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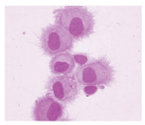

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/khvi20

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To cite this article: Takeshi Yoda & Hironobu Katsuyama (2020): Analysis of antibody-negative medical students after hepatitis B vaccination in Japan, Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2020.1788309

To link to this article: https://doi.org/10.1080/21645515.2020.1788309

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Published online: 05 Aug 2020.

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HUMAN VACCINES & IMMUNOTHERAPEUTICS
https://doi.org/10.1080/21645515.2020.1788309

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Analysis of antibody-negative medical students after hepatitis B vaccination in Japan

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ABSTRACT

Hepatitis B virus (HBV) vaccination is recommended for health-care professionals because of their frequent contact with blood. At one medical school, new students undergo HBV antibody tests upon admission, and antibody-negative individuals receive the HBV vaccine. We aimed to characterize individuals who remained antibody negative after HBV vaccination. Between 2009 and 2017, we enrolled 1064 first-year students from a medical school where their HBV antibody test and vaccination records remained. We analyzed data regarding the hepatitis B surface antibody (anti-HBs) test record during admission, vaccination record for antibody-negative participants, anti-HBs test result after completing the three vaccination doses, drug name of the vaccine used, sex, body mass index (BMI), and age. We calculated the yearly percentage of antibody-negative individuals and analyzed the characteristics of vaccine-refractory cases by logistic regression analysis. Of the 1064 participants, 999 were initially antibody negative. They were vaccinated with HBV thrice and tested for antibodies after vaccination. The average age of participants was 20.1 y, with 677 males. Although the type of vaccine has been changed since 2016, the average rate of refractoriness from 2009 to 2015 was 6.9% per year and 18.6% after 2016. Logistic regression analyses showed that sex (male vs. female; OR, 1.787), BMI (OR. 1.171), and vaccine type (genotype A vs. genotype C: OR, 3.144) were significant factors associated with antibody-negative individuals. Vaccine type differences altered the proportion of antibody-refractory individuals, with no association with age. The data on vaccine refractoriness will be continuously analyzed in the future while considering other factors.

ARTICLE HISTORY
Received 12 March 2020
Revised 3 June 2020
Accepted 22 June 2020

KEYWORDS
Hepatitis B virus; hepatitis B surface antibody; hepatitis B vaccine; medical students; Japan

Introduction

The World Health Organization (WHO) has reported that 2 billion people worldwide are infected with hepatitis B virus (HBV), 350 million people are infected with persistent HBV, and 500,000–700,000 people die of HBV-related diseases annually.[1] Regions such as Asia and Africa have a high frequency of HBV carriers, accounting for more than 8% of the population, whereas regions such as Japan, Europe, and North America have only less than 2% of HBV carriers.[2] Tanaka et al. reported that approximately 481,470 individuals are HBV latent carriers[3] based on the first blood donor group and the health checkup group for HBV prevention, suggesting that "the carriers do not know that they are infected." Persistent HBV infection results from infection at birth or in infancy; primary infection in adulthood rarely becomes persistent, except in immunocompromised conditions, such as a debilitating disease and terminal cancer. In transient infections, 70% to 80% end with subclinical infection, whereas the remaining 20% to 30% develop acute hepatitis. Around 2% of these patients develop fulminant hepatitis, with approximately 70% fatality rate. Chronic HBV infection progresses to cirrhosis in up to 40% of untreated patients, with an associated risk of decompensated cirrhosis (defined as developing symptomatic complications of liver fibrosis such as jaundice, ascites, variceal hemorrhage, and hepatic encephalopathy) and hepatocellular carcinoma.[4-6]

