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Prevalence of Non-Responsiveness to an Indigenous Recombinant Hepatitis B Vaccine: A Study among Health Care Workers in A Tertiary Hospital

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ABSTRACT

Background and Aim:

Health care workers (HCW) are at higher risk of contracting HBV infection. Non-response to HBV vaccine is one of the major impediments to prevent healthcare associated HBV infection (HAHI). We estimated the prevalence of non-responsiveness to initial 3-dose regimen of an indigenous recombinant HBV vaccine (GeneVac-B) among South Indian HCWs and typed the HLA in non-responders.

Study Design and Method:

Of the 778 subjects screened over 1 year, 454 completed all three doses of the hepatitis B vaccination. Anti-HBs titers were estimated by microparticle enzyme immunoassay Automated ELISA. HLA typing was done using AllSet+™ Gold SSP.

Conclusion:

Our findings suggest that non-response to HBV vaccine is not a major impediment to prevent HAHI. Robust seroprotection rates can be achieved using this indigenous HBV vaccine. However, gender and BMI might influence the level of anti-HBs titers. We recommend the use of this cost effective HBV vaccine as well as post vaccination anti-HBs testing to prevent HAHI among HCWs.

KEYWORDS: *Hepatitis B vaccine, health care workers, non-responders*

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I. INTRODUCTION

Hepatitis B virus (HBV) infections are a serious global health problem resulting in 500,000 to 1.2 million deaths per year caused by chronic hepatitis, cirrhosis, and hepatocellular carcinoma. [1] Among the high risk groups, health care workers B(HCW) are more prone to contracting this debilitating disease. They are vulnerable to contaminated sharp injuries which constitute a major source of hepatitis B infection, with an estimated 66,000 cases and 261 death sannually, in developing countries. [2]

Vaccination is the most effective strategy in prevention and control of HBV infection. There have been efforts to make HBV vaccination a part of the standard childhood immunization scheme in

many countries. However, even strict adherence as per the recommended schedule does not always assure protection, and the phenomenon of non-response or inadequate response is being increasingly reported. [3],[4] Several factors have been postulated to influence response to the vaccine. HLA polymorphism is one of the crucial host genetic factors known to influence vaccine response. [5] Based on antibody titers to the viral surface antigen (anti-HBs titer), 1 month after the final dose, vaccines can be categorized as non-responsive (< l0 mIU/mL) or hypo-responsive (<100 mIU/mL). [6] Despite completing vaccination, non-responsive subjects are more at risk of acquiring the infection with potential progression to fatal sequelae. Various studies have shown that prevalence of non-responsiveness to the initial 3-dose regimen ranges between 10 and 15%. [5],[7],[8],[9] Given this prevalence rate, estimation of post-vaccination anti-HBs titers is of utmost importance in the protection of health care workers. There have been no vaccine efficacy studies conducted among HCWs in a South Indian population. Hence, in this study, we estimated the prevalence of non-responsiveness among South Indian Health Care Workers in a tertiary hospital and profiled their HLA alleles.

II. METHODS

Sample size:

The sample size was calculated based on the prevalence of non-responsiveness to the initial 3-dose regimen (5-10%) to the HBV vaccine. The sample size was calculated to be 239 with 5% α level and 99% power.

Study design:

In this longitudinal study, staff and students were recruited in Saveetha Medical College, Chennai, from May 2018 to September 2019. The study was approved by the Institutional Review Board (IRB) prior to commencement and subjects were recruited after informed written consent.

Subjects were recruited from persons undergoing a routine health check-up at the hospital staff and student health clinic or as part of a pre-employment check-up. The subjects comprised various categories of hospital personnel including doctors (2%), nursing staff and students (48%), technical staff (18%), support staff consisting of clerks, accountants and medical records personnel (20%) and house-keeping staff (12%). Recruitment criteria were as follows: Subjects belonging to one of the four South Indian states, negative for HBsAg and HIV, and having no past history of hepatitis B vaccination. Subjects ranged in age between 16 and 50 years. In addition, total anti-HBc positivity (anti-HBc), which suggests past exposure to HBV, was used as an exclusion criterion.

