


REVIEW

 OPEN ACCESS



Revaccination against hepatitis B in late teenagers who received vaccination during infancy: Yes or no?

Hong Zhao^a and Yi-Hua Zhou ^b

^aDepartment of Infectious Diseases, The Second Hospital of Nanjing, The Second Affiliated Hospital of Southeast University, Nanjing, Jiangsu, China;

^bDepartments of Laboratory Medicine and Infectious Diseases, Nanjing Drum Tower Hospital and Jiangsu Key Laboratory for Molecular Medicine, Nanjing University Medical School, Nanjing, Jiangsu, China

ABSTRACT

The significance of vaccination against hepatitis B during infancy is recognized worldwide, however, whether booster or revaccination after a period of time following the primary vaccination is required remains controversial. Recently, cross-sectional epidemiological surveys found that HBsAg prevalence in subjects born after the implementation of mass vaccination was increased with age, which was attributed to waning of anti-HBs over time. However, comprehensive analysis of the closely related cross-sectional surveys showed that the age-specific increased HBsAg prevalence was more likely associated with the carry-over of the infection occurred in early life, likely due to imperfect coverage of hepatitis B vaccination at the beginning of its introduction. Latest studies showed that booster response could be observed in the majority of individuals vaccinated 30 years ago. Moreover, confirmed breakthrough HBV infection with severe consequences in successfully vaccinated individuals is extremely rare. Thus far no compelling evidence has been acquired to support booster vaccination in adolescence. The uncertainty regarding the duration of protection of hepatitis B vaccination, especially beyond 30 years after the primary vaccination, merits a systematically designed study to follow the same cohort of participants longitudinally, which differs from the cross-sectional studies reported previously, can hopefully offer more direct evidence to help us to determine whether revaccination of hepatitis B vaccine is necessary.

ARTICLE HISTORY

Received 15 August 2017
Revised 2 October 2017
Accepted 23 October 2017

KEYWORDS

anti-HBs; booster;
breakthrough infection;
hepatitis B vaccine

Introduction



Vaccination is the most effective way to prevent hepatitis B virus (HBV) infection. By the end of 2015, 185 countries had included hepatitis B vaccination in their national Expanded Program on Immunization (EPI).¹ All infants in these countries can receive a primary course of vaccination, including three serial doses at 0, 1, and 6 months after birth. In other countries where hepatitis B vaccination has not been incorporated into the EPI, infants of mothers with positive hepatitis B surface antigen (HBsAg) are usually administered with hepatitis B vaccine either alone or in combination with hepatitis B immunoglobulin (HBIG). However, whether revaccination is needed after a known period of time following the primary vaccination remains controversial, although the issue has been around ever since the vaccine was launched some 30 years ago.²

Historically, based on the assumption that an anti-HBs level ≥ 10 mIU/ml is essential for protection, and the facts that antibody responses to hepatitis B vaccine is heterogeneous and vaccine-induced anti-HBs levels may be progressively decreased, it was suggested to offer a booster dose to vaccinees at 5–6 years after the completion of the primary vaccination course.³ However, as numerous long-term follow-up studies demonstrated brisk anamnestic immune responses to a booster dose, and clinical

hepatitis B or chronic infections were rarely reported in vaccinees with protective responses initially, the recommendation of revaccination has been in question. A European Consensus in 2000 proposed that routine booster vaccination is not required in the immunocompetent vaccinees at 15 years after the primary vaccination.⁴

As time goes on, two to three decades have passed since the implementation of universal vaccination against hepatitis B. Some scholars considered that booster vaccination after adolescence is required in individuals vaccinated in infancy or early childhood.^{5–10} However, whether the evidence is conceivable remains in debates.^{11,12}

To summarize and analyze the most recent publications and provide an updated view on the topic, we searched PubMed for all articles published until July 2017 using the key words “hepatitis B revaccination” or “hepatitis B vaccine booster” respectively. A total of 1028 and 846 articles in any language were identified from the two searches, of which articles only in English were further screened. Original articles on revaccination against hepatitis B were further analyzed. Since no randomized clinical trials on this topic has yet been conducted,¹³ we analyzed all relevant cross-sectional or cohort studies,

CONTACT Yi-Hua Zhou, MD, PhD  zgr03summer@126.com  Departments of Laboratory Medicine and Infectious Diseases, Nanjing Drum Tower Hospital, 321 Zhong Shan Road, Nanjing 210008, China.

© 2018 Hong Zhao and Yi-Hua Zhou. Published with license by Taylor & Francis

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

particularly those that were long-term (>15 years) follow-ups. The studies with short-term (<5 years) follow-up after primary vaccination, involving subjects with mentally retardation diseases or immunodeficiencies such as AIDS/HIV positive or involving subjects vaccinated with a combination of other vaccines such hepatitis A, were excluded from this analysis.

Postulated premise for booster vaccination against hepatitis B

Decline or loss of anti-HBs

Although some scholars still considered that decrease of anti-HBs titers below the seroprotective level (≥ 10 mIU/ml) or loss of anti-HBs requires the booster,¹⁰ it is generally accepted that, in immunocompetent subjects including the “high-risk” health care workers, the decline or loss of anti-HBs is not the indication for booster, because it has been demonstrated that humoral immune memory can persist long-term at least 28–30 years.^{14–16} Moreover, the cellular immune memories, regardless of anti-HBs titers, may maintain in subjects vaccinated during childhood at least 32 years.¹⁷ The long incubation period of HBV infection leaves the immune system enough time to mount anamnestic response to HBsAg to protect against the clinical disease or chronic infection.

Loss of humoral immune memory

The brisk anti-HBs response, increased from <10 mIU/ml to ≥ 10 mIU/ml or four-fold elevation within one month following a booster dose vaccine, is generally considered to have humoral immune memory, whereas the circumstance that anti-HBs level does not reach to ≥ 10 mIU/ml after booster may be considered to have lost humoral immune memory.