Vaccination can effectively prevent HBV infection. WHO recommends HBV vaccination as a means of achieving a 5-y-old child HBV carrier rate of 1% or less, and it has already introduced "universal vaccination" in which all newborns and schoolchildren in many countries and regions are vaccinated. The three-dose series of HBV vaccine for children, including an HBV birth dose and at least two additional doses, is the most effective tool for preventing HBV infection and the chronic sequelae of cirrhosis and liver cancer. This three-dose series is more than 90% effective in preventing HBV transmission to infants from chronically infected mothers, and more than 95% effective in preventing horizontal transmission during childhood and later during adulthood. The universal vaccination not only prevents HBV infection to inoculated infants but also prevents such infection from infancy to adulthood.[7] As a result of introducing the universal vaccination in the USA, the number of acute hepatitis B cases, except for those under the universal vaccination target age, decreased. Meanwhile, "selective vaccination" is an infection prevention program for children born to HBV-carrier mothers; in Japan, it has been implemented since 1986 as a project to prevent mother-to-child transmission. Complete implementation of this program can result in a high prevention rate of being carriers of up to 94% to 97%, but difficulties such as prenatal infection, leakage of prenatal examinations, complications and incomplete implementation of the program, lack of cooperation between obstetrics and gynecology and pediatrics, and horizontal

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transmission within the family may be encountered. In addition, target infants escape infection and become resistant to HBV, whereas other infants remain susceptible to HBV. According to the annual trend of the number of reported cases of acute hepatitis B by country, the number of acute cases has decreased in the USA and Italy where many cases were reported after introducing universal vaccination.[8] Countries with low patient numbers tend to choose selective vaccination, but some of these countries, such as Norway, encounter an epidemic spreading from high-risk populations to HBV-susceptible individuals through sexual transmission; in Japan, the HBV vaccine has been changed to universal vaccination since October 1, 2016.[9]

At present, HBV vaccination is recommended for high-risk groups. These groups include medical workers because they are likely to come into contact with blood. Some universities also provide such vaccination to medical students, even to those who perform vaccination, at the early stage of their medical course. HBV vaccination of health-care professionals generally involves subcutaneous or intramuscular injection of 10 μg (0.5 ml) of HBs antigen (HBsAg) protein. A total of three vaccinations, that is, first vaccination, second vaccination 1 month after, and third vaccination 6 months after the first vaccination, will be used as a series, and HBs antibody (anti-HBs) titers will be measured 1–2 months after completing one series to confirm the presence or absence of positivity. When the antibody titer is less than 10 mIU/ml, the antibody is not acquired, and the inoculation of the second series is recommended. Antibody prevalence by universal vaccination in childhood is over 95%, which tends to decrease in adulthood; the prevalence becomes 92% in individuals under 40 y old, and it further decreases to 84% in those over 40 y old.[10] Factors that contribute to the decrement of antibody prevalence include genetic predisposition, immunosuppression, certain chronic illnesses, and age.[11-13]

In one medical school in Japan, the HBV vaccine of one-series inoculation is enforced in the first grade, and the HBV antibody titer is measured afterward; then, HBV prevention measures are performed during clinical training. Until 2015, a genotype C vaccine was used, but from 2016, genotype A vaccine has been used. We raised the question of whether the prevalence of antibodies has a difference. To confirm the question, we conducted a study that aimed to check vaccination records and compare the proportion of antibody-negative individuals between 2009 and 2017, when vaccination records were still available, and to determine the cause or the contributing factors that led to the negative antibody response by using logistic regression analysis.

Methods

Study design

From 2010 to 2018, when the HBV antibody test and vaccination records remained, 1064 individuals who were enrolled as first-year students in a medical school in Japan were the target participants of the study. All first-year students in each fiscal year underwent HBsAg and anti-HBs tests in April, and all antibody-negative students were inoculated with the HBV vaccine. The second vaccination was given 4 weeks after the first vaccination, and the third vaccination was given 20–24 weeks after the first vaccination according to the vaccination guidelines of the Japanese Society for Infection Prevention and Control.

