

Chronological Reduction in Hepatitis B Virus Antibody Titer After Vaccination in Adult Humans

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Abstract

Objective: Blood exposure and subsequent blood-borne infections are major risk factors for acquired occupational diseases. Hepatitis B (HB) viral infection is among them, and it is well known that it causes cirrhosis and liver cancer in two or three decades. It can be prevented with HB vaccination, which is recommended for medical staff. However, the antibody titer for acquired immunization generally decreases with time. The authors investigated the time-dependent decrease in HB virus antibody titers after vaccination.

Methods: Three hundred and seventy-five (70 males and 305 females) hospital employees were immunized with HB vaccine at their workplace and thereafter when needed. HB virus surface antibody titers were measured in 2004, 2007, 2010 and 2015, using a semi-quantitative photo-hemagglutination assay. Measured titers were defined as negative for 8 times or less and positive for 16 times or more.

Results: Out of the total of 375 persons who had been injected with HB vaccine, there had been significant titer loss in 132 (35%) in five years. There was no significant statistical difference between two subgroups, one of them consisting of persons who had continued to have positive results and the other of persons who had newly obtained immunity. Conversion from a positive to a negative result was more likely in males than in females (50% vs 32%, $p < 0.01$).

Conclusions: The titers of approximately one-third of the subjects converted from positive to negative in five years. After HB vaccination, periodical antibody titer measurements and additional vaccination may be recommended for persons with negative results.

Keywords hepatitis B antibody titer, titer reduction, hepatitis B vaccination, occupational vaccination

Blood exposure and subsequent blood-borne infections are among major risks for acquired occupational diseases, and are most likely to occur in medical institutions and ambulances. Hepatitis B (HB) virus is typically transmitted via the blood from human to human and results in HB viral infection¹. It is well known that persistent infection causes liver cirrhosis and cancer in two or three decades^{2,3}. HB viral infection can probably be prevented with HB vaccination, which is highly recommended for medical staff⁴.

After three injections of HB vaccine, immunity is thought to continue for decades. However, the efficacy or antibody titer of acquired immunity generally decreases with time, and the duration of efficacy differs among individuals⁵. A preliminary study revealed that HB virus antibody titers after vaccination decreased

more rapidly than expected. Therefore, periodical measurement of HB virus antibody titers in high-risk persons may be important. The authors investigated the time-dependent decrease in HB virus surface antibody titers after vaccination in employees of a general hospital in the present study.

Methods

Study Population

Out of 408 persons who were employed at a designated hospital in January 2016, 375 were evaluated in this study. Thirty-three were excluded for the following reasons: 1) non-responder⁵, 2) refused vaccination, 3) HB virus surface antibody positive and 4) person who had not completed the full vaccination course in January 2016.

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All persons enrolled were Japanese and had physical performance status I. Their laboratory data were not considered in this study, but they had not been restricted in their work by doctors. The subjects enrolled in this study consisted of 70 males and 305 females. Their age ranged from 18 to 68 years, and employment periods ranged from one to 49 years.

Vaccination

Each person was subcutaneously vaccinated with 0.5 mL of recombinant sedation HB vaccine (General Incorporated Foundation, The Chemo-Sero-Therapeutic Research Institute (Kaketsuken), Kumamoto, Japan) three times – 1) first shot, 2) second shot (1 month later) and 3) third shot (4–6 months after first shot), as recommended⁶. Each employee was vaccinated against HB virus unless they refused, and was further vaccinated when the measured titer was negative unless the person was a non-responder.

Outcome Measures

Peripheral blood was withdrawn and HB virus surface antibody titers were measured using a semi-quantitative photohemagglutination assay. Measured titers were classified as negative for 8 times or less and positive for 16 times or more.

Study Design

HB virus surface antibody titers were measured in 2004, 2007, 2010 and 2015. Persons whose titers were negative in 2004, 2007 and 2010 received further vaccine injections. The titers were again measured in 2015.

Statistical Analysis

Statistical significance was evaluated by the chi-

squared test with Yates modification and considered to be $p < 0.05$.

Results

The distribution of antibody titers measured in 2015 is shown in **Table 1**.

Ninety-five persons received vaccine shots in 2010 or later. They included those who became negative in 2010 and those who were employed in 2010 or later. Out of the 95 persons, 31 (33%) became negative in 2015. Out of 280 persons who continued to have a positive response in 2010, 101 (36%) became negative in 2015. There was no statistical difference between these two subgroups (**Table 2**). There was also no significant difference in gender ratio, age distribution or employment years between the two groups. Out of the total of 375 (280 + 95), 132 (31+101) (35%) became negative in five years.

