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Predictive factors for anti-HBs status after 1 booster dose of hepatitis B vaccine

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Abstract

In Taiwan, infants need to receive 3 doses of hepatitis B virus (HBV) vaccine under the public health policy from the government. However, there are many young adults who even though received complete HBV vaccination in their childhood would lose the positive response of anti-hepatitis B surface antibody (HBs) and need the booster dose of HBV vaccine. The aim of our study is to determine the powerful predictive factor for screening the candidates who need only 1 booster dose of HB vaccine then they can regain positive postbooster anti-HBs status (≧10 mIU/mL) or protective postbooster anti-HBs status (≧100 mIU/mL).

We recruited 103 university freshmen who were born after July 1986 with complete HBV vaccination in childhood, but displayed negative results for hepatitis B surface antigen and anti-HBs levels at their health examinations upon university entry. They received 1 booster dose of HB vaccine, and their anti-HBs titers were rechecked 4 weeks after the booster administration. Multivariate analysis logistic regression for positive postbooster anti-HBs status (≧10 mIU/mL, model 1) and protective postbooster anti-HBs status (≧100 mIU/mL, model 2) was done with predictive factors of prebooster anti-HBs level, body mass index, serum glutamate pyruvate transaminase level, and sex.

Twenty-four students got positive postbooster anti-HBs status (10–100 mIU/mL) and 50 students got protective postbooster anti-HBs status (≧100 mIU/mL). In the model of multivariate analysis logistic regression for positive postbooster anti-HBs status (≧10 mIU/mL), prebooster anti-HBs level was the strongest predictive factor. The odds ratio was 218.645 and the *P* value was 0.001. Even in the model of multivariate analysis logistic regression for protective postbooster anti-HBs status (≧100 mIU/mL), prebooster anti-HBs level was still the strongest predictive factor, but the odds ratio of a protective booster effect was 2.143, with 95% confidence interval between 1.552 and 2.959, and the *P* value was less than 0.001.

Prebooster anti-HBs level can be the powerful predictive factor for positive postbooster anti-HBs status (≧10 mIU/mL) and protective postbooster anti-HBs status (≧100 mIU/mL). According to the result of this study, if someone received complete HBV vaccination in childhood, but displayed negative results for hepatitis B surface antigen and anti-HBs levels around 2 decades later, 1 booster dose of HBV vaccine could help him or her to regain positive postbooster anti-HBs status (≧10 mIU/mL) under the strong predictive factor of prebooster anti-HBs level higher than 1 mIU/mL. The other 2 HBV vaccines could be saved and the case could also save money and time.

Abbreviations: 95% CI = 95% confidence interval, ANOVA = analysis of variance, anti-HBs = anti-hepatitis B surface antibody, CMIA = Chemiluminescent Microparticle ImmunoAssay, HB = hepatitis B, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, NPV = negative predictive value, PPV = positive predictive value, ROC = receiver-operating characteristic.

Keywords: HB vaccine, HB vaccine booster, HBV, HBV vaccine, hepatitis B

1. Introduction

Hepatitis B virus (HBV) infection is one of the most important forms of virus-related hepatitis, and can induce acute and chronic hepatitis, cirrhosis, and fatal hepatocellular carcinoma.[1–9] It is estimated that there are as many as 350 to 360 million people chronically infected with HBV, and HBV induces approximately 0.5 to 0.7 million deaths each year worldwide.[10] Antiviral treatment shows the long-term potential ability to decrease the progression from chronic HBV-related hepatitis to cirrhosis or even hepatocellular carcinoma.[11,12] However, there is no effective way to cure the condition of chronic HBV infection.

The hepatitis B (HB) vaccine has proven to be a powerful and useful method for prevention of HBV infection and HBV-related hepatocellular carcinoma.[13–16] Many countries enforce a public health policy that supplies HB vaccine to infants, especially those born to HBV-positive mothers.[17,18] Since the initiation of these vaccination policies for hepatitis B in July 1984, the prevalence of hepatitis B surface antigen (HBsAg) carriers has dramatically declined in most countries, and the HB vaccine offers efficacious protection in most populations.[9] The incidence of HBV-related hepatocellular carcinoma has also decreased.[9] This is the first time in the history of humanity that cancer has been fought with a vaccine. At first, we used plasma-derived HB vaccines at the health policy of HB vaccination for newborns. Then, we changed

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to use recombinant HB vaccines after October 1992. According to the information from National Immunization Information System (NIIS) at Taiwan, the percentage of students who received complete HBV vaccination before they entered elementary school was higher than 99%. The policy of HBV vaccination in Taiwan is excellent and widespread.

