Original Article

Access this article online

Quick Response Code:

Website: www.jacmjournal.org

DOI: 10.4103/jacm.jacm_63_16

Hepatitis B vaccination - immune response and persistence of protection in susceptible population

Nasha Kollathodi, Anitha Puduvail Moorkoth, Kalpana George, Mini Palathingal Narayanan, Shabina Methele Pangat Balakrishnan, Sarada Devi Karunakaran LelithaBai

Abstract:

BACKGROUND: Hepatitis B vaccine confers long-term protection, and anti-HBs titre is a marker for protective immune response. The evaluation of immune status following vaccination is important in susceptible individuals as up to 10% immunised individuals tend to be non-responders who continue to be at risk of acquiring hepatitis B.

AIM: The aim of the study was to determine the immune response and persistence of protective antibody levels after basic course of hepatitis B vaccination in susceptible individuals and to determine the factors affecting it.

MATERIALS AND METHODS: A cross-sectional study on 400 susceptible participants who were tested for anti-HBs by quantitative ELISA at a tertiary care centre in North Kerala for a period of 1 year. The study population included healthcare workers and medical students divided into Category I: those vaccinated with 0-1-6 schedule within the past six months and Category II: beyond six months but within 10 years. Individuals who have taken booster doses were excluded from the study.

RESULTS: 97.75% showed adequate anti-HBs levels (≥10 mIU/ml) after basic course of immunisation. Category I showed 99% response and Category II showed 96.5%. On giving one additional booster, the remaining 2.25% also responded. No non-responders were detected. 80.4% participants in the 10–20 age group showed anti-HBs >1000 mIU/ml, whereas only 25% participants in the 51–60 age group showed such high response. 97.9% males and 97.7% females had adequate response. Diabetic patients (66.7% vs. 98%) and smokers (66.7% vs. 98.2%) had a lower response ($P < 0.001$).

CONCLUSION: Protective immune response was achieved in all participants after an additional dose in indicated individuals. There is a decline in antibody levels with time, but a good immunological memory persists up to 10 years after vaccination. Vaccine response is adversely affected by advancing age, smoking and diabetes.

Keywords:

Anti HBs, hepatitis B vaccine, vaccine response

Introduction

Hepatitis B virus infects more than 500 million people worldwide. It is a leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. Prevention of hepatitis B is of paramount importance in the susceptible population including healthcare workers who have frequent exposure to blood and body fluids. Hepatitis B vaccine confers long-term protection against both clinical illness and its sequel. Although vaccination against hepatitis B virus is highly successful, up to 10% of individuals do not develop an adequate immune response to hepatitis B vaccine.[1] These individuals continue

Department of Microbiology, Government Medical College, Kozhikode, Kerala, India

Address for correspondence:
Dr. Nasha Kollathodi, Department of Microbiology, Government Medical College, Kozhikode, Kerala, India.
E-mail: knasha@gmail.com

How to cite this article: Kollathodi N, Moorkoth AP, George K, Narayanan MP, Balakrishnan SM, LelithaBai SD. Hepatitis B vaccination - immune response and persistence of protection in susceptible population. J Acad Clin Microbiol 2017;19:42-6.

to be at risk for acquiring the infection. An easily detectable anti-hepatitis B surface antigen (Anti HBs) level is a marker for protection. Furthermore, the immune status following vaccination is important in deciding the type of prophylaxis to be given in case of exposures.

Studies on immune response to hepatitis B vaccine indicate that 5%–10% of people fail to respond to the initial vaccine series globally and may need additional doses.[2] According to Centers for Disease Control and Prevention (CDC), the immune memory following primary vaccination may persist from 4 to 23 years as shown in various studies.[1] Studies from North India also suggest that there is a good response to recombinant hepatitis B vaccine with persistence up to 10 years.[3] However, studies regarding the vaccine response and persistence of antibodies to hepatitis B are lacking in South India to the best of our knowledge.

We hence planned a study (1) to evaluate immune response and duration of persistence of protective immune response in susceptible population including medical students and healthcare workers, (2) to determine the factors affecting the immune response and (3) to categorise the HBV vaccinees based on immune response and to administer additional doses as recommended.

Materials and Methods

A cross-sectional study done at a tertiary care centre at North Kerala, during the period of April 2012 to March 2013 after getting approval from the Institutional Research Committee and Ethics Committee. The study population included medical students and healthcare workers.

