBV-DNA load $\geq 6 \log_{10}$ copies/mL (53). For the infants born to mothers with HBV DNA loads < 6 , 6–6.99, 7–7.99 or $\geq 8 \log_{10}$ copies/mL, the infant vertical infection rates were 0%, 3.2% (3/95), 6.7% (19/282) and 7.6% (5/66), respectively ($P < 0.001$) (56).

HBV mutations occur frequently under immune pressure, which lead to HBV mutant breakthrough infection in vaccinated children and adults by escaping from the protective immunity provided by vaccination (57–59). Among vaccinated individuals with breakthrough HBV infection, sG145R and sT126A/S mutations are prominent and account for 48% of the detected mutants in Taiwan (57). Several B- and T-cell epitopes related to HBV mutants, such as sS45T/A, sN131T, sI194V and sS207N, were detected in vaccinated children, that might escape from immune response and cause HBV infection (58). In China, the mutations in the large HBV surface protein (LHBs) sequences of HBV variants were analyzed between 1992 and 2005 to estimate the impact of universal HBV vaccination program on circulating HBV strains after

13 years (59). A total of 116 children and 112 adults of HBsAg+ samples were collected from the 2005 national survey. For comparison with HBV variants before universal immunization was initiated, samples from 157 children and 78 adults HBsAg+ were also collected from the 1992 national survey prior to mandatory vaccination. The prevalence of LHBs mutants was compared between the 1992 and 2005 surveys in child and adult populations. The prevalence of mutations in the S region of HBV mutants increased from 6.5% to 14.8% in vaccinated children, as well as significantly increasing in immunized adults after implementation of the universal infant HBV vaccination program nationwide. The G145R mutant occurred most frequently, but the frequency of this mutation was not significantly different between the vaccinated and non-vaccinated populations.

OBI in vaccinated population

Beyond breakthrough infection, a small proportion of individuals from the vaccinated population have been found HBV DNA positive but HBsAg negative (HBV DNA+/HBsAg–), meeting the definition of OBI (60). A few publications reported the prevalence of OBIs in HBV vaccinated children and adults in the Chinese population (9,55,61–63). In one such study, 186 HBV vaccinated infants born to HBsAg-positive mothers in northwestern

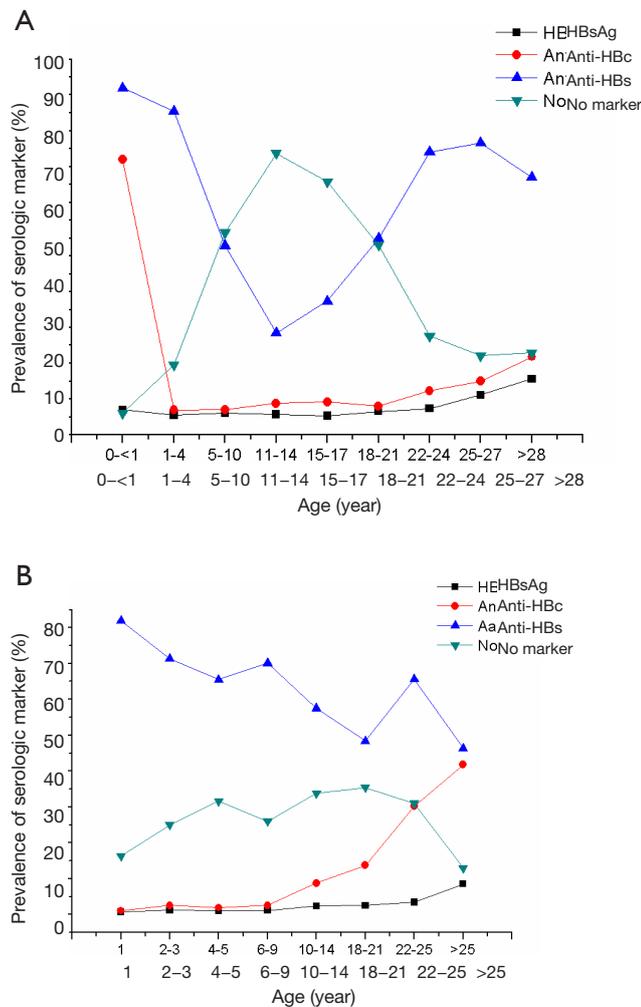


Figure 3 Distribution of HBV serologic markers in vaccinated Chinese population. (A) The survey was conducted in Taiwan (21); (B) the survey was conducted in Shandong Northern China (2,947). HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen.