Vaccine types and serum HBV marker assay

For each inoculation, a single dose of 0.5 ml (10 μg of HBsAg protein) was injected subcutaneously into the right upper arm or the extensor part of the left upper arm. Recombinant adsorbed HBV vaccine derived from genotype C was used from 2009 to 2015, and recombinant adsorbed HBV vaccine derived from HBV genotype A was used from 2016 onwards. A vial (0.5 ml) of Middle of Genotype C vaccine contains 0.005 mg of thimerosal, 0.11 mg of aluminum hydroxide, 4.09 mg of sodium chloride, 1.29 mg of sodium hydrogen phosphate hydrate, and 0.22 mg of sodium dihydrogen phosphate as additives.[14] Meanwhile, a vial (0.5 ml) of Middle of Genotype A vaccine contains 0.25 mg of aluminum hydroxyphosphate sulfate, 4.5 mg of sodium chloride, and 35 μg of borax as an additive; notably, thimerosal is not used in this vial.[15] The anti-HBs titer was measured again after 8 ~ 16 weeks from the third inoculation end. The antibody titer was measured by the chemiluminescent enzyme-linked immunosorbent assay (CLEIA) We defined antibody negative as anti-HBs titer at less than 10mIU/ml according to the CDC guidelines.[16]

Data analysis

The data used in the analysis included the anti-HBs test record upon admission, the vaccination record for antibody-negative students, the anti-HBs test result after completing the three doses of vaccination, the name of the drug used for vaccination, sex, and age. The annual percentage of antibody-negative individuals was calculated, and the difference between the average until 2015 and the average after 2016 was examined using the *t*-test. Continuous variables were presented as Mean ±standard deviation (SD). We also analyzed the characteristics of vaccine-refractory cases through logistic regression analysis, with anti-HBs positive and negative after vaccination as dependent variables, and vaccine type (genotype A or C), sex, body mass index (BMI), and age as independent variables. In both cases, the significance level was set at less than 0.05.

For the study analysis, we only included those who posted an opt-out document stating that data analysis should be performed only from records without identifying personal information and agreed to it. The Ethics Committee of Kawasaki Medical School approved this study (Approved number: 3466).

Results

Of the 1064 participants, 1023 were initially antibody negative. Among these 1023 participants, 999 were vaccinated with HBV thrice and tested for antibodies after vaccination. The average age of these 999 participants (677 males) was 20.09 ± 5.49 y, and

Table 1. Characteristics of students who received three doses of HBV vaccine for the first time.

Vaccinated year	2009	2010	2011	2012	2013	2014	2015	2016	2017
Genotype of vaccine				Genotype C				Genotype A	
Total number	112	117	109	123	107	102	114	113	102
Male	67	73	72	77	69	73	70	70	63
Female	45	44	37	46	38	29	44	43	39
Average age ± SD	19.5 ± 1.8	19.9 ± 1.8	20.0 ± 2.5	19.7 ± 1.8	20.0 ± 1.9	19.7 ± 2.1	20.8 ± 2.4	21.3 ± 1.4	20.3 ± 1.9
Average BMI ± SD	21.3 ± 2.7	21.9 ± 3.4	21.7 ± 2.8	21.3 ± 3.0	21.2 ± 2.8	21.6 ± 3.0	21.4 ± 2.5	21.5 ± 2.9	21.3 ± 3.2
Total number of HBsAb-negative students	15	6	2	11	6	8	6	22	18
Male	13	5	2	10	5	7	6	14	11
Female	2	1	0	1	1	1	0	8	7
BMI (average ± SD)	23.0 ± 3.4	23.9 ± 3.6	26.8 ± 6.0	25.6 ± 4.0	21.6 ± 1.6	24.7 ± 5.7	21.2 ± 1.0	22.4 ± 2.8	22.0 ± 4.2
Anti-HBs negativity ratio by genotype				6.9%				18.6%	

SD: standard deviation.