The pro forma was filled by directly interviewing the participants. Both height and weight of participants were measured. With consent from participants, 2–5 ml blood was collected by direct venepuncture, and sera were separated and stored at −20°C until the test was performed.

Antibody to hepatitis B surface antigen (HBsAg) (anti-HBs) was determined using quantitative ELISA-direct antibody sandwich enzyme immunoassay – Monolisa anti-HBs plus 72566 from BIO-RAD was used. Assay procedure was done as per the manufacturer's instructions. For each assay, anti-HBs negative control and calibrators corresponding to 10, 100, 400 and 1000 mIU/ml of anti-HBs were used. The sero-protection was defined as the presence of anti-HBs ≥10 mIU/ml.

For quantitative interpretation, a graph was plotted with the OD of controls against their assigned concentrations, using a linear regression with Microsoft Excel 2010 and equation formulated.

The participants were first tested for the anti-HBs antibody titre after the zero, one and six months immunisation schedule. They were divided into two groups: Category I: Those who have completed the immunisation schedule within the past six months. Category II: Those who have completed the immunisation schedule beyond six months but within 10 years. The participants who have completed immunisation schedule beyond 10 years and those who have taken booster doses were excluded from the study.

The participants having inadequate titre values <10 mIU/ml were tested for HBsAg by both card test (HEPAVIEW HBsAg-QUALPRO) and ELISA (Erba Lisa – Erba). HBsAg-negative individuals were given an additional dose of hepatitis B vaccine and tested after one month for anti-HBs.

The data were analysed using PASW Statistics 18 (BM Corp. in Armonk, New York) and Chi-square test applied to find the association between two variables. $P \leq 0.05$ was considered statistically significant. The variables considered in the study included age, sex, body mass index (BMI), diabetes mellitus, smoking and alcoholism.

Results

A total of 400 immunocompetent participants were included in the study. The study population was categorised into two groups - Category I and II with 200 participants each [Table 1].

Of the 400 participants tested, 391 (97.75%) showed adequate anti-HBs levels. Of this, Category I showed 99% response compared to 96.5% by Category II. Nine (2.25%) participants had inadequate levels - two in Category I and seven participants in Category II.

Anti-HBs levels more than 1000 mIU/ml were shown by 155 (77.5%) participants in Category I and 115 (57.5%) in Category II [Figure 1].

Table 1: Characteristics of study population

Population variables	Number (%)
Age (years)	
≤30	341 (85.5)
>30	59 (14.5)
Sex	
Males	94 (23.5)
Females	306 (76.5)
Occupation	
Healthcare worker	166 (41.5)
Medical student	234 (58.5)

On giving one additional booster dose to the nine participants who had inadequate antibody levels, all of them showed a titre >10 mIU/ml. Four of these individuals had levels >1000 mIU/ml and three had more than 100 and two had between 10 and 100 mIU/ml. There were no non-responders detected in our study.

A decline in anti-HBs level with time was noted in the study. The percentage of participants showing response more than 1000 mIU/ml showed a decreasing trend in relation to the time since the last dose of vaccine ($P < 0.001$) [Figure 2].

In the study, 156 (80.4%) participants in the 10–20 age group showed anti-HBs >1000 mIU/ml. Only two (25%) participants in the 51–60 age group had a similar response. There was an inverse relation between age and high response to vaccine ($P < 0.001$) [Figure 3].

Males and females in the study group showed similar vaccine response. Out of the 94 males tested, 92 (97.9%) responded while 299 (97.7%) out of 306 females showed adequate response ($P = 0.927$). Participants with BMI <18.5 showed 78.1% hyper-response (anti-HBs >1000 mIU/ml) compared to 33.3% by obese patients (BMI >30) ($P = 0.338$). Compared to 389 (98%) healthy participants, only two (66.7%) diabetic patients showed anti-HBs ≥10 mIU/ml ($P < 0.001$). Six (66.7%) smokers had adequate antibody levels compared to 385 (98.5%) non-smokers. No serious adverse effects to vaccine were reported in any of the participants in the study group.