At the time of recruitment, subjects were given a detailed explanation about the importance of adherence to the vaccination schedule, the need for anti-HBs estimation and the implications of vaccine failure. A questionnaire to elicit past medical history concerning smoking, alcoholism, diabetes, allergic reactions, and drug history, specifically related to immunosuppression was administered. In addition, ethnic background, past history and or family history of jaundice, possible exposure to infected sharps (including tattoo-needles)/instruments/blood products, were obtained. Further, anthropometric details (height and weight) to determine BMI were also elicited.

Vaccine administration:

An indigenous recombinant vaccine-GeneVac-B (Serum Institute of India Ltd., Hadapsar, Pune, India), containing 20 mcg of HBsAg, was administered intramuscularly in the deltoid muscle of individuals who were negative for total anti-HBc. Vaccination was done according to the Centers for Disease Control and Prevention (CDC) schedule (0, 1 and 6). Anti-HBs titers were measured, 1 month from the date of receiving the third dose.

Screening assays:

Blood samples were obtained by venepuncture using sterile precautions. Anti-HBc was done using the AxSYM Core Assay. HIV testing was done using the AxSYM HIV Ag/Ab Combo Assay, hepatitis B surface antigen using AxSYM HBsAg (V2). All assays were done strictly adhering to the manufacturer's instructions. Internal quality controls (IQCs) were included to monitor the routine performance of the screening assays. The performance of the screening assays was consistently satisfactory.

Quantification of anti-HBs

Quantification of anti-HBs was done by the AxSYM AUSAB, which is a microparticle enzyme immunoassay Automated ELISA. The standards and positive controls of this assay are traceable to the World Health Organization international reference preparation for antibody to HBsAg. In addition low level IQC was included in every run; the precision and accuracy of the runs were within the limits.

HLA typing

The low resolution typing of class I (A and B) and II (DR and DQ) alleles were performed using commercial assay by *AllSet*+™ Gold SSP. Manufacturer's instructions were followed.

Statistical analysis

The correlations between antibody levels and BMI, gender, ethnicity, and deviation from the CDC regimen of vaccination were assessed using Chi-square tests on Epi Info version 6 and SPSS version-13 software. The $P \leq 0.05$ was considered significant.

III. RESULTS

Over the study period, we screened 778 HCWs. Fifty-nine were anti-HBc positive, manifesting as a prevalence rate of 7.5% (5.6-9.5%, 95% CI) in this group of South Indian population. Among the HCWs found to be anti-HBc negative, 125 did not complete all three doses or did not provide a sample for post-vaccination antibody titers. A further 140 vaccines had their third dose beyond the study period and hence could not be followed up. The main ethnic groups represented in the study group were Adidravida (n = 239), Syrian Christian (n = 45), Nadar (n = 33), Mudaliyar (n = 27), Vanniyar (n = 26), Naidu (n = 13). Other groups constituted 71 additional vaccinees.

Of the 778 HCWs, 454 completed all three doses of the vaccine and had estimations of their post-vaccination antibody titers. The seroconversion rate (anti-HBs >10 mIU/mL) was 98.89%. There were 412 (90.8%) subjects with a titer >1000 mIU/mL, 35 (7.6%) with a titer of 100-1000mI/mL, 2 (0.43%) were hyporesponsive with a titer <100 mIU/mL and 5 (1.1%) were non-responsive [Table 1].

TABLE: 1 CATEGORIES AND INFLUENCE OF GENDER ON THE VACCINE RESPONSE:

RESPONSE LEVEL mIU / ml	TOTAL [n=454] n [%]	GENDER [%]		P Value
		MALE [n = 148]	**FEMALE [n = 306]**	
Negative	5 [1.1]	3 [2.06]	2 [0.65]	0.088
>1000	412 [90.8]	130 [89.6]	282 [92.7]	
100 – 1000	35 [7.6]	13 [8.96]	22 [7.23]	
10 – 100	2 [0.43]	2 [1.37]	0	

The seroprotection rate was similar in subjects who adhered to the CDC 0, 1, 6 month regimen and those who deviated from it (P = 0.36) (data not shown). There was no significant association between levels of antibody titers and the ethnic background (P = 0.62). Although a larger number of female subjects tended to have antibody levels (>1000 mIU/mL) compared to male subjects, there was no significant difference in the rates of seroprotection between gender (P = 0.088) [Table 1].