Based on above criterion, Jan et al reported that as high as 24.4% of the 18–23 years old subjects with negative anti-HBs, who had been vaccinated during infancy, were categorized as having lost humoral immune memory and more than 90% subjects produced protective antibody levels after two booster doses at one month interval, and thus proposed that at least two doses are required in young adults vaccinated during infancy.¹⁸ However, the clinical implication of the loss of humoral immune memory in these subjects is obscure because of the two issues. One is that the anti-HBs levels in the subjects after primary vaccination were unknown, leaving the possibility of non- and poor-responders not excluded. The immune response to booster vaccination should be observed in those who had developed protective anti-HBs levels after the primary vaccination as McMahon et al did.¹⁹ Second, it was not clear the anti-HBs negativity means totally absence of anti-HBs or <10 mIU/ml, since the post-booster response depends upon the pre-existing anti-HBs levels.^{19,20} It was reported that >97% of vaccinees developed protective anti-HBs levels following one booster dose in young adults vaccinated 18–20 years ago.^{21–23} In the healthcare workers vaccinated as adults, a long-term follow-up study up to 28 years did not define any individual with positive HBsAg or HBV DNA, and almost all subjects had a rapid anamnestic anti-HBs response to a single booster dose.¹⁵ These results suggest that the loss of humoral immune memory is not common. Even if the

loss of immune memory based on the above criterion is true, the relationship between the assumed loss of humoral immune memory and the loss of immunity to hepatitis B has not been substantiated. More compelling evidence on the critical endpoint, protection against breakthrough infection with severe outcomes, should be acquired.²⁴

Anti-HBc seroconversion

Although it is generally considered that anti-HBc seroconversion, without symptoms or persistence of HBsAg, is just to indicate sub-clinical transient infection and needs no booster,^{24,25} some investigators think that anti-HBc seroconversion may be an indication for booster due to the occurrence of occult HBV infection in anti-HBc-positive individuals who received neonatal vaccination.²⁶ In fact, the occult HBV infection in vaccinees with positive anti-HBc is extremely rare,^{27,28} and the reported high prevalence of occult infection²⁹ was highly possibly caused by the occult cross-contamination.³⁰ Therefore, anti-HBc seroconversion alone in vaccinees should not be the indication for booster.

Breakthrough clinical or chronic HBV infection

Undoubtedly, breakthrough infection with severe consequences, including acute hepatitis B or chronic infection, in vaccine recipients who had produced protective levels of anti-HBs is the indication for booster vaccination.^{24,25} Then the question is who may develop severe breakthrough infection following to HBV exposure after a successful primary vaccination. Individuals with protective anti-HBs levels are almost impossible to be infected with wild-type HBV with severe outcomes, whereas vaccinees with undetectable level of anti-HBs or <10 mIU/ml are assumed to have relatively higher chance of being infected. Thus, the vaccine recipients with anti-HBs <10 mIU/ml appear to be the candidates for booster vaccination. Here comes a paradoxical situation. Aforementioned decline or loss of anti-HBs is not an indication for booster because loss of anti-HBs does not indicate loss of immunity to HBV. The key point to solve this paradox is to clarify whether and how frequency the severe breakthrough infection of wild type HBV may occur in successfully vaccinated individuals.

Age-specific increased HBsAg prevalence in persons born after the initiation of mass vaccination against hepatitis B

Recently, several seroepidemiological surveys showed that the HBsAg prevalence in subjects born after the implementation of mass vaccination was increased with age, which was explained by the loss of vaccine-induced anti-HBs in older vaccinees.^{6,7,31} Thus, it was considered that these results provided the supporting evidence for booster. However, such results should be interpreted cautiously.

Is the age-specific increased HBsAg prevalence mainly associated with the loss of immunity to HBV?

In Hong Kong, a survey conducted 2001–2009, including a total of 2688 first-year college students, showed that the overall

HBsAg prevalence was 2.9% and that in those born before (1983) the availability of hepatitis B vaccine, during the period (1983–1988) of vaccination in selective individuals, and after (1988) the introduction of universal vaccination was 4.2%, 3.0%, and 1.4%, respectively.³¹ The detailed results are summarized in Table 1. Table 1 also shows the age-specific increased HBsAg prevalence in 14–19 years old teenage mothers conducted 1998–2008.⁶ The age-related increased HBsAg prevalence was considered to be associated with the waning of anti-HBs over time, which led to reduced protection against horizontal transmission of HBV, and the requirement of booster in adolescents vaccinated in infancy was proposed.⁵ However, these data appeared to be insufficient to support the assumption because of the following reasons.

First, the vaccination in the participants was just based on their birth dates, but not verified by vaccination card or other convincing documents such as the presence of anti-HBs. They were born just around the beginning of vaccination, at which the vaccine coverage was suboptimal. In Taiwan, the vaccine coverage of the first, second, third, and fourth dose in infants of 55620 HBsAg positive mothers during the first 15 months of vaccination program started in July 1984 was 88%, 86%, 84%, and 71%, respectively.³² This is in agreement with the fact that 18 (12%) of 150 subjects, born after 1984 and before 1992, enrolled in another study could not be confirmed with complete neonatal vaccination,¹⁸ although non-confirmation does not necessarily indicate no vaccination. By the end of 2002, the overall vaccine coverage among 5,188,929 neonates in Taiwan increased to 96.6%, 95.2%, and 92.8% for the first, second, and third dose (0-, 1-, and 6-month schedule), respectively.³³ Therefore, the individuals born right after the initiation of

vaccination program might be not all vaccinated. It was very likely that a considerable proportion of them was actually not vaccinated or received incomplete vaccination. In Tajikistan, the age-related increased HBsAg prevalence was also observed, with 0.4%, 2.1%, 3.5%, and 6.8% in 1–6, 7–8, 9–14, and 15–24 years old subjects respectively, but the difference was attributed to the different vaccine coverage, with $\geq 80\%$, $< 80\%$, not targeted for vaccination, and completely not vaccinated in above four groups respectively.³⁴

Second, due to unknown status of HBV markers during their infancy or early childhood, it was impossible to differentiate whether the HBsAg positivity in adolescents or young adults was caused by carry-over from early life or by the novel infection after childhood. A seroepidemiologic survey in Hong Kong adolescents (11–20 years old) conducted during 1996–1997 may provide helpful clues for the differentiation.³⁵ In this report, the HBsAg positive rates in female students were 2.2%, 4.8%, 3.5%, and 5.0% at the age of 11–12, 13, 14, and 15 years, respectively. The 11–13 years old students in 1996–1997 were born during 1983–1986, just the period of selective vaccination, and the 14–15 years old students in 1996–1997 were born before 1983. The calculated HBsAg prevalence in the students born during the period of selective vaccination and of no vaccine available was 3.1% and 4.2%, respectively,³⁵ which were almost same as the prevalence of 3.0% and 4.2% in the first-year college students born during 1983–1988 and before 1983 in Suen et al's report.³¹ As numerous studies demonstrated that successfully vaccinated infants can barely become chronic carriers during childhood,^{36–38} it was very likely that the higher HBsAg prevalence in older students³¹ or old teenage mothers⁶ was related with the infection occurred during infancy or the early life, rather than occurred after childhood.