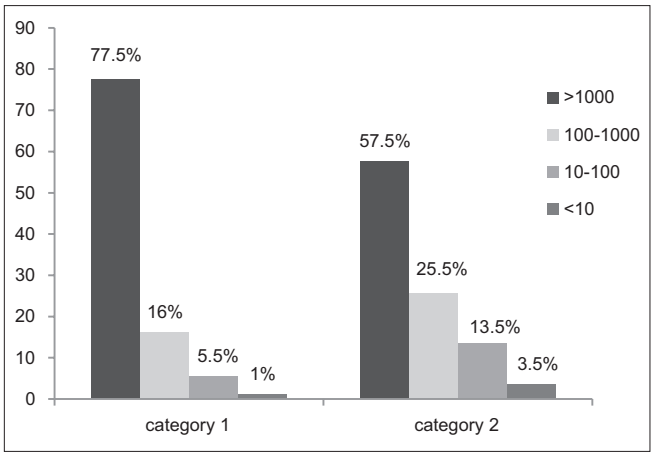

Figure 1: Vaccine response in mIU/ml within categories of study population

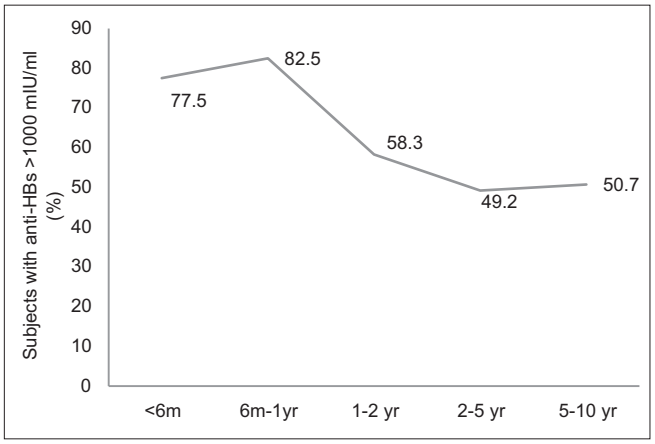

Figure 2: Decline in response in relation to time since the last dose of vaccine

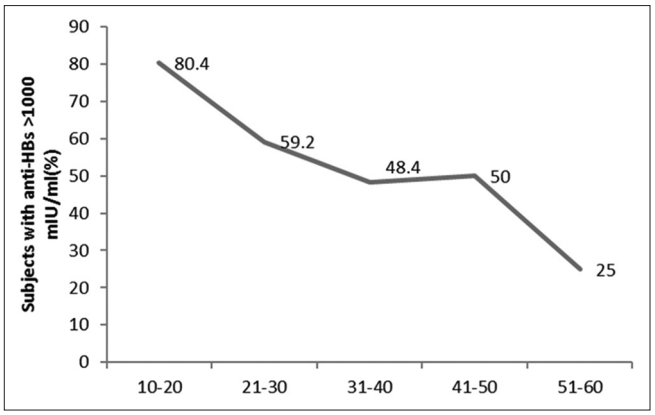

Figure 3: Decline in vaccine response with advancing age

Discussion

In our study, we evaluated the immune response following a 0-1-6 schedule of hepatitis B vaccine in 400 susceptible individuals in two categories. The total initial response to the basic vaccine schedule was 97.75% irrespective of the categories studied. In the Category I participants who were vaccinated within six months, the response was 99% with 77.5% showing a level >1000 mIU/ml. Even though the antibody response is usually looked for within one to six months of vaccination, in the Category II participants who were vaccinated six months to 10 years back, we could find a 96.5% response with 57.5% showing levels >1000 mIU/ml. In a study by Vijayakumar *et al*., there was a 100% response after one month of vaccination.[4]

A decline in antibody levels with time was noticeable with maximum fall after the 1st year following vaccination. Chaudhari *et al*. showed a decline in antibody levels similar to our study.[3] A long-term follow-up study by Wang *et al*. also reported a loss of antibodies over the years.[5] As per CDC, anti-HBs levels decline rapidly within the 1st year and more slowly thereafter.[1] However, in our study, even up to 5–10 years of primary vaccination, there was the persistence of antibodies more than the protective level of 10 mIU/ml in 94.8% participants. A 10-year serological follow-up study by Chadha and Arankalle also reported persistence of immunological memory at least 10 years after HBV vaccination.[6] Various studies have shown long-term

persistence of anti-HBs after vaccination against HBV for 15–18 years.[7-9]

In the present study, two participants in the Category I and 7 participants in Category II failed to show adequate antibody levels after the basic vaccine course. However, after single additional/booster dose, all of them responded. According to various studies, 74%–100% of persons vaccinated 4–23 years back showed an anamnestic response following additional dose indicating the persistence of vaccine-induced immune memory.[1]