China were examined for serologic markers and HBV DNA. Among them, 1.6% (3/186) infants were HBsAg positive, and 4.9% (9/183) infants with HBsAg-negative were identified as OBI (62). Six of nine OBI infants were positive for anti-HBs <100 IU/L and only one OBI infant was positive for anti-HBc with HBV DNA load of 3×10^7 IU/mL, who was born to an HBeAg positive mother with 4.0×10^8 IU/mL viral load. Three OBI strains were genotype C, and four recombinants genotype C/D contain an escape mutation s143L. A recent publication reported a population-based study of children and adolescents in Taiwan. The occurrence of OBI was analyzed for the impact

of universal HBV infant immunization between vaccinated and un-vaccinated cohorts (63). Among anti-HBc negative subjects, the frequency of OBI was lower in the vaccinated than in the unvaccinated cohort (0/392 vs. 4/218, $P=0.007$), while the frequency of OBI was higher in vaccinated than unvaccinated anti-HBc positive subjects [16/334 (4.8%) vs. 3/181 (1.7%)] although the difference was not statistically significant ($P=0.072$). Among both anti-HBs and anti-HBc positive subjects, OBI frequency was higher in the vaccinated than in the unvaccinated groups [13/233 (5.6%) vs. 3/170 (1.8%), $P=0.025$]. In the vaccinated cohort, OBI frequency was higher in anti-HBc-positive subjects than in anti-HBc-negative subjects (16/334 vs. 0/392, $P<0.001$). OBI carriers had lower viral load ($P<0.001$) and a higher mutation rate in the S region than HBsAg positive subjects. This study concluded that breakthrough HBV infections in vaccinated subjects might be associated with increased frequency of OBI compared to natural infections in unvaccinated subjects.

A total of 2,028 blood donors aged 18–25 years who had been systematically vaccinated at birth were recruited in a study at Shenzhen blood center in Southern China conducted between 2012 and 2013 (9). Twenty-four blood samples from anti-HBc+ donors were identified carrying HBV DNA+/HBsAg- with low viral load (25 ± 22 IU/mL), in which 93.3% (14/15) strains were genotype B and 6.7% (1/15) genotype C. The follow-up of those 24 donors allowed to identify four recent infections, 17 OBIs and 3 primary OBIs. Seventy-five percent (18/24) HBV DNA+/HBsAg- donors carried anti-HBs, while half of them (9 donors) had an anti-HBs level below 100 IU/L, 8 donors between 890 and 200 IU/L, and only 1 donor over 1,000 IU/L, respectively. Among the vaccinated blood donors, the prevalence of anti-HBc, mostly associated with anti-HBs, increased from 10.7% at age 18% to 31.5% at age 25. The level of anti-HBs was significantly higher in anti-HBc positive donors than in anti-HBs only donors ($P<0.0001$), which suggested that recent contact with HBV boosted the anti-HBs response (9). The most likely origin of contact/infection was through sexual activity with HBsAg+ partners, although evidence of such etiology was only preliminary (9,10).

Potential causes of HBV infection in vaccinated population

None or low immune responders to HBV vaccine

In the above-described hepatitis B in 18–21 years old vaccinated Chinese population, approximately 45% of

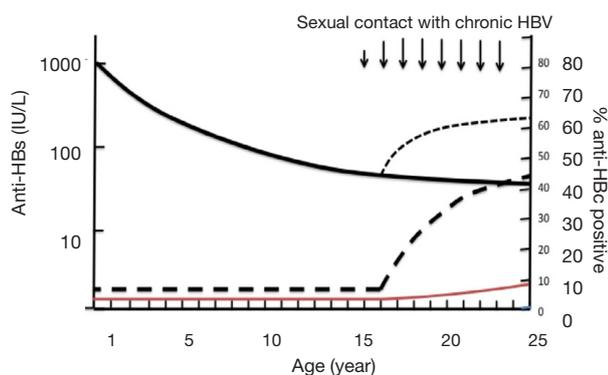


Figure 4 Hypothetical summary of HBV infection in vaccinated population. The continuous black line represents the decline of vaccine-related anti-HBs level. The branching thin dotted line indicates the anti-HBs response after contact with HBV. The large dotted line indicates the percentage of HBV infected (anti-HBc positive) vaccinated blood donors, initially through maternal exposure, subsequently through sexual exposure. The red line indicates the percentage of DNA positive anti-HBc positive blood donors.