Third, the status of anti-HBc, a critical marker for current or resolved HBV infection, was lacking in the relevant reports,^{6,31,39} which made the interpretation of the acquired data difficult. The chronicity of HBV infection depends mainly upon the age. More than 90% of the infection occurred after 10 years old will be self-resolved and only fewer than 10% may become chronic carriers. Thus, if the increased HBsAg prevalence in the old pregnant women or college students were really caused by the novel infection after late childhood due to the loss of protective anti-HBs, the proportion of anti-HBc positivity should be much higher than that in young subjects with a lower HBsAg prevalence. Therefore, the anti-HBc prevalence is very helpful to determine the infection occurred in infancy/early childhood or in late childhood/adolescence. Unfortunately, the prevalence of anti-HBc in these subjects was not investigated. Thus, future studies should include not only the positive rates of HBsAg and anti-HBs but the anti-HBc seroprevalence as well.

Fourth, the HBsAg prevalence in Hong Kong is progressively reducing since the implementation of universal vaccination. Dr. Lao considered that the current HBV infection rate among pregnant women in Hong Kong appeared even worse than the situation three decades ago before the introduction of the vaccination program,⁵ because they found that, among the pregnant women at 25 years of age, those born in or after 1984 (supposedly vaccinated) had relatively higher HBsAg positive rate (8.4%) than women around the same age born before 1984

Table 1. Age-specific increased HBsAg prevalence reported in Hong Kong.*

1st year college students (reference 31)			
Born 1983–1988			
Age (years)	Subject No	HBsAg+ No (%)	P value
≤ 18	324	3 (0.9)	< 0.001
19	854	21 (2.5)	
20	262	12 (4.6)	
≥ 21	82	8 (9.8)	
≥ 21 -year-old, birth date			
1982	38	5 (13.2)	N/A [§]
1983	33	4 (12.1)	
1985	16	2 (12.5)	
1986	9	1 (11.1)	
Age (years) of teenage mothers (reference 6)			
Born before and after 1984			
≤ 16	118	3 (2.5)	0.004
17	223	6 (2.7)	
18	421	37 (8.8)	
19	724	58 (8.0)	
Born after 1984			
≤ 16	N/A	N/A (1.2)	0.008
17	N/A	N/A (1.5)	
18	N/A	N/A (7.1)	
19	N/A	N/A (8.3)	

*Hepatitis B vaccine was not available for infants born before 1983, but they received catch-up vaccination in 1998. Selective vaccination program (hepatitis B immunoglobulin at birth and a series of three doses vaccine) was given to infants born to HBsAg-positive mothers 1983–1988. Since November 1988, universal vaccination has been implemented to cover all neonates.

[§]Detailed results were not available in the original articles.

(supposedly not vaccinated; 7.8%).³⁹ However, as the universal vaccination program in Hong Kong was started from November 1988, those born in 1984 and before November 1988 were not all vaccinated. The data from the Department of Health of Hong Kong showed that, after the universal vaccination, the reported number of acute hepatitis B decreased steadily from 250 cases in 1988 to 41 cases in 2014, the HBsAg seroprevalence in antenatal pregnant women and pre-marital/pre-pregnancy screening clients was respectively reduced from 11.3% and 9.6% in 1990 to 6.2% and 5.5% in 2014.⁴⁰ Therefore, it may be expected that the pregnant women at 25 years age in Hong Kong born after November 1988 should have much lower HBsAg prevalence.

The experience in Taiwan may help clarify the reasons for age-specific HBsAg prevalence

Taiwan and Hong Kong shared similar hepatitis B vaccination programs. Taiwan started the program from July 1984, with first two years (July 1984–June 1986) selectively in neonates of HBsAg-positive mothers and then in all newborn infants since July 1986.³³ During 2000–2006, Lin et al tested HBV serologic markers in 6184 freshmen students (~15 years old, 97.2% female) from a university.⁴¹ Table 2 shows that the HBsAg prevalence in subjects born earlier was higher than that in those born later. Similarly, two other surveys^{42,43} involving 15 years female freshmen revealed that the HBsAg prevalence in subjects born in earlier time was relatively higher (Table 2). Because they were tested all at the age of ~15 years, the difference of HBsAg prevalence was unlikely due to the loss of anti-HBs over the time. Had these students been tested at same time, the higher HBsAg prevalence in the students born earlier would have been attributed to the more significant decline in anti-HBs titers because they were older than those born later. Study of the first graders (6 or 7–8 years old) in elementary schools also displayed that, when they were tested for HBsAg at similar age, 1.7% of the children born just one year after the initiation of the universal vaccination were HBsAg positive, whereas only 0.78% of those born 11–12 years after the initiation of universal vaccination were positive (Table 2). Together,

these results indicate that the protective efficiency of the vaccination program at the beginning was somewhat less efficient.

Another cross-sectional investigation conducted in 2009,⁴⁶ together with four other similar surveys at different time points, provided more compelling evidence against the association of age-specific increased prevalence with wane of anti-HBs. The HBsAg prevalence in 2857 participants appeared to be age specific, 0.6% and 2.1% in subjects at the ages of <1–19 and 20–24 years respectively.⁴⁶ However, compared with the data in four previous surveys conducted by the same authors, the HBsAg prevalence was not increased with age by the birth cohorts: among the subjects born in 1987–1988, the HBsAg positive rate was 1.46%, 0.81%, 0, 1.74%, and 1.91% in 1989, 1994, 1999, 2004, and 2009, respectively ($P = 0.07$); in those born in 1989–1993, the rate was 0.35%, 1.54, 0.81%, and 1.01% in 1994, 1999, 2004, and 2009, respectively ($P = 0.19$).⁴⁶ Thus, better designed cross-sectional studies, together with the previously published results, may also provide reliable evidence to clarify whether severe breakthrough infection really occurs in adults with successfully vaccinated during infancy.

What causes the increased HBsAg prevalence in old adolescents or young adults born in the vaccination era?

Evidently, individuals born right after the start of mass vaccination have higher HBsAg positive rates. The less protective efficiency is very likely due to the suboptimal implementation of vaccination, rather than due to the anti-HBs decline. Actually, at the beginning of plasma-derived vaccine available, physicians' unawareness of the relevant knowledge and suboptimal compliance with standard recommendations, parents' fear of potential adverse effects (then having no abundant safety data), preterm birth, neonate illness, and other factors impeded the use of the vaccine. Even in middle 1990s, 18.4% of California pediatricians did not agree with and did not plan to implement the universal vaccination,⁴⁷ 21% of the physicians who provide obstetric services in San Francisco did not believe that hepatitis B vaccine should be administered to all infants at birth,⁴⁸ and only 65% of the hospitals in Wisconsin routinely offered hepa-

Table 2. HBsAg prevalence in vaccinees vaccinated in different years in Taiwan.