However, many studies have demonstrated that the HB vaccine lacks lifetime potency. The titer of vaccine-induced anti-hepatitis B surface antibody (anti-HBs) declines rapidly in the first year and then declines gradually year by year. Frequently, the titer decreases to less than 10 mIU/mL in the teenage group. In previous studies, it was demonstrated that immune memory was also lost 15 to 20 years after vaccination in a significant percentage of subjects.[19,20] Fortunately, we have not found an elevated incidence of hepatitis B infection in young adults who received HB vaccination in childhood in Taiwan. Thus, the public health policy of the Department of Health, Executive Yuan, R.O.C. (Taiwan) does not recommend that people whose anti-HBs levels are less than 10 mIU/mL and who have a history of complete HB vaccination in childhood receive a booster dose of HB vaccine.

Most hospitals in Taiwan carry out an infection control policy in which employees with negative serum tests for anti-HBs are required to receive HB vaccination, as per the Healthcare Personnel Vaccination Recommendations by the Centers of Disease Control, R.O.C. (Taiwan). The employees should obtain sero-protective anti-HBs to prevent occupation-related HBV infection in needle puncture accidents. If the employees display negative results for both HBsAg and anti-HBs serum tests at pre-employment or regular health examinations, they are required to receive a HB vaccination even if they received a complete HB vaccination in childhood. However, it is still controversial whether these employees should receive only 1 booster dose or complete 0, 1, and 6-month 3-dose HB vaccine regimen. Theoretically, 1 booster dose of HB vaccine is enough to induce adequate immune response and obtain sero-protective anti-HBs for people who still have an immune memory to HBV. The complete 0, 1, and 6-month 3-dose HB vaccine regimen will thus incur unnecessary clinical visits and vaccinations for such people. However, 1 booster dose of the HB vaccine is insufficient for those who have lost their immune memory to HBV. The immune response may not be adequately induced, and they may not obtain sero-protective anti-HBs. Furthermore, even if they got positive postbooster anti-HBs status (≧10 mIU/mL), the titer of anti-HBs would decline rapidly in the first year. So, if we want to keep their anti-HBs higher than 10 mIU/mL for a long period, maybe we should elevate the postbooster anti-HBs status from positive (≧10 mIU/mL) to protective (≧100 mIU/mL).

International policies require the documentation that anti-HBs were ever positive after a full 3-dose vaccination regimen. If this documentation exists, a booster may not be needed owing to the existing cellular immunity, which cannot be quantified as easily as antibody titers. However, if the documentation of positive anti-HBs cannot be provided, a new 3-dose regimen should be started in those with titers below 10 IU/mL, with anti-HBs check at least 4 weeks after the last dose. In Taiwan, almost all infants who received the complete HBV vaccination would not have the check of anti-HBs at their childhood. Though most of them do not have the documentation of positive anti-HBs, clinically we found that a part of these young adults who received complete HBV vaccination in their childhood, but their anti-HBs titers were below 10 IU/mL today, need only 1 booster dose of HBV vaccine to regain the positive postbooster anti-HBs status (≧10 mIU/mL) or protective postbooster anti-HBs status (≧100 mIU/mL).

It is a great challenge for us to determine a simple and helpful method to find the people who need only 1 booster dose of HB vaccine in the clinic. The aim of our study is to determine the powerful predictive factor for screening the candidates who need only 1 booster dose of HB vaccine then they can regain positive postbooster anti-HBs status (≧10 mIU/mL) or protective postbooster anti-HBs status (≧100 mIU/mL).

2. Methods

Health-screening examination, including a survey of HBsAg and anti-HBs, of the freshmen of a university in South Taiwan from 2006 to 2012, was conducted. We used the Abbott ARCHITECT i2000 and i1000 to check the titer of serum anti-HBs and HBsAg for our cases. It is the way of Chemiluminescent Microparticle ImmunoAssay (CMIA). The overall sensitivity was 97.54% and the overall specificity was 99.67% for the detection of serum anti-HBs. The sensitivity was less than 0.05 IU/mL and the specificity was 95% for the detection of serum HBsAg. Students with both negative serum tests for HBsAg (<0.05 IU/mL) and anti-HBs (<10 mIU/mL) were notified to visit the outpatient department of Family Medicine at E-DA hospital in Kaohsiung City of Taiwan. Those born after July 1986 with complete HBV vaccination in their childhood were administered 1 booster dose of HB vaccine (IM, 20 mcg/dose; Engerix-B, GSK), and their anti-HBs titers were rechecked 4 weeks later. The definition of a positive result in the CMIA test for serum anti-HBs level is an anti-HBs titer ≧10 mIU/mL, and the definition of a protective result in the CMIA test for serum anti-HBs level is an anti-HBs titer ≧100 mIU/mL.