the average BMI was 21.51 ± 2.96. Although the type of vaccine changed from 2016, the average percentage of antibody-negative participants in 2009 to 2015 was 6.9%, compared with 19.4% and 17.6% in 2016 and 2017, respectively, and the average percentage for 2 y was 18.6% (Table 1). The characteristics of anti-HBs negative students by vaccine genotype are shown in Table 2. There were no significant differences in average BMI, average age, and anti-HBs titer, except annual average number-, among all participants. We also analyzed anti-HBs titer after three vaccinations. The titer data were obtained only from 2013; thus, the data were not considered full-set data. In accordance with the previous study,[17] we quadrisected all participants by anti-HBs titer as follows: negative group (<10 mIU/ml), low response (10–100 mIU/ml), middle response (100–1000 mIU/ml), and high response (>1000 mIU/ml). Table 3 summarizes the characteristics of these four groups. There was a tendency of average BMI changing from low to high. Furthermore, logistic regression analyses revealed that BMI (OR: 1.171, 95%CI: 1.-094–1.252), sex (male vs. female; OR: 1.787, 95% CI: –1.044–-3.057) and vaccine type (genotype A vs. genotype C; OR: 3.144, 95% CI: 1.970–5.018) were significant factors associated with antibody negativity after vaccination (Table 4).

Table 2. Characteristics of anti-HBs-negative students by vaccine genotype.

	Genotype C	Genotype A	p^a
Total number	54	40	-
Male	48	25	-
Female	6	15	-
Average number/year ± SD	7.71 ± 4.19	20.0 ± 2.82	<0.001
Average age ± SD	20.7 ± 2.5	20.3 ± 2.2	0.98
Average BMI ± SD	23.6 ± 3.9	22.2 ± 3.4	0.07
Average of anti-HBs titer[b] ± SD	4.095 ± 1.874	4.408 ± 3.129	0.68

[a]Binominal *t*-test.
[b]Anti-HBs titer data were obtained after 2013.

Table 3. Comparison between quadrisection groups by anti-HBs titer after the first course of HBV vaccination.

Quadisection groups anti-HBs titer (mIU/ml)	Negative <10	Low 10–100	Middle 100–1000	High >1000
Genotype C (%)	20 (6.3)	89 (28.2)	160 (50.6)	47 (14.9)
Genotype A (%)	40 (19.2)	61 (29.3)	83 (39.9)	24 (11.6)
Male (%)	43 (12.9)	97 (29.1)	147 (44.2)	46 (13.8)
Female (%)	17 (8.9)	53 (27.8)	96 (50.2)	25 (13.1)
Average age ± SD	20.76 ± 2.77	20.15 ± 1.97	20.59 ± 10.52	19.63 ± 1.41
Average BMI ± SD	22.39 ± 3.60	21.51 ± 2.91	21.24 ± 2.75	21.01 ± 2.74

Table 4. Results of logistic regression analysis.

		AOR	95% CI	*p*
Sex	Female	1	-	
	Male	1.787	1.044–3.057	0.034
Age		1.001	0.970–1.033	0.922
BMI		1.171	1.094–1.252	<0.001
Vaccine type	Genotype C	1	-	
	Genotype A	3.144	1.970–5.018	<0.001

AOR: adjusted odds ratio.
CI: confidence interval.
AICc: 555.645, BIC: 579.901, $R^2 = 0.085$.