Birth date	Years after vaccination program ^a	Age (years)	Test year	Subject No	HBsAg+ No (%)	Ref
9/1984–8/1985	1 st year SVP	15	2000	974	48 (4.9)	41
9/1985–8/1986	2 nd year SVP	15	2001	957	33 (3.4)	
9/1986–8/1987	1 year after UVP	15	2002	840	21 (2.5)	41
9/1987–8/1988	2 years after UVP	15	2003	824	19 (2.3)	
9/1988–8/1989	3 years after UVP	15	2004	848	20 (2.4)	41
9/1989–8/1990	4 years after UVP	15	2005	870	13 (1.5)	
9/1990–8/1991	5 years after UVP	15	2006	871	18 (2.1)	41
1985–1986	First two years SVP	15	2000–2001	904	22 (2.4)	
1993–1997	7–11 years after UVP	15	2008–2012	887	6 (0.7)	43
9/1982–8/1983	Before vaccination	6	1989	1500	158 (10.5)	44
9/1984–8/1985	1 st year SVP	6	1991	1500	94 (6.3)	44
9/1986–8/1987	1 year after UVP	6	1993	1500	26 (1.7)	
1997–1998	11–12 years after UVP	7–8	2005	1545	12 (0.78%)	45 [§]
	12–13 years after UVP	8–9	2006	1488	12 (0.85%)	
	13–14 years after UVP	9–10	2007	1344	10 (0.74%)	

^aHepatitis B vaccination program was started in Taiwan from July 1984, with first two years (July 1984–June 1986) selectively in neonates of HBsAg-positive mothers and then in all newborn infants since July 1986. SVP, selective vaccination program. UVP, universal vaccination program.

[§]This study followed same cohort of subjects within two years, without novel HBsAg seroconversion.

titis B vaccine to all infants.⁴⁹ The situation was even worse in France.⁵⁰ The worst thing was that some parents in Taiwan refused their infants being vaccinated even the mothers were positive for both HBsAg and HBeAg.⁵¹ In addition, only 77% of the infants in Taiwan born to highly infectious mothers were administered HBIG at the earlier time.³² In Hong Kong, a recent survey showed that the public awareness of HBV infection was insufficient.⁵²

As the administration of HBIG and/or hepatitis B vaccine in neonates is being continuously improved, the HBsAg prevalence in children and adolescents is being progressively reduced. Recent surveys show that the HBsAg prevalence was only 0.3% in 1–17 years old subject in Singapore,⁵³ 0.5% in <15 years old children in Taiwan,⁴⁶ and 0.5%–0.8% in children at 1–12 years old in Mainland China.^{38,54}

Therefore, the recently reported age-specific increased HBsAg prevalence does exist, but it is less likely due to the loss of anti-HBs. It is very likely associated with the carry-over of the infection from early life to young adulthood, because of the relatively less protective efficiency at the beginning due to the under optimal use of HBIG and/or hepatitis B vaccine. As such, age-specific increased HBsAg prevalence is not the evidence to support the booster in late teenagers.

Rare events of confirmed authentic breakthrough infection with severe consequences

The premise for the booster vaccination should be based on the evidence of severe breakthrough infection of wild type HBV in successfully vaccinated individuals. Numerous studies were conducted to observe the long-term protection, but to date chronic infection or clinical disease after exposure to wild-type HBV has been very rarely reported. A meta-analysis included 34 cohorts with 9356 participants showed that the overall cumulative incidence of HBV breakthrough infection within 5–20 years post-primary vaccination was 0.7%, whereas the chronic infection appeared to be only one case (0.015%) of the 6466 subjects with the completed follow-up.⁵⁵ Even so, it was not known whether this case was infected before the

development of anti-HBs or after the wane of anti-HBs.⁵⁶ Other studies with similar or longer observation period reported that chronic infection is still a rare event in successfully vaccinated individuals (Table 3). In addition, the population based study demonstrated the long-term protection duration of hepatitis B vaccine. After universal newborn vaccination in Alaska Native people from 1984, the incidence of acute clinical HBV infection in persons <20 years of age dropped from 19/100,000 in 1981–1982 to 0/100,000 in 1993–1994; no acute hepatitis B case has occurred in individuals <20 years of age since 1992, and the identified HBsAg-positive subjects <20 years in the Alaska Native population declined from 657 in 1987 to only 2 in 2008.⁶⁵

While many studies showed the rare events of severe breakthrough infection in successfully vaccinated individuals, several other surveys reported the breakthrough infection occurred in vaccinated subjects or in adolescents or young adults.^{3,66,67} However, since the participants in these studies were not same cohort or the studies were cross-sectional, it was impossible to ascertain the age of infection in the great majority of chronic carriers, i.e., the infection might occur during infancy, rather than after the development of anti-HBs. For an example, a cross-sectional survey in Gambia showed that, among 1099 subjects vaccinated during infancy or <5 years old, the HBsAg prevalence was 0, 1.0, 0.4, 0.9, and 2.1% in the groups with the age of 1–4, 5–9, 10–14, 15–19, and 20–24 years, respectively.⁶⁷ Yet the same authors reported the most of the chronic infections occurred before the age of 5 years.⁶⁸ Thus, the carriers with relatively older ages can not be definitely considered to be infected after the decline or loss of vaccine-induced anti-HBs.⁶⁹ Only individuals who were vaccinated and confirmed to have produced protective levels of anti-HBs and to be not infected for a period of time become persistent HBsAg positive with evidence of no mutations in the *a* determinant of HBV S gene, may they be considered to be infected due to waning or loss of anti-HBs.

So far, only a few breakthrough infections with clinical disease or chronic carriage reported in successfully vaccinated individuals in literature may be definitely attributed to waning or loss of anti-HBs. Lu et al reported that one (1.3%) of 78 children (15 years old) who were born to HBeAg positive mothers

Table 3. Summary of long-term studies reporting rare severe breakthrough infections in successfully vaccinated subjects.

Ref	Region	Subject No	Mother HBsAg+	Vaccination age	Follow-up years	Test age (years)	Booster No	HBsAg +	Clinical disease	a-HBs \geq 10 mIU/ml, %	a-HBc+/HBsAg-, N (%)
36	Taiwan	165/118	Yes	Infancy	10	5, 10	18 at 5 y	0	0	83.4 (66.9 [§])	14 (11.9)
57	Taiwan	805/539	Yes	Infancy	10	2, 3, 4, 5, 10	None	3 [†]	0	85.0	110 (14.8)
58	Palau	193/60	17.8%	Infancy	15	10, 15	75	0	0	7.5	10 (5.2)
59	Czech	640/640	Yes	Infancy	15–16	1, 5, 10, 15	272	0	0	25.0	10 (1.6)
60	Thailand	266/198	Partial	Infancy	15–17	\geq 2 tests	None	0	0	N/A	53 (19.9)
61	Italy	571/571	N/A	Infancy	17	10, 17	199 at 10 y	0	0	72.9	0
15	USA	159/159	N/A	18–60 y, HCW	10–31	Once	None	0	0	77.4	4 (2.5)
62	American Samoa	212/212	N/A	Infancy	18–23	18–23	None	0	0	N/A	2 (0.9)
22	Iran	300/300	N/A	Infancy	20	20	None	0	0	37.0	0
63	Thailand	222/109	165	Infancy	20	Yearly	65 at 5 y	0	0	N/A	11 (10.1)
64	Hong Kong	1044/246	Yes	infancy	30	3, 5, 7, 10, 13, 16, 21, 25, 30	None	0	0	37.4	97 (9.0)
16	USA	1578/243	N/A	Children & adults	30	After primary vaccination, 22, 30	None	0	0	51.0	N/A

[‡]Initial enrollment number/last follow-up number.