There were 103 subjects who received 1 booster dose of HB vaccine, and their anti-HBs titers were rechecked 4 weeks after the booster administration. The numbers for male and female subjects were counted. The mean for the age and prebooster anti-HBs level was calculated. We also performed a multivariate analysis logistic regression to identify the predictive factors for positive (≧10 mIU/mL, model 1) and protective (≧100 mIU/mL, model 2) postbooster anti-HBs status. IBM (Chicago, IL) SPSS version 14 was used for the statistical analysis, including receiver-operating characteristic (ROC) curve plotting and multivariate analysis logistic regression. The positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity were calculated by different prebooster anti-HBs intervals for the prediction of protective (≧100 mIU/mL) postbooster anti-HBs status. This study was reviewed and approved by the institutional review board (IRB) of E-Da Hospital (EDAH IRB No EMRP4710N). Informed consents were obtained from all subjects.

3. Results

The mean age of the 103 subjects was 18.6 years (standard deviation [SD] 0.84). The distribution of sex was 61 male (59.2%) and 42 female (40.8%) subjects. The mean level of prebooster anti-HBs was 2.067 mIU/mL (SD 2.4757). The median level of prebooster anti-HBs was 0.85 mIU/mL. The distribution of prebooster anti-HBs was closer to a right-skewed distribution. Table 1 shows the descriptive analysis of the 3 groups separated by postbooster anti-HBs status (<10 mIU/mL, 10–100 mIU/mL, ≧100 mIU/mL). Twenty-four students got positive postbooster

Table 1

Descriptive analysis for the 3 groups separated by postbooster anti-HBs status (<10 mIU/mL, 10–100 mIU/mL, ≧100 mIU/mL).

	Postbooster anti-HBs <10 mIU/mL (n = 29)	Postbooster anti-HBs 10–100 mIU/mL (n = 24)	Postbooster anti-HBs ≧100 mIU/mL (n = 50)
Mean (SD)	1.470 (2.2667)	43.042 (26.1278)	525.489 (347.0361)
Prebooster anti-HBs, mIU/mL*	0.121 (0.1988)	1.387 (1.6335)	3.523 (2.6177)
BMI, kg/m^2	21.984 (3.6665)	22.388 (3.2710)	21.922 (3.9550)
GPT, U/L	29.0 (23.84)	23.1 (19.97)	26.1 (19.41)
Sex (female/male)	10/19	13/11	19/31

BMI = body mass index, HBs = hepatitis B surface antibody, SD = standard deviation.
* *P* value of ANOVA < 0.001.

anti-HBs status (10–100 mIU/mL) and 50 students got protective postbooster anti-HBs status (≧100 mIU/mL). The result of analysis of variance (ANOVA) test revealed that in the 3 groups, the prebooster anti-HBs was quite different and the *P* value of ANOVA was less than 0.001. Table 2 lists the results of multivariate analysis logistic regression for positive (>10 mIU/mL) and protective (>100 mIU/mL) postbooster anti-HBs status with predictive factors of prebooster anti-HBs level, body mass index (BMI), serum glutamate pyruvate transaminase level, and sex. Prebooster anti-HBs level was the strongest predictive factor of the positive postbooster positive status (>10 mIU/mL). The odds ratio (OR) was 214.645 and the *P* value was 0.001. Even in model 2 of multivariate analysis logistic regression, it still showed the significant OR as 2.143 (*P* value < 0.01) at the prediction of protective postbooster anti-HBs status.

Figures 1 and 2 showed the two ROC curves concerning sensitivity and specificity of positive postbooster anti-HBs (≧10 mIU/mL) and protective postbooster anti-HBs (≧100 mIU/mL). The area under the ROC curve was 0.915 and 0.873. Table 3 shows the PPV, NPV, sensitivity, and specificity at different cut-off values of prebooster anti-HBs to predict positive postbooster anti-HBs (≧10 mIU/mL). The PPV would reach 100% at the cut-off value of prebooster anti-HBs higher than 1 mIU/mL (47.6%; around half of the subjects got the prebooster anti-HBs higher than 1 mIU/mL). Table 4 shows the PPV, NPV, sensitivity, and specificity at different cut-off values of prebooster anti-HBs to predict protective postbooster anti-HBs (≧100 mIU/mL). The PPV would reach 100% at the cut-off value of prebooster anti-HBs higher than 6 mIU/mL (only 9.7% of our subjects got the prebooster anti-HBs higher than 6 mIU/mL).