Among the five subjects non-responsive after the initial 3-dose regimen, three were in the lower limit of normal range of BMI (18.90 Kg/m ^{2}, 18.65 Kg/m ^{2} and 18.29 Kg/m ^{2}) and two (30.02 Kg/m ^{2} and 25.46 kg/m ^{2}) were in the overweight category as per the latest recommendations for the Indian population. [10] We observed that antibody titers <1000 mIU/mL are significantly associated with the highest quartile of BMI (P < 0.001).

The results of the low resolution HLA typing of the 5 subjects non-responsive to the initial 3-dose regimen are shown in [Table 2].

TABLE 2 : Demographic features, HLA typing and Vaccination schedule of the subjects non – responsive to the first 3 dose schedule [0,1 and 6] of HBV vaccination:

Ethnic group	Age	Gender	Category *	HLA alleles			
Adidravida	26	M	2	A*02 and *24	B*15 and *35	DRBI *15 and *16	DQBI*05
Vanniyar	32	F	3	A*03 and *31[N]	B*15 and *40	DRBI *04 and *11	DQBI*05
Christian	44	F	2	A*02 and *24	B*13 and *37	DRBI *07 and *10	DQBI*05 and 02
Adidravida	36	M	1	A*11 and *68	B*51 and *58	DRBI *15 and *03	DQBI*06 and 02
Adidravida	22	M	3	A*01 and *24	B*08 [N] and *52	DRBI *03 and *14	DQBI*05 and 02

DISCUSSION

This is the first South Indian study to assess the efficacy of an indigenous recombinant HBV vaccine among HCW. Our study showed an excellent vaccine response, with the prevalence rate of non-responsiveness to the initial 3-dose regimen being 1.1%. This prevalence rate of non-responsiveness was much lower than that reported in North India (5-15%) and in other parts of the world. [5],[7],[8],[9] As the North Indian study followed the same CDC schedule, we speculate that this difference could be due to genetic differences between the two regions in the Indian sub-continent. Vaccination with various HBV

recombinant vaccines (GeneVac-B, Engerix B, Shanvac B) has been shown to achieve good sero-protection rate in the Indian population. [11],[12] Furthermore, recombinant HBV vaccines have been shown to elicit good sero-protection rates among health care workers. [13]

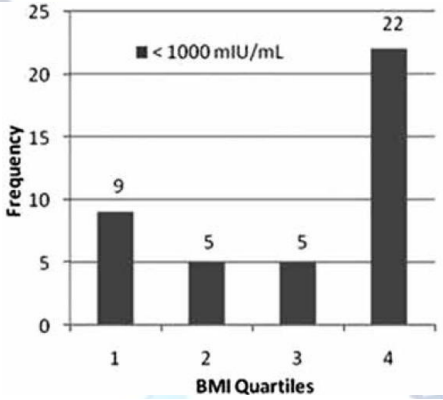
Despite issuing reminders to complete vaccination and check antibody levels, only 230 subjects (50.7%) strictly adhered to the CDC schedule and checked their antibody titers on time. We classified individuals who deviated from the recommended schedule into eight categories as described in [Table 2]. The seroprotection rate was similar in subjects who adhered to the CDC schedule and those who completed three doses within a year at varying intervals (P = 0.36). Since we have not assessed the longevity of immune response, we would still recommend strict adherence to the CDC regimen of HBV vaccination.

In our study, age of subjects ranged between 16 and 50 years, while the ratio of males to females was about 1:2 (148:306). Gender and age have been shown to play a significant role in immune response to vaccine. The female gender has been known to mount a better response. [7],[14] Even though there were more female subjects recruited into the study, we found no significant difference in seroprotection (>10 mIU/mL) rates between males and females (P = 0.088) However higher levels of anti-HBs titers were seen in female subjects.