[§]The positive rate in subjects without booster.

[†]Defined positive at 18, 24, and 30 months old respectively; N/A, not available.

and were vaccinated after birth was chronically infected with HBV (mixed genotypes B and C, no mutation in the *a* determinant); the child had anti-HBs 21 mIU/ml at 1.5-year old and was HBsAg negative at 7 years old.⁷⁰ Another case was a 50-year-old homosexual healthcare worker. He developed borderline positive anti-HBs after the full primary vaccination (1985–1986), still borderline positive after a booster dose (1987), and >1000 mIU/ml after a second booster dose (1993), but suffered from acute hepatitis B caused by wild-type virus in 2007; retrospective analysis of his serum stored in 2004 showed negative for HBsAg and anti-HBc and total absence of anti-HBs.⁷¹

More recently, Wang et al reported that, among 936 children who were born to HBsAg-positive mothers and who received neonatal vaccination and showed HBsAg negative at the age of 10–11 years, 12 (2.12%) of 566 children with positive anti-HBs and 16 (4.32%) of 370 children with negative anti-HBs were identified with chronic HBV infection at the age of 23–28 years respectively.⁸ However, several critical issues in this article were not ascertained, such as the vaccination histories and the identities of the participants in the two surveys at age of 10–11 years and 23–28 years respectively. Moreover, the article contains some obviously exceptional results, including the high chronic infection rates in subjects with positive anti-HBs and in anti-HBs positive individuals with booster vaccination at 11–12 years old (2.12% and 2.0% respectively), and very high negative conversion rate (66%) of anti-HBc. Therefore, the clinical implication of this study is not clear in assessment of the effect of adolescent booster of hepatitis B vaccine.

Conclusion

In brief, a booster is not required for at least 30 years after successful vaccination in infancy or early infancy, since to date the HBsAg prevalence or the incidence of acute hepatitis B does not have a trend to increase in vaccinated subjects. This should be globally applicable since the supportive data were derived from the whole world. The age-specific increased HBsAg prevalence is more likely associated with the relatively imperfect implementation of vaccination at the beginning of the program. The premise for booster vaccination against hepatitis B should be based on the evidence of severe breakthrough infection of wild-type HBV in successfully vaccinated, uninfected individuals. The uncertainty on protection duration of hepatitis B vaccine, especially beyond 30 years after the primary vaccination, merits a well-designed follow-up investigation in high-risk or exposure-prone populations vaccinated during infancy longitudinally, which differs from the cross-sectional studies reported previously, can hopefully offer more direct evidence to help us to determine whether revaccination of hepatitis B vaccine is necessary.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by the grant of the Jiangsu Provincial Department of Health (H201537), the National Natural Science Foundation of

China (81672002), the Science and Technology Department of Jiangsu Province (BK20161105), and the Key Medical Center of Jiangsu Provincial Department of Health (YXZXB2016004), China.

ORCID

Yi-Hua Zhou  <http://orcid.org/0000-0001-8880-0392>

References

- Casey RM, Dumolard L, Danovaro-Holliday MC, Gacic-Dobo M, Diallo MS, Hampton LM, Wallace AS. Global Routine Vaccination Coverage, 2015. *MMWR Morb Mortal Wkly Rep.* 2016;65(45):1270–3. doi:10.15585/mmwr.mm6545a5. PMID:27855146
- Hadler SC. Are booster doses of hepatitis B vaccine necessary? *Ann Intern Med.* 1988;108(3):457–8. doi:10.7326/0003-4819-108-3-457. PMID:2963571
- Coursaget P, Yvonnet B, Chotard J, Sarr M, Vincelot P, N'doye R, Diop-Mar I, Chiron JP. Seven-year study of hepatitis B vaccine efficacy in infants from an endemic area (Senegal). *Lancet.* 1986;2:1143–5. doi:10.1016/S0140-6736(86)90543-X. PMID:2877284
- Banatvala J, Van Damme P, Van Hattum J. Boosters for hepatitis B. European Consensus Group on Hepatitis B Immunity. *Lancet.* 2000;356(9226):337–8. doi:10.1016/S0140-6736(05)73618-7. PMID:11071210
- Lao TT. Immune persistence after hepatitis B vaccination in infancy – Fact or fancy? *Hum Vaccin Immunother.* 2016;12(5):1172–6. doi:10.1080/21645515.2015.1130195. PMID:26810256
- Lao TT, Sahota DS, Suen SS, Chan PK, Leung TY. Impact of neonatal hepatitis B vaccination programme on age-specific prevalence of hepatitis B infection in teenage mothers in Hong Kong. *Epidemiol Infect.* 2013;141(10):2131–9. doi:10.1017/S0950268812002701. PMID:23211684
- Li H, Li GJ, Chen QY, Fang ZL, Wang XY, Tan C, Yang QL, Wang FZ, Wang F, Zhang S, et al. Long-term effectiveness of plasma-derived hepatitis B vaccine 22–28 years after immunization in a hepatitis B virus endemic rural area: is an adult booster dose needed? *Epidemiol Infect.* 2017;145(5):887–94. doi:10.1017/S0950268816003046. PMID:28065199
- Wang Y, Chen T, Lu LL, Wang M, Wang D, Yao H, Fan C, Qi J, Zhang Y, Qu C. Adolescent booster with hepatitis B virus vaccine decreases HBV infection in high-risk adults. *Vaccine.* 2017;35(7):1064–70. doi:10.1016/j.vaccine.2016.12.062. PMID:28069363
- Carmody E. Time to re-evaluate the effect of the adolescent booster of hepatitis B vaccine. *Int J Infect Dis.* 2017;60:88–90. doi:10.1016/j.ijid.2017.04.019. PMID:28473203
- Pinto M, Dawar M, Krajden M, Naus M, Scheifele DW. Will Infant Hepatitis B vaccination protect into adulthood?: Extended canadian experience after a 2-, 4- and 6-month immunization schedule. *Pediatr Infect Dis J.* 2017;36(6):609–15. doi:10.1097/INF.0000000000001543. PMID:28134742
- Van Damme P. Long-term protection after hepatitis B vaccine. *J Infect Dis.* 2016;214(1):1–3. doi:10.1093/infdis/jiv750. PMID:26802140
- Trevisan A. Long-term persistence of immunity after hepatitis B vaccination: A fact, not a fancy. *Hum Vaccin Immunother.* 2017;13(4):916–7. doi:10.1080/21645515.2016.1257451. PMID:27905837
- Poorolajal J, Hooshmand E. Booster dose vaccination for preventing hepatitis B. *Cochrane Database Syst Rev.* 2016;(6):CD008256. PMID:27271960
- Wang ZZ, Gao YH, Lu W, Jin CD, Zeng Y, Yan L, Ding F, Li T, Liu XE, Zhuang H. Long-term persistence in protection and response to a hepatitis B vaccine booster among adolescents immunized in infancy in the western region of China. *Hum Vaccin Immunother.* 2017;13(4):909–15. doi:10.1080/21645515.2016.1250990. PMID:27874311
- Gara N, Abdalla A, Rivera E, Zhao X, Werner JM, Liang TJ, Hoofnagle JH, Rehermann B, Ghany MG. Durability of antibody response against hepatitis B virus in healthcare workers vaccinated as adults. *Clin Infect Dis.* 2015;60(4):505–13. doi:10.1093/cid/ciu867. PMID:25389254