4. Discussion

We noted that the distribution of the prebooster anti-HBs level was not normal and was closer to a right-skewed distribution. We found that prebooster anti-HBs level was the most powerful predictive factor for both the positive postbooster anti-HBs status (≧10 mIU/mL) and the protective postbooster anti-HBs status (≧100 mIU/mL) in the multivariate analysis logistic regression. The OR of the positive booster effect was 214.645 for every 1 mIU/mL increase of serum prebooster anti-HBs level (*P* value = 0.001). Even in the prediction of protective postbooster anti-HBs status (≧100 mIU/mL), the prebooster anti-HBs level also showed significant OR as high as 2.143 (*P* value < 0.001). It was thus quite obvious that the levels of the serum prebooster anti-HBs were potentially powerful predictive factors for the effect of 1 booster dose of HB vaccine.

The ROC curve can aid us in identifying the most specific cut-off value of prebooster anti-HBs level. The area under the curve was 0.915 and 0.873 of the ROC curve concerning sensitivity and specificity of positive postbooster anti-HBs (≧10 mIU/mL) and protective postbooster anti-HBs (≧100 mIU/mL). Compared with the other study in Italy, the area under the curve was 0.93 of the ROC curve concerning sensitivity and specificity of positive response in postboosted individuals with prebooster anti-HBs below 10 mIU/mL.[21] However, the subjects in that study received first-time HBV vaccination in adolescents, but not in childhood. The race is also different in these 2 studies. The results of our study show the unique ROC curve concerning sensitivity and specificity of positive postbooster anti-HBs (≧10 mIU/mL) and protective postbooster anti-HBs (≧100mIU/mL) in the subjects who received complete HBV vaccination in childhood and received the other booster dose of HB vaccine when they were young adults.

Although the difference in booster effect in different prebooster anti-HBs level ranges in this study is significant, the study population is relatively small. However, even under the small sample size, we still note that if we want to use the prebooster anti-HBs level as the prediction tool for the protective postbooster anti-HBs status, the PPV would reach 100% only at the cut-off value of prebooster anti-HBs higher than 1 mIU/mL,

Table 2

Descriptive analysis for the 103 subjects and multivariate analysis logistic regression for positive postbooster anti-HBs status (≧10 mIU/mL, model 1) and protective postbooster anti-HBs status (≧100 mIU/mL, model 2) with predictive factors of prebooster anti-HBs level, BMI, serum GPT level, and sex.

	Mean (SD)	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Postbooster anti-HBs, mIU/mL	265.535 (350.1562)	—	—	—	—
Prebooster anti-HBs, mIU/mL	2.067 (2.4757)	214.645 (8.762–5258.122)	0.001	2.143 (1.552–2.959)	<0.001
BMI, kg/m^2	22.048 (3.6950)	1.069 (0.857–1.332)	0.554	0.985 (0.837–1.160)	0.860
GPT, U/L	26.2 (20.77)	0.966 (0.917–1.017)	0.185	0.999 (0.968–1.031)	0.947
Sex (female/male)	42/61	3.347 (0.761–14.715)	0.110	0.792 (0.277–2.265)	0.663

BMI = body mass index, CI = confidence interval, HBs = hepatitis B surface antibody, SD = standard deviation.