Our study reiterated the inverse relation between age at vaccination and vaccine immunogenicity. Younger individuals showed higher response compared to older people. There was a 98.2% response in participants <30 years of age, whereas only 87.5% of participants >50 years age responded to the initial vaccine schedule. Chaudhari *et al*. discussed in their study in healthcare workers of armed force that age is one of the important factors affecting vaccine response.[3] He showed a 93.8% response in participants <30 years compared to 77.5% response in those who were >30 years of age. Various studies also reported higher age as the most important factor in reduced immunogenicity of HBV vaccine.[10-12] This highlights the importance of HBV vaccination at the earliest for better immunogenicity and protection from occupational risk of HBV. In this study, we could not find any relation with gender and immune response. Similarly, Chaudhari *et al.* could not establish a statistically significant correlation between gender and vaccine response in their study but showed a higher response in females (89.9%) compared to males (87%).[3] Various other studies show that females show a higher response compared to males.[10,13] In the present study, though individuals with higher BMI had a lower immune response, this correlation was not statistically significant. A study by Ghanaei *et al*. also failed to show a statistically significant correlation between BMI and vaccine response.[14] However, investigation by Wood *et al*. in Minnesota healthcare workers related obesity as an independent risk factor for vaccine non-response.[15]

In our study, 98.2% of non-smokers in the study population responded, whereas only 66.7% smokers had protective antibody levels. The association between smoking and good vaccine response seems to be statistically significant ($P < 0.001$). Nejad *et al*. in their study in Iranian healthcare workers established that smoking was one of the significant factors associated with vaccination failure response.[16] Study by Shaw *et al*. confirmed a depressant effect of cigarette smoking on antibody response after hepatitis B vaccination.[17] Wood *et al*. also related smoking as an independent risk factor for vaccine non-response.[15] No significant relation between alcoholism and vaccine response was evident in our study. Even though the number of diabetic patients was very low in this study, there was a statistically significant association ($P < 0.001$) showing lesser vaccine response in diabetes. In a study by Bouter *et al*. comparing immune response to hepatitis B vaccine in diabetic patients and healthy adults, a 25% non-response was shown by people with diabetes.[18]

In our study, majority of participants were unaware of the brand of vaccine used. A comparison of the efficacy of different brands, hence could not be done. A study by Shivananda S *et al*. showed 95% to 96% response by different vaccine brands.[19] In another comparative study by Vijayakumar *et al*., Genevac-B, Engerix-B and Shanvac-B showed 99.5%, 98.5% and 98.4% response, respectively. All these studies show that efficacy of different vaccine brands is comparable.[19,20]

Conclusion

All the participants in the study population achieved adequate antibody levels after additional vaccine doses in indicated individuals. It was also found that immune response following vaccination is adversely affected by advancing age, smoking and diabetes. Gender, BMI and alcoholism had no effect on vaccine response. In the present study, no non-responders were detected.

Post-vaccination testing is essential to administer additional doses and also to determine the type of post-exposure prophylaxis.[1] This study indicates the need for routine early immunisation with hepatitis B vaccine and emphasises the importance of knowing the immune status following immunisation in healthcare workers and other susceptible individuals. An adequate anti-HBs level within one to six months following vaccination is shown to provide near lifelong protection. Those who show inadequate levels after primary HBV schedule may respond after additional doses. A non-responder is a person who does not develop protective surface antibodies after completing two full series of the hepatitis B vaccine and for whom an acute or chronic hepatitis B infection has been ruled out.[21] Non-responders do not benefit from routine post-exposure prophylaxis, they require HBIG. Hence, it is extremely important to be aware of the immune status following vaccination and practice effective modes of prevention of the dreadful hepatitis B infection.

Limitation of the study

Geometric Mean titre (GMT) of anti-HBs was not found out, as we could not perform dilutions of samples showing >1000 mIU/ml, due to cost restraints.

Financial support and sponsorship
State Board Medical Research, Kerala.

Conflicts of interest
There are no conflicts of interest.