16. Bruce MG, Bruden D, Hurlburt D, Zanis C, Thompson G, Rea L, Toomey M, Townshend-Bulson L, Rudolph K, Bulkow L, et al. Antibody levels and protection after hepatitis B vaccine: Results of a 30-year follow-up study and response to a booster dose. *J Infect Dis.* 2016;214(1):16–22. doi:10.1093/infdis/jiv748. PMID:26802139
17. Simons BC, Spradling PR, Bruden DJ, Zanis C, Case S, Choromanski TL, Apodaca M, Brogdon HD, Dwyer G, Snowball M, et al. A longitudinal hepatitis B vaccine cohort demonstrates long-lasting hepatitis B Virus (HBV) cellular immunity despite loss of antibody against HBV surface antigen. *J Infect Dis.* 2016;214(2):273–80. doi:10.1093/infdis/jiw142. PMID:27056956
18. Jan CF, Huang KC, Chien YC, Greydanus DE, Davies HD, Chiu TY, Huang LM, Chen CJ, Chen DS. Determination of immune memory to hepatitis B vaccination through early booster response in college students. *Hepatology.* 2010;51(5):1547–54. doi:10.1002/hep.23543. PMID:20209603
19. McMahon BJ, Dentinger CM, Bruden D, Zanis C, Peters H, Hurlburt D, Bulkow L, Fiore AE, Bell BP, Hennessy TW. Antibody levels and protection after hepatitis B vaccine: results of a 22-year follow-up study and response to a booster dose. *J Infect Dis.* 2009;200(9):1390–6. doi:10.1086/606119. PMID:19785526
20. Chiara F, Bartolucci GB, Cattai M, Piazza A, Nicolli A, Buja A, Trevisan A. Hepatitis B vaccination of adolescents: significance of non-protective antibodies. *Vaccine.* 2013;32(1):62–8. doi:10.1016/j.vaccine.2013.10.074. PMID:24188755
21. Chiara F, Bartolucci GB, Mongillo M, Ferretto L, Nicolli A, Trevisan A. Hepatitis B vaccination at three months of age: a successful strategy? *Vaccine.* 2013;31(13):1696–700. doi:10.1016/j.vaccine.2013.01.046. PMID:23384750
22. Bagheri-Jamebozorgi M, Keshavarz J, Nemati M, Mohammadi-Hosainabad S, Rezayati MT, Nejad-Ghaderi M, Jamalizadeh A, Shokri F, Jafarzadeh A. The persistence of anti-HBs antibody and anamnestic response 20 years after primary vaccination with recombinant hepatitis B vaccine at infancy. *Hum Vaccin Immunother.* 2014;10(12):3731–6. doi:10.4161/hv.34393. PMID:25483689
23. Van Der Meeren O, Behre U, Crasta P. Immunity to hepatitis B persists in adolescents 15–16 years of age vaccinated in infancy with three doses of hepatitis B vaccine. *Vaccine.* 2016;34(24):2745–9. doi:10.1016/j.vaccine.2016.04.013. PMID:27095043
24. Hall AJ. Boosters for hepatitis B vaccination? Need for an evidence-based policy. *Hepatology.* 2010;51(5):1485–6. doi:10.1002/hep.23674. PMID:20432250
25. FitzSimons D, Hendrickx G, Vorsters A, Van Damme P. Hepatitis B vaccination: a completed schedule enough to control HBV lifelong? Milan, Italy, 17–18 November 2011. *Vaccine.* 2013;31(4):584–90. doi:10.1016/j.vaccine.2012.10.101. PMID:23142301
26. Wu TW, Lin HH, Wang LY. Reply To: Chronic hepatitis B infection in adolescents vaccinated at birth: an alarm bell in favor of the need for a booster? *Hepatology.* 2014;59(1):349–50. doi:10.1002/hep.26462. PMID:23695983
27. Liu Y, Wen J, Chen J, Xu C, Hu Y, Zhou YH. Rare detection of occult hepatitis B virus infection in children of mothers with positive hepatitis B surface antigen. *PLoS One.* 2014;9(11):e112803. doi:10.1371/journal.pone.0112803. PMID:25383543
28. Mendy M, Peterson I, Hossin S, Peto T, Jobarteh ML, Jeng-Barry A, Sidibeh M, Jatta A, Moore SE, Hall AJ, et al. Observational study of vaccine efficacy 24 years after the start of hepatitis B vaccination in two Gambian villages: no need for a booster dose. *PLoS One.* 2013;8(3):e58029. doi:10.1371/journal.pone.0058029. PMID:23533578
29. Shahmoradi S, Yahyapour Y, Mahmoodi M, Alavian SM, Fazeli Z, Jazayeri SM. High prevalence of occult hepatitis B virus infection in children born to HBsAg-positive mothers despite prophylaxis with hepatitis B vaccination and HBIG. *J Hepatol.* 2012;57(3):515–21. doi:10.1016/j.jhep.2012.04.021. PMID:22617152
30. Zhou YH. Occult hepatitis B virus infection, or occult cross-contamination, in children of HBsAg-positive mothers. *J Viral Hepat.* 2016;23(10):830. doi:10.1111/jvh.12559. PMID:27333952