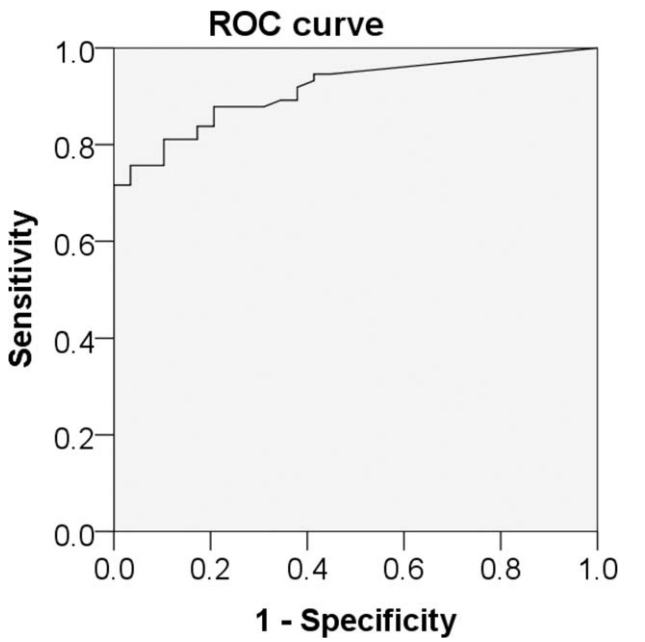

Figure 1. ROC curve (AUC 0.915) concerning sensitivity and specificity of positive postbooster anti-HBs (≧10 mIU/mL). AUC = area under the curve, HBs = hepatitis B surface antibody, ROC = receiver-operating characteristic.

and nearly half (47.6%) of our subjects got the prebooster anti-HBs higher than 1 mIU/mL. So, in clinical use, we can set the prediction level of prebooster anti-HBs as high as 1 mIU/mL. More studies are needed and possibly from non-Asian populations before accepting the norm that prebooster anti-HBs is a predictor for a complete benefit of a re-immunization.[22]

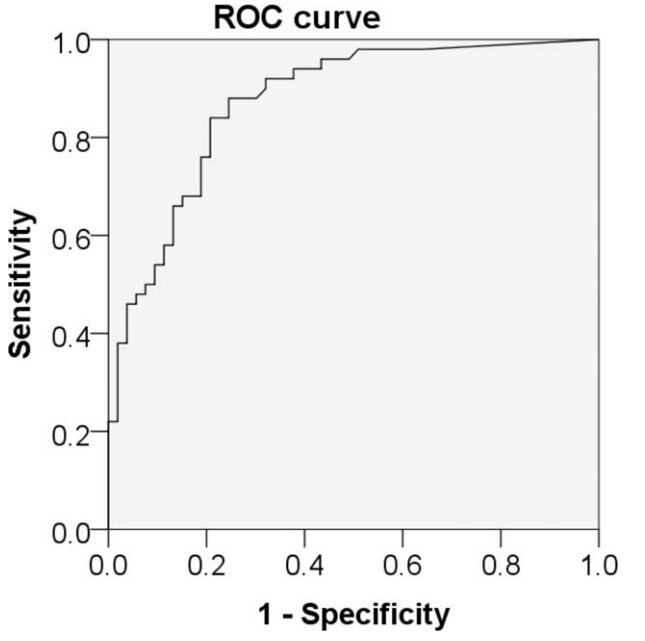

Figure 2. ROC curve (AUC 0.873) concerning sensitivity and specificity of protective postbooster anti-HBs (≧100 mIU/mL). AUC = area under the curve, HBs = hepatitis B surface antibody, ROC = receiver-operating characteristic.

According to the findings in this study, the prebooster anti-HBs level is a good clinical predictive factor for positive protective postbooster anti-HBs status (≧10 mIU/mL) and postbooster anti-HBs status (≧100 mIU/mL) that identify who requires only 1 booster dose of HB vaccine instead of a 0, 1, and 6-month HB vaccine regimen. This can save money and time for the people who need to obtain sero-positive anti-HBs, such as healthcare workers in the hospitals. However, the clinical reporting for the serum anti-HBs test typically only indicates "positive" or "negative." No statement on the method used for anti-HBs detection, nor the titer of serum anti-HBs level, is shown. If physicians can obtain additional relevant information, they can supply better suggestions to their patients.

Some studies indicate that it is unnecessary to administer HB vaccine boosters because the immune response to the booster dose can be observed in most cases after the administration of the HB vaccine booster itself.[23,24] This indicates that the immune memory to HBV has persisted. People with the immune memory to HBV could protect them against HBV infection even if their anti-HBs titer is less than 10 mIU/mL. Cellular immunity could have rapid response after the exposure to HbsAg. However, the follow-up time for these studies is only approximately 10 years after initial HB vaccination. If we extend the duration of follow-up to 15 to 20 years, we can note that a significant percentage of subjects appear to lose the immune memory as measured by the development of an anamnestic response to booster HB vaccine administration.[25] Some studies also suggest considering booster HB vaccine administration 15 to 18 years after initial HB vaccination, especially for groups at high risk of HBV infection.[20,26–28]