Out of the 70 males, 35 (50%) became negative in 2015 and out of the 305 females 97 (32%) became negative in the same period of time. The gender difference for the positive-to-negative conversion rate was statistically significant ($p < 0.01$) (**Table 3**).

Discussion

The number of asymptomatic HB virus carriers in Japan has decreased since the national pre-blood transfusion HB virus screening program started in 1972⁷, and was estimated to have dropped to less than 1% of general population by 2002⁸. Seventy to eighty percent of patients with HB viral infection are asymptomatic²,

Table 1. Distribution of Measured HB Virus Antibody Titers and Numbers of Persons in 2015

Titer	Male	Female	Total
8 or less	35	97	132
16	9	42	51
32	6	33	39
64	6	41	47
128	4	30	34
256	6	26	32
512	2	15	17
1024	1	9	10
2048	1	8	9
4096 or more	0	4	4

Table 2. No Significant Difference in Negative Conversion Rates for HB Virus Antibody Titers between Persons with Positive Conversion in 2010 or Later and Persons who Continued to be Positive in 2010

	Total	persons		% negative conversion
		positive in 2015	negative in 2015	
Persons with positive conversion in 2010 or later	95	64	31	33%
Persons continuing to be positive in 2010	280	179	101	36%

NS: not statistically significant

Table 3. Gender Difference in Negative Conversion Ratio

Immunity	Male	Female
Negative	35	97
Positive	35	208

Out of 70 men, there was negative conversion in 35, and out of 305 women, there was negative conversion in 97, in five years

and most of them are not aware of their infection unless blood tests are carried out. Persons at risk of HB viral infection should be provided with immunity against it. This study revealed that acquired antibody titers against HB virus diminished much more rapidly than thought. HB vaccination over a single period of time may not be sufficient for persons who work for decades in an environment with possible exposure to the virus. In the absence of a new antigenic stimulus, antibody levels generally diminish in the long term. The status of persons who have low positive titers for HB virus antibodies, such as 16 times or 32 times, tended to be converted from positive to negative status in this study. Persons who had high positive titers, such as 64 times or more, tended to continue to be positive in five years (data not shown).

A scientist at the vaccine supplier stated in a personal communication that acquired HB viral antibody titers after vaccination decreased by approximately half in three years. This was consistent with the above observations. Therefore, continuous monitoring and additional vaccination may be crucial for persons at risk of HB viral infection.

There are a few limitations in the present study. It was a retrospective study, and was based on analyses of data under occupational health care regulations. Thus, the vaccination and observation periods varied among the persons enrolled. In consideration of cost, the titers were measured using a semi-quantitative assay, not a quantitative one. There is also the issue of variation in the stereo structure of the HB virus antigen epitope used in manufacturing the vaccine among companies, which may affect efficacy⁹. This is given as a limitation because there are 2 commercial suppliers of HB vaccine in Japan and many more worldwide. Prospective studies are required in the future to confirm our observations and determine the optimal schedule for titer monitoring and additional vaccination.

Several studies^{10,11} have reported that persons who received HB vaccination were at low risk of acute or chronic hepatitis over the long term even if their HB virus antibody titers subsequently decreased. There is some skepticism regarding the requirement for booster vaccination to protect against acute and chronic hepatitis¹², and it is controversial in terms of preventing liver cirrhosis or cancer.

The World Health Organization (WHO) has recommended universal vaccination. The recommendation for HB vaccination is three injections, including the first injection within 24 hours after birth¹³. The Japanese Government has started an HB vaccination program following the WHO recommendation.

Approximately 10% of persons were reported to be non-responders¹⁴, which is consistent with this study. The ability to acquire a significant antibody titer is reported to be higher in young people than in those who are older⁸. The possibility of age and gender influencing titer decreases and negative conversion rates is under investigation.

The implementation of the WHO's universal vaccination policy will probably increase the number of persons who have effective immunity against HB viral infection for decades. The content of this study will be subject to further consideration one generation later.

Conclusion

The HB virus surface antibody titers acquired through vaccination gradually decreased, and converted from positive to negative in approximately one-third of the subjects in five years. Titer monitoring after HB vaccination may be important for protecting those who are at risk of HB viral infection and subsequent onset of liver cirrhosis and cancer. Periodical titer measurements and additional vaccination may be recommended for persons with negative results.

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Conflicts of Interest

The authors disclose no conflicts of interest. This study was approved by the Institutional Committee of Ethics of Hayashi General Hospital.

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