31. Suen SS, Lao TT, Chan OK, Lau TK, Leung TY, Chan PK. Relationship between age and prevalence of hepatitis B infection in first-year university students in Hong Kong. *Infection.* 2013;41(2):529–35. doi:10.1007/s15010-012-0379-6. PMID:23233215
32. Chen DS, Hsu NH, Sung JL, Hsu TC, Hsu ST, Kuo YT, Lo KJ, Shih YT. A mass vaccination program in Taiwan against hepatitis B virus infection in infants of hepatitis B surface antigen-carrier mothers. *JAMA.* 1987;257(19):2597–603. doi:10.1001/jama.1987.03390190075023. PMID:3573257
33. Chien YC, Jan CF, Kuo HS, Chen CJ. Nationwide hepatitis B vaccination program in Taiwan: effectiveness in the 20 years after it was launched. *Epidemiol Rev.* 2006;28:126–35. doi:10.1093/epirev/mxj010. PMID:16782778
34. Khetsuriani N, Tishkova F, Jabirov S, Wannemuehler K, Kamili S, Pirova Z, Mosina L, Gavrilin E, Ursu P, Drobeniuc J. Substantial decline in hepatitis B virus infections following vaccine introduction in Tajikistan. *Vaccine.* 2015;33(32):4019–24. doi:10.1016/j.vaccine.2015.05.092. PMID:26072015
35. Lee A, Cheng FF, Chan CS, Lau LC, Lo AS. Sero-epidemiology and risk factors of positive hepatitis B surface antigen amongst Chinese adolescents. *Asia Pac J Public Health.* 2001;13(1):30–5. doi:10.1177/101053950101300107. PMID:12109258
36. Huang LM, Chiang BL, Lee CY, Lee PI, Chi WK, Chang MH. Long-term response to hepatitis B vaccination and response to booster in children born to mothers with hepatitis B e antigen. *Hepatology.* 1999;29(3):954–9. doi:10.1002/hep.510290349. PMID:10051503
37. Yuen MF, Lim WL, Cheng CC, Lam SK, Lai CL. Twelve-year follow-up of a prospective randomized trial of hepatitis B recombinant DNA yeast vaccine versus plasma-derived vaccine without booster doses in children. *Hepatology.* 1999;29(3):924–7. doi:10.1002/hep.510290327. PMID:10051499
38. Lin X, Yang J, Lu H, Zhou Y, Zhou G, Wu H, Xu C, Wu Q, Liu J, Chen S, et al. Minimization of hepatitis B infection among children in Jiangsu, China, 12 years after integration of hepatitis B vaccine into the expanded program on immunization. *Vaccine.* 2016;34(51):6458–63. doi:10.1016/j.vaccine.2016.11.022. PMID:27866767
39. Lao TT, Sahota DS, Law LW, Cheng YK, Leung TY. Age-specific prevalence of hepatitis B virus infection in young pregnant women, Hong Kong Special Administrative Region of China. *Bull World Health Organ.* 2014;92(11):782–9. doi:10.2471/BLT.13.133413. PMID:25378739
40. Lin AW, Wong KH. Surveillance and response of hepatitis B virus in Hong Kong special administrative region, 1988–2014. *Western Pac Surveill Response J.* 2016;7(1):24–8. doi:10.5365/wpsar.2015.6.3.003. PMID:27757251
41. Lin CC, Chang CK, Huang YL, Tseng HF. Low seroprevalence of hepatitis B surface antibody among nursing students in Taiwan: an implication for boosting. *Vaccine.* 2007;25(51):8508–11. doi:10.1016/j.vaccine.2007.10.018. PMID:18006122
42. Hsu HM, Lu CF, Lee SC, Lin SR, Chen DS. Seroepidemiologic survey for hepatitis B virus infection in Taiwan: the effect of hepatitis B mass immunization. *J Infect Dis.* 1999;179(2):367–70. doi:10.1086/314585. PMID:9878020
43. Chen CY, Hsu HY, Liu CC, Chang MH, Ni YH. Stable seroepidemiology of hepatitis B after universal immunization in Taiwan: A 3-year study of national surveillance of primary school students. *Vaccine.* 2010;28(34):5605–8. doi:10.1016/j.vaccine.2010.06.029. PMID:20598405
44. Lin HH, Wang LY, Hu CT, Huang SC, Huang LC, Lin SS, Chiang YM, Liu TT, Chen CL. Decline of hepatitis B carrier rate in vaccinated and unvaccinated subjects: sixteen years after newborn vaccination program in Taiwan. *J Med Virol.* 2003;69(4):471–4. doi:10.1002/jmv.10333. PMID:12601753
45. Chen YS, Chu CH, Wang JH, Lin JS, Chang YC. Predictors of booster response to hepatitis B vaccine at 15 years of age: A cross-sectional school-based study. *Pediatr Neonatol.* 2016;57(4):302–9. doi:10.1016/j.pedneo.2015.09.006. PMID:26750404
46. Ni YH, Chang MH, Wu JF, Hsu HY, Chen HL, Chen DS. Minimization of hepatitis B infection by a 25-year universal vaccination program. *J Hepatol.* 2012;57(4):730–5. doi:10.1016/j.jhep.2012.05.021. PMID:22668640