Non-genetic factors including obesity, smoking, drug abuse, alcoholism, chronic infections, diabetes, renal failure and immunosuppression, are known to affect response to the hepatitis B vaccine. [7],[15],[16] We speculate that the high rate of seroconversion in our study could be attributed to the elimination of the above mentioned factors among majority of our study subjects, because of the strict exclusion criteria and the stringent physical examination as part of pre-employment evaluation. Active HBV infection is also known to influence the HBV vaccine response, which was ruled out in our study by performing HBsAg and total core antibody (anti-HBc), prior to the initiation of HBV vaccination.

BMI has been reported to influence the level of vaccine respose. [17] Our study also supports this observation as we found that antibody titres <1000 mIU/mL are significantly associated with the highest quaratile of BMI (p<0.001) [Figure : 1]. Though the value of <1000 mIU / mL has no significant clinical implication, the difference observed between those with high BMI versus those with normal or low BMI warrants further evaluation.

Figure : 1 Comparison of BMI and anti HBs titre <1000 mIU / mL among HBV vaccines. BMI was categorized into the following 4 quartiles (kg/m2): [1] <18 [2] 18 – 20 [3] 20 – 23 [4] >23. Anti HBs titres <1000 mIU / mL are significantly associated with the highest quartile of BMI [>23kg/m2] p < 0.001



With regard to the ethnic background, the largest groups in our study population belonged to the Dravidian communities (Adidravida and Nadar) from the state of Tamil Nadu and Syrian Christian community from the state of Kerala. Genetic factors are known to influence the HBV vaccine response. [5] Studies have shown the association of HLA alleles with the response to hepatitis B vaccine. [5] In the present study, all five subjects non-responsive to the initial 3-dose schedule had HLA alleles associated with non-responsiveness to the vaccine, as reported in the North Indian study. [9] One of the limitations of the study is that the HLA alleles were not typed for responders to the vaccine. Hence, no firm conclusion can be drawn between HLA polymorphisms and non-response to the HBV vaccine.

A study in North India has shown that A1, B15, B40, A10, DR53 and DQ2 alleles were associated with non-response to HBV vaccine. [9] An earlier published study has shown a representation of these alleles in the south Indian population. [18] However, despite the presence of these alleles among the various South Indian ethnic groups in this study, our study participants on the whole mounted a good response to the vaccine as compared to the earlier study. This finding suggests that HLA polymorphisms are not solely responsible in determining vaccine response.

The prevalence rate of anti-HBc positivity was 7.58% (5.6-9.5%; 95% CI) in this group of South Indian population. This prevalence rate is lower

than that observed in other parts of the country and blood donors in our hospital (18-24%). [19] As the screened population of HCWs underwent an extensive clinical evaluation prior to enrollment into the institution, we speculate their risk factors for acquisition of such parenteral viruses were fewer.

Previous studies in India have shown the rate of vaccination among HCW was 55% while 45% of them were unaware of their vaccination status. [20] In an intermediate HBV endemic zone like India, the results of our study only augments the existing recommendation towards inclusion of HBV vaccination in the universal immunization program. Also, health care institutions must formulate a policy to vaccinate all categories of employees and trainees who have risks of occupational exposure to HBV and also measure post-vaccination titers. In the process of conducting our study, we not only imparted information to our HCW regarding the level of seroprotection among vaccines but also identified sections of the hospital staff that had not previously been vaccinated despite being at a high risk of contracting the infection.

In conclusion, non-response to HBV vaccine is not a major impediment to prevent healthcare associated HBV infection. Cost effective indigenous HBV vaccine is sufficient to achieve robust seroprotection rate among HCWs. Gender and BMI levels might influence the level of anti-HBs titers. We recommend the use of this cost effective HBV vaccine as well as post vaccination anti-HBs testing for successful prevention of HAHI.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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