Discussion

Our study results clarified that the proportion of antibody-negative students after a one-series inoculation was clearly changed by the type of vaccine, BMI, and sex difference. Female sex, intramuscular vaccination, young age, and being a nonsmoker are associated with a higher response rate for HBV vaccination.[18] According to the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), the seroconversion rate of HBsAg from genotype C is 100% (193/193) for 10–19 y of age at 1 month after vaccination and 97.8% (751/768) for 20–29 y of age.[14] For genotype A vaccines, the seroconversion rate after three doses in adults was reportedly 92.4% (1438/1557).[15] However, in our study, the anti-HBs conversion rate was 93.1% (730/784) after completing one series of genotype C, and antibody-positive conversion was 81.4% (175/215) for genotype A; both of which were lower than those reported by PMDA. According to the PMDA report, the seroconversion rate of the genotype C vaccine differs in terms of sex (92.7% for males and 98.2% for females; the proportion of antibody-positive individuals at 1 month after vaccination in one series). Our study results were similar to the previous report and PMDA reports (seroconversion rate: 90.7% in males and 98.0% in females for genotype C vaccine). In this study, the male-to-female ratio was 677:385, thereby lower than those reported by PMDA. However, no sex differences have been reported for genotype A. Regarding the difference according to the inoculation route, the intramuscular injection is slightly higher than the subcutaneous injection.[19] Ogawa et al. reported that the seroconversion rate of genotype A was 66.6% after subcutaneous injection and increased to 89.1% after intramuscular injection (Ogawa M. et al. 2019, unpublished data). In the current study, the administration route was subcutaneous injection uniformly; hence, the difference could not be examined. The change of the inoculation route is also one of the problems that needs to be examined in the future inoculation.

BMI is also significantly related to antibody negativity after one-series vaccination. Liu et al. reported that obesity was significantly associated with non-response to HBV vaccine immunization.[20]

Though genotype C and genotype A vaccines have been widely distributed in Japan with the approval from the Ministry of Health, Labor and Welfare that the effect is equivalent as an HBV vaccine, the significant difference has been observed in this research result. According to the logistic regression analysis, factors that influence post-vaccination antibody negativity include sex type and the vaccine type, and the vaccine type showed a greater odds ratio than sex.

The two HBV vaccines used in this study differ greatly in genotype as described above, but differences were noted with respect to additives. Differences in additives other than genotypes may also have an effect but cannot be concluded in this study.

Age also influences the rate of positivity after vaccination,[16,21] although it had a minimal effect in this study. The minimal effect was probably because of a limited age group, considering that the analysis was performed on a group of first-year medical students.

Moreover, the route of administration (subcutaneous, intramuscular, or intradermal) also influences antibody positivity. Intradermal injection has a higher prevalence of antibody positivity. However, the vaccine administration method has been standardized by subcutaneous injection in all age groups and has not been affected by differences in dosage form.

Our study has some limitations. First, a slight bias was observed in the comparison of vaccine types; genotype A vaccines were only used for 2 y. Second, no personal information such as family history, medical history, childhood immunization records, drug treatment, and genetic information was included in the analysis. Recent evidence suggests that several genes of the immune system are linked to variable immune responses to HBV vaccination.[22-24] In our study, some students cooperated for research about genetic information, although such information remains incomplete. Third, the participants are limited to first-year medical students in a region, and sample extraction is not randomized. Forth, we could not obtain anti-HBs titer data before one-series vaccination and the data were only shown to be positive or negative, without numerical values. In addition, before 2013, no numerical data were available after one-series vaccination. Therefore, we analyzed anti-HBs titer data after 2013.

Despite these limitations, a significant difference was found in the antibody-positive conversion rate according to the type of vaccine used. Furthermore, female sex, BMI, and genotype A vaccine were associated with a higher response rate for HBV vaccination. In Japan, the HBV vaccine has become a universal vaccine for children since 2016. Although the two types of vaccines, namely, genotypes A and C, are licensed for vaccination, the prevalence of antibody positivity has been significantly different in this study. Hence, an additional one course should be provided to antibody-negative individuals after one course of inoculation. Receiving two courses of inoculation clearly has disadvantages, such as pain in the injection needle insertion by the inoculation frequency increase, increase in the side effects, and burden of cost and time. Vaccines with significant benefits should be recommended if the prevalence of antibodies is clearly different according to the type of vaccine. Therefore, overall, the results of this study play a major role as part of the evidence for vaccine-type selection.

Acknowledgments

We have gratefully appreciated the staff of the health-care center of the Kawasaki Medical School and administrated members of the Health Check-up Center, Kawasaki Medical School Hospital, Kurashiki, Japan. The authors would like to thank Enago (www.enago.jp) for the English language review.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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