47. Wood DL, Rosenthal P, Scarlata D. California pediatricians' knowledge of and response to recommendations for universal infant hepatitis B immunization. *Arch Pediatr Adolesc Med.* 1995;149(7):769–73. doi:10.1001/archpedi.1995.02170200059009. PMID:7795767
48. Zola J, Smith N, Goldman S, Woodruff BA. Attitudes and educational practices of obstetric providers regarding infant hepatitis B vaccination. *Obstet Gynecol.* 1997;89(1):61–4. doi:10.1016/S0029-7844(96)00389-4. PMID:8990439
49. Hurie MB, Saari TN, Proctor ME, Davis JP. Hospitals' responses to universal infant hepatitis B vaccination recommendations. *Pediatrics.* 1995;96(5 Pt 1):875–9. PMID:7478828
50. Stahl JP, Denis F, Gaudelus J, Cohen R, Lepetit H, Martinot A. Hepatitis B vaccination and adolescents: A lost generation. *Med Mal Infect.* 2016;46(1):1–3. doi:10.1016/j.medmal.2015.11.002. PMID:26746325
51. Lo KJ, Tsai YT, Lee SD, Wu TC, Wang JY, Chen GH, Yeh CL, Chiang BN, Yeh SH, Goudeau A, et al. Immunoprophylaxis of infection with hepatitis B virus in infants born to hepatitis B surface antigen-positive carrier mothers. *J Infect Dis.* 1985;152(4):817–22. doi:10.1093/infdis/152.4.817. PMID:2931490
52. Chung PW, Suen SH, Chan OK, Lao TH, Leung TY. Awareness and knowledge of hepatitis B infection and prevention and the use of hepatitis B vaccination in the Hong Kong adult Chinese population. *Chin Med J (Engl).* 2012;125(3):422–7. PMID:22490396
53. Ang LW, Tey SH, Cutter J, James L, Goh KT. Seroprevalence of hepatitis B virus infection among children and adolescents in Singapore, 2008–2010. *J Med Virol.* 2013;85(4):583–8. doi:10.1002/jmv.23496. PMID:23400872
54. Zhou Y, He H, Deng X, Yan R, Tang X, Xie S, Yao J. Significant reduction in notification and seroprevalence rates of hepatitis B virus infection among the population of Zhejiang Province, China, aged between 1 and 29 years from 2006 to 2014. *Vaccine.* 2017;35(34):4355–61. doi:10.1016/j.vaccine.2017.06.078. PMID:28687404
55. Poorolajal J, Mahmoodi M, Majdzadeh R, Nasseri-Moghaddam S, Haghdoost A, Fotouhi A. Long-term protection provided by hepatitis B vaccine and need for booster dose: a meta-analysis. *Vaccine.* 2010;28(3):623–31. doi:10.1016/j.vaccine.2009.10.068. PMID:19887132
56. Liao SS, Li RC, Li H, Yang JY, Zeng XJ, Gong J, Wang SS, Li YP, Zhang KL. Long-term efficacy of plasma-derived hepatitis B vaccine: a 15-year follow-up study among Chinese children. *Vaccine.* 1999;17(20–21):2661–6. doi:10.1016/S0264-410X(99)00031-6. PMID:10418916
57. Wu JS, Hwang LY, Goodman KJ, Beasley RP. Hepatitis B vaccination in high-risk infants: 10-year follow-up. *J Infect Dis.* 1999;179(6):1319–25. doi:10.1086/314768. PMID:10228050
58. Chaves SS, Fischer G, Groeger J, Patel PR, Thompson ND, Teshale EH, Stevenson K, Yano VM, Armstrong GL, Samandari T, et al. Persistence of long-term immunity to hepatitis B among adolescents immunized at birth. *Vaccine.* 2012;30(9):1644–9. doi:10.1016/j.vaccine.2011.12.106. PMID:22245310
59. Roznovsky L, Orsagova I, Kloudova A, Tvrdek J, Kabieszova L, Lochman I, Mrazek J, Hozakova L, Zjevickova A, Pliskova L. Long-term protection against hepatitis B after newborn vaccination: 20-year follow-up. *Infection.* 2010;38(5):395–400. doi:10.1007/s15010-010-0039-7. PMID:20589522
60. Poovorawan Y, Chongsrisawat V, Theamboonlers A, Srinivasa K, Huta-galung Y, Bock HL, Hoet B. Long-term benefit of hepatitis B vaccination among children in Thailand with transient hepatitis B virus infection who were born to hepatitis B surface antigen-positive mothers. *J Infect Dis.* 2009;200(1):33–8. doi:10.1086/599331. PMID:19473096
61. Spada E, Romanò L, Tosti ME, Zuccaro O, Paladini S, Chironna M, Coppola RC, Cuccia M, Mangione R, Marrone F, et al. Hepatitis B immunity in teenagers vaccinated as infants: an Italian 17-year follow-up study. *Clin Microbiol Infect.* 2014;20(10):O680–6. doi:10.1111/1469-0691.12591. PMID:24528380
62. Spradling PR, Xing J, Williams R, Masunu-Faleafaga Y, Dulski T, Mahamud A, Drobeniuc J, Teshale EH. Immunity to hepatitis B virus (HBV) infection two decades after implementation of universal infant HBV vaccination: association of detectable residual antibodies and response to a single HBV challenge dose. *Clin Vaccine Immunol.* 2013;20(4):559–61. doi:10.1128/CVI.00694-12. PMID:23408522
63. Poovorawan Y, Chongsrisawat V, Theamboonlers A, Leroux-Roels G, Kuriyakose S, Leyssen M, Jacquet JM. Evidence of protection against clinical and chronic hepatitis B infection 20 years after infant vaccination in a high endemicity region. *J Viral Hepat.* 2011;18(5):369–75. doi:10.1111/j.1365-2893.2010.01312.x. PMID:20384962
64. Lin AW, Wong KH. Long-term protection of neonatal hepatitis B vaccination in a 30-year cohort in Hong Kong. *J Hepatol.* 2013;59(6):1363–4. doi:10.1016/j.jhep.2013.08.021. PMID:23994385
65. McMahon BJ, Bulkow LR, Singleton RJ, Williams J, Snowball M, Homan C, Parkinson AJ. Elimination of hepatocellular carcinoma and acute hepatitis B in children 25 years after a hepatitis B newborn and catch-up immunization program. *Hepatology.* 2011;54(3):801–7. doi:10.1002/hep.24442. PMID:21618565
66. Wu TW, Lin HH, Wang LY. Chronic hepatitis B infection in adolescents who received primary infantile vaccination. *Hepatology.* 2013;57(1):37–45. doi:10.1002/hep.25988. PMID:22858989
67. van der Sande MA, Waight P, Mendy M, Rayco-Solon P, Hutt P, Fulford T, Doherty C, McConkey SJ, Jeffries D, Hall AJ, et al. Long-term protection against carriage of hepatitis B virus after infant vaccination. *J Infect Dis.* 2006;193(11):1528–35. doi:10.1086/503433. PMID:16652281
68. Whittle H, Jaffar S, Wansbrough M, Mendy M, Dumpis U, Collinson A, Hall A. Observational study of vaccine efficacy 14 years after trial of hepatitis B vaccination in Gambian children. *BMJ.* 2002;325(7364):569. doi:10.1136/bmj.325.7364.569. PMID:12228132
69. Lao TT. Long-term persistence of immunity after hepatitis B vaccination: Is this substantiated by the literature? *Hum Vaccin Immunother.* 2017;13(4):918–20. doi:10.1080/21645515.2016.1267084. PMID:28277087
70. Lu CY, Chiang BL, Chi WK, Chang MH, Ni YH, Hsu HM, Twu SJ, Su IJ, Huang LM, Lee CY. Waning immunity to plasma-derived hepatitis B vaccine and the need for boosters 15 years after neonatal vaccination. *Hepatology.* 2004;40(6):1415–20. doi:10.1002/hep.20490. PMID:15565627
71. Boot HJ, van der Waaij LA, Schirm J, Kallenberg CG, van Steenbergen J, Wolters B. Acute hepatitis B in a healthcare worker: a case report of genuine vaccination failure. *J Hepatol.* 2009;50(2):426–31. doi:10.1016/j.jhep.2008.07.040. PMID:19091440