References

1. Mast EE, Margolis HS, Fiore AE, Brink EW, Goldstein ST, Wang SA, *et al*. Center for disease control and prevention: A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: Recommendation of the advisory committee on immunization practices (ACIP) Part II: Immunization of adults. MMWR Recomm Rep 2006;55:1-23.
2. Sjogren MH Prevention of hepatitis B in nonresponders to initial hepatitis B virus vaccination. Am J Med 2005;118 Suppl 10A: 34S-9S.
3. Chaudhari CN, Bhagat MR, Shah T, Misra RN. Antibody to hepatitis B surface antigen in vaccinated health care workers. Med J Armed Forces India 2008;64:329-32.
4. Velu V, Nandakumar S, Shanmugam S, Thyagarajan SP. Persistence of anti-HBs titers after two different doses of Genevac B, a recombinant hepatitis B vaccine, in healthy adolescents. Indian J Gastroenterol 2007;26:48.
5. Wang CW, Wang LC, Chang MH, Ni YH, Chen HL, Hsu HY, *et al*. Long-term follow-up of Hepatitis B Surface antibody levels in subjects receiving universal Hepatitis B vaccination in infancy in an area of hyperendemicity: Correlation between radioimmunoassay and enzyme immunoassay. Clin Diagn Lab Immunol 2005;12:1442-7.
6. Chadha MS, Arankalle VA. Ten-year serological follow up of hepatitis B vaccine recipients. Indian J Gastroenterol 2000;19:168-71.
7. McMahon BJ, Bruden DL, Petersen KM, Bulkow LR, Parkinson AJ, Nainan O, *et al.* Antibody levels and protection after hepatitis B vaccination: Results of a 15-year follow-up. Ann Intern Med 2005;142:333-41.
8. Floreani A, Baldo V, Cristofoletti M, Renzulli G, Valeri A, Zanetti C, *et al.* Long-term persistence of anti-HBs after vaccination against HBV: An 18 year experience in health care workers. Vaccine 2004;22:607-10.
9. Williams JL, Christensen CJ, McMahon BJ, Bulkow LR, Cagle HH, Mayers JS, *et al.* Evaluation of the response to a booster dose of hepatitis B vaccine in previously immunized healthcare workers. Vaccine 2001;19:4081-5.
10. Zeeshan M, Jabeen K, Ali AN, Ali AW, Farooqui SZ, Mehraj V, *et al.* Evaluation of immune response to hepatitis B vaccine in health care workers at a tertiary care hospital in Pakistan: An observational prospective study. BMC Infect Dis 2007;7:120.
11. Havlichek D Jr., Rosenman K, Simms M, Guss P. Age-related hepatitis B seroconversion rates in health care workers. Am J Infect Control 1997;25:418-20.
12. Fisman DN, Agrawal D, Leder K. The effect of age on immunologic response to recombinant hepatitis B vaccine: A meta-analysis. Clin Infect Dis 2002;35:1368-75.
13. Struve J, Aronsson B, Frenning B, Granath F, von Sydow M, Weiland O. Intramuscular versus intradermal administration of a recombinant hepatitis B vaccine: A comparison of response rates and analysis of factors influencing the antibody response. Scand J Infect Dis 1992;24:423-9.
14. Ghanaei FM, Fallah MS, Arami M. The immunologic response to anti-hepatitis B vaccination among medical students of Guilan University of Medical Sciences, Guilan, Iran. Hepat Mon 2006;6:63-6.
15. Wood RC, MacDonald KL, White KE, Hedberg CW, Hanson M, Osterholm MT. Risk factors for lack of detectable antibody following hepatitis B vaccination of Minnesota health care workers. JAMA 1993;270:2935-9.
16. Nejad EM, Jafari S, Rabirad N. Hepatitis B virus antibody levels in high-risk health care workers. Hepat Mon 2011;11:662-3.
17. Shaw FE Jr., Guess HA, Roets JM, Mohr FE, Coleman PJ, Mandel EJ, *et al.* Effect of anatomic injection site, age and smoking on the immune response to hepatitis B vaccination. Vaccine 1989;7:425-30.
18. Bouter KP, Diepersloot RJ, Wismans PJ, Gmelig Meyling FH, Hoekstra JB, Heijtink RA, *et al.* Humoral immune response to a yeast-derived hepatitis B vaccine in patients with type 1 diabetes mellitus. Diabet Med 1992;9:66-9.
19. Shivananda S, Somani V, Srikanth BS, Mohan M, Kulkarni PS. Comparison of two hepatitis B vaccines (GeneVac-B and Engerix-B) in healthy infants in India. Clin Vaccine Immunol 2006;13:661-4.
20. Vijayakumar V, Hari R, Parthiban R, Mehta J, Thyagarajan SP. Evaluation of immunogenicity and safety of Genevac B: A new recombinant hepatitis B vaccine in comparison with Engerix B and Shanvac B in healthy adults. Indian J Med Microbiol 2004;22:34-8.
21. Vaccine Non Responders, Hepatitis B Foundation. Available from: http://www.hepb.org/professionals/vaccine_non-responders.htm. [Last accessed on 2013 Oct 03].