General policy in Taiwan does not recommend young adults to receive booster doses of HB vaccine because statistics indicate that the incidence of hepatitis B infection does not increase even though most of the population of young adults has lost their sero-protection for HBV and have anti-HBs levels <10 mIU/mL. However, for employees in Taiwanese hospitals, sero-positive anti-HBs is necessary to prevent unexpected hepatitis B infection due to needle puncture accidents for employees with both negative results on serum tests for HBsAg and anti-HBs. The Healthcare Personnel Vaccination Recommendations by the Centers of Disease Control, R.O.C. (Taiwan) also suggest the healthcare workers receive HB vaccination if they have negative results on HBsAg and anti-HBs serum tests. Our study showed after 1 booster dose of HBV vaccine, 74 over 103 students regain the positive or protective anti-HBs levels. This is only a pilot study, and according to the results, we do not have enough evidence to suggest administering the booster dose sooner rather than later. Maybe we need further studies to prove it. The study does not appear to have the long-term follow-up data, and we have no way of knowing for how long the obtained anti-HBs titers will persist after this booster dose.

5. Conclusions

In clinical practice, regarding HBV vaccination recommendation, we should first ask patients their previous history of HB vaccination. If they have received a complete HB vaccination before, they should be advised to receive 1 booster dose of HB vaccine, and their postbooster anti-HBs level should be rechecked 4 weeks later. If the serum test for postbooster anti-HBs remains negative, then the patients should be advised to receive further second and third HB vaccines. If we use prebooster anti-HBs level as the predictive tool, we can try to identify the people who need

Table 3

The positive predictive value, negative predictive value, sensitivity, and specificity at different cut-off values of prebooster anti-HBs for the prediction of postbooster anti-HBs ≧10 mIU/mL.

Cut-off value of prebooster anti-HBs (N)	Positive predictive value	Negative predictive value	Sensitivity	Specificity
≧1 mIU/mL (49)	100.0%	53.7%	66.2%	100.0%
≧2 mIU/mL (38)	100.0%	44.6%	51.4%	100.0%
≧3 mIU/mL (29)	100.0%	39.2%	39.2%	100.0%
≧4 mIU/mL (24)	100.0%	36.7%	32.4%	100.0%
≧5 mIU/mL (15)	100.0%	33.0%	20.3%	100.0%
≧6 mIU/mL (10)	100.0%	31.2%	13.5%	100.0%
≧7 mIU/mL (6)	100.0%	29.9%	8.1%	100.0%
≧8 mIU/mL (2)	100.0%	28.7%	2.7%	100.0%
≧9 mIU/mL (1)	100.0%	28.4%	1.4%	100.0%

HBs = hepatitis B surface antibody.

Table 4

The positive predictive value, negative predictive value, sensitivity, and specificity at different cut-off values of prebooster anti-HBs for the prediction of postbooster anti-HBs ≧100 mIU/mL.

Cut-off value of prebooster anti-HBs (N)	Positive predictive value	Negative predictive value	Sensitivity	Specificity
≧1 mIU/mL (49)	77.6%	77.8%	76.0%	79.2%
≧2 mIU/mL (38)	81.6%	70.8%	62.0%	86.8%
≧3 mIU/mL (29)	86.2%	66.2%	50.0%	92.5%
≧4 mIU/mL (24)	91.7%	64.6%	44.0%	96.2%
≧5 mIU/mL (15)	93.3%	59.1%	28.0%	98.1%
≧6 mIU/mL (10)	100.0%	57.0%	20.0%	100.0%
≧7 mIU/mL (6)	100.0%	54.6%	12.0%	100.0%
≧8 mIU/mL (2)	100.0%	52.5%	4.0%	100.0%
≧9 mIU/mL (1)	100.0%	52.0%	2.0%	100.0%

HBs = hepatitis B surface antibody.

only 1 booster dose of HB vaccine and help them avoid unnecessary clinical visits, laboratory examinations, and vaccination expenses. Another study on HB vaccination also revealed that subjects with higher prebooster anti-HBs could achieve greater anamnestic response to booster HB vaccine.[29] Based on these findings, we suggest to use the prebooster anti-HBs as the prediction tool to identify the people who need only 1 booster dose of HB vaccine in clinical practice. According to the result of this study, if someone received complete HBV vaccination in childhood, but displayed negative results for HBsAg and anti-HBs levels around 2 decades later, only 1 booster dose of HBV vaccine could help him or her to regain positive postbooster anti-HBs status (≧10 mIU/mL) under the strong predictive factor of prebooster anti-HBs level higher than 1 mIU/mL. The other 2 HBV vaccines could be saved and the case could also save money and time.

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