

Immune response to hepatitis B vaccine: An evaluation

Anitha Madhavan, Dhanya Sasidharan Palappallil¹, Jayalakshmy Balakrishnapanicker², Anjana Asokan

Department of Microbiology, Government TD Medical College, Alappuzha, ¹Department of Pharmacology, Government Medical College, Kottayam, ²Department of Microbiology, Government Medical College, Idukki, Kerala, India

Abstract

Background: Hepatitis B virus infection is a major public health problem in India, and all health-care workers (HCWs) need to be immunized to prevent occupational exposure. This study was done to find the hepatitis B vaccination rates, immune response, and predictors of titer < 10 mIU/ml among students and HCWs of a tertiary care institution in the state of Kerala.

Materials and Methods: This was a cross-sectional study conducted in the Department of Microbiology, Government TD Medical College, Alappuzha, Kerala, India, for a period of 1½ years between January 1, 2016, and June 30, 2017. Vaccination rates were collected through a screening proforma. Of the 1321 participants who filled the screening proforma, 5 ml of blood was collected aseptically from 579 participants who were fully vaccinated (all the three doses of vaccine) and stored at –20°C until antibody to hepatitis B surface antigen (anti-HBs) assay was done using Microlisa (Biorad). Data were analyzed using SPSS for Windows, version 16.0. (SPSS Inc., Chicago, IL, USA) (trial version).

Statistical Analysis: Descriptive data were expressed using frequencies and percentages, and Chi-square test was applied to find the association between antibody titer < 10 mIU/ml and independent variables.

Results: Of the 1321 participants who filled up the screening proforma, the vaccination rate was 72.6%. Majority of the participants, i.e. 83.5% of doctors, 81.1% of nurses, 69.7% of students, and 21.4% of technicians, had taken all the three doses of hepatitis B vaccine. Of the fully vaccinated ($n = 959$) participants, 76.9% had the vaccination during adulthood and only 26.1% had it during childhood. The correlate of protection was defined as the presence of anti-HBs ≥ 10 mIU/ml. The mean antibody titer was 448 ± 284.97 mIU/ml ranging from 9.8 to 2000. Of the 579 participants whose titer was checked, 71 (12.3%) had a nonprotective titer of < 10 mIU/ml. We found that age > 35 (odds ratio [OR]: 3.85, 95% confidence interval [CI]: 2.12–6.99), last dose > 10 years (OR: 5.01, 95% CI: 2.94–8.55), no boosters or revaccination (OR: 2.94, 95% CI: 1.42–6.07), and body mass index (BMI) > 25 (OR: 2.51, 95% CI: 1.44–3.39) were associated with nonprotective titer.

Conclusion: More than a quarter of the study population who were at high risk of exposure were unvaccinated or partially vaccinated. Even after taking the full course of hepatitis B vaccine, 12.3% had titer < 10 mIU/ml. Nonprotective titer was found to be associated with age > 35 years, last dose taken > 10 years ago, no boosters/revaccination, and BMI ≥ 25 .

Keywords: Antibody titer, health-care workers, hepatitis B, immune response, occupational exposure, vaccine

Address for correspondence: Dr. Dhanya Sasidharan Palappallil, Department of Pharmacology, Government Medical College, Kottayam, Kerala, India.

E-mail: drspdhanya@gmail.com

Received: 27-07-19, **Revised:** 24-11-19, **Accepted:** 15-12-19, **Published:** 07-05-20.

Access this article online	
Quick Response Code:	Website: www.piconline.org
	DOI: 10.4103/picr.PICR_119_19

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Madhavan A, Palappallil DS, Balakrishnapanicker J, Asokan A. Immune response to hepatitis B vaccine: An evaluation. *Perspect Clin Res* 2021;12:209-15.

INTRODUCTION

Hepatitis B virus (HBV) infection causes acute and chronic hepatitis through horizontal and vertical transmission and accounts for disease burden of 50 million cases in India with a prevalence of 2%–7%, amounting to an intermediate endemicity.^[1] Hospital-based studies conducted in Kerala reveal a prevalence of 6.3%.^[2] While acute hepatitis B characterized by acute inflammation and hepatocellular necrosis is self-limiting, chronic hepatitis B with persistence of hepatitis B surface antigen (HBsAg) in blood and serum for more than 6 months presents in myriad forms ranging from carrier state with no clinical manifestations to cirrhosis, end-stage liver disease, or hepatocellular carcinoma.^[3,4] Long-term viral suppression, which remains the only modality of treatment, is challenging owing to the poor adherence due to high cost, causing a vicious cycle of disease progression and transmission. Vaccination strategies and health education need to be aggressively imparted in high-risk population which also includes the health-care workers (HCWs).

Hepatitis B vaccination for HCWs is a key component of the WHO Hepatitis B Elimination Strategy 2016–2021.^[5] In developing countries, 40%–65% of HBV infections among HCWs are attributable to percutaneous occupational exposure, whereas the corresponding risk in developed countries is as low as 10%.^[6] HBV is more infectious than human immunodeficiency virus or hepatitis C virus and as little as 10^{-5} mL of blood can be infectious.^[7] HBV vaccine has been available since 1982 and recombinant DNA vaccine since 1987 with a seroprotection of 85%–90%.^[8] HBV vaccination has been adopted in the Universal Immunization Programme in India in 2007–2008 following its recommendation by the World Health Organization in the 1990s, and several studies have been done on vaccination efficacy among children.^[3,9] Occupational Safety and Health Act