vaccinees did not carry HBV sero-markers due to the relatively rapid decline of vaccine-related antibodies (Table 2). Anti-HBs levels had been associated with protective efficacy in a vaccinated Gambian population, indicating that non-responders (anti-HBs <10 IU/L) remained susceptible to HBV and low-responders (anti-HBs <100 IU/L) were at high risk of HBV breakthrough or chronic infection (64,65). Previous vaccine trials showed up to 99% seroprotection rate in children or female adolescents (34,66). However, in adults 3–7% remained non-responders unprotected by anti-HBs <10 IU/L and 30% were low-responders 4 weeks after the last dose of a yeast-derived vaccine injection (66,67). In Shenzhen, Southern China, about 29% donors had no HBV markers who might include a small portion of non-responders (67) and a majority of vaccinees who had lost detectable anti-HBs while 40% low-responders were found in 1,494 presumably vaccinated blood donors aged 18–21 years (9). Those vaccinees with anti-HBs <100 IU/L might be vertically or horizontally associated with breakthrough or OBI as described previously (9,53,59,63). In a different study, American students with an anti-HBs level of 1 to 9 IU/L were more likely to respond to the challenge dose than those with a baseline level of 0 IU/L, which suggested that a long-term immune memory is sustained even in the absence of any detectable anti-HBs (68).

HBV genotype A2 vaccine efficacy

Current hepatitis B vaccines are derived from HBV genotype A2 clones expressing the S protein in yeast. Evidence was obtained by a study from the American red-cross that 6 of 9 HBsAg negative HBV DNA positive blood donors ranging in age between 17 and 44 years had been vaccinated (10). Five of these donors had anti-HBs <100 IU/L and had been infected with non-A2 (genotype B, C, F or D) or mixed HBV strains, while one anti-HBs negative donor was infected with HBV genotype A2 strain. This data suggested that the immunoprophylaxis efficacy of genotype A2 hepatitis B vaccine was not fully protective for individuals exposed to non-A2 strains such as genotype B, C or D.

Sexual contact with partner who carry high HBV load

Besides vertical transmission from mothers carrying both HBsAg and HBeAg, HBV infection occurs in some vaccinated persons mostly with anti-HBs <100 IU/L or undetectable through sexual contacts with infected partners carrying high viral load HBV. It is likely that these infections are sub-clinical and do not lead to chronic infection (9,10,46,69). In those subjects, the most frequently circulating HBV strains are genotypes B, C, D or E but not A2. Persons infected with genotype C or B tend to maintain high viral load long-term correlating with high risk of sexual or vertical transmission (10,53,56), but only 20% of genotype E infected adults keep a viral load >10⁴ (70). The evidence was further supported by the above described vaccinated American blood donors who were infected by their sexual partners carrying non-A2 HBV DNA load >1.8×10⁶ (10). In the vaccinated Chinese blood donor population aged 18–25 years from Shenzhen blood center, approximately 60% of them were either seronegative or carrying anti-HBs <100 IU/L (9,71). Among vaccinated blood donors, the increasing proportion of anti-HBc with age is consistent with an increasing cumulative risk of HBV exposure through sexual activity (9,71), suggesting that those with low level immune response were poorly protected from contact with high HBV DNA load (10,72). To summarize the reported data, Figure 4 was constructed, which suggests that, in the vaccinated population, a small number of individuals become OBI carriers, mostly from highly infectious mothers (9,55,62,63). Later on, while they grow in age, anti-HBs levels decline to either undetectable or below 100 IU/L. When those vaccinees reaching low

protective immunity are exposed to high viral load from HBV chronic carriers either vertically or sexually, an anamnestic response of anti-HBs is triggered, together with the occurrence of HBV DNA, occasionally HBsAg and the development of anti-HBc in 3–4% of cases in the vaccinated Chinese population.

Conclusions

The universal infant hepatitis B vaccination program developed in China has successfully prevented more than 90% HBV chronic infection. However, the anti-HBs <10 IU/L of non-responders and the decline of anti-HBs of vaccinees to levels below 100 IU/L appear at risk of breakthrough or OBIs. Among the vaccinated Chinese population aged between 18 and 25 years approximately 3–4% become HBV DNA carriers, after viral exposure through either vertical or horizontal or sexual contact with high viral load HBV. A new general vaccine developed from genotype B or C strains might be helpful to further reduce HBV prevalence in China in accordance with the limited data currently available in the literature. From a transfusion point of view, as previously suggested, an HBV vaccine boost between age 15 and 17 years (prior to starting sexual activity) might prevent non-clinical infections that may or may not be infectious by transfusion. Boosting at age 18–24 years would trigger an anamnestic response reaching >100 IU/L sero-protective anti-HBs levels in young adults such as college students (28,68,72). The implementation of a systematic free hepatitis B boosting vaccination program for non- and low-responders of children and adolescents can be recommended in China, which might be cost-saving and providing health benefits for the Chinese people.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aob.2017.04.02>). YF serves as the Editor-in-Chief of *Annals of Blood*. JPA serves as an unpaid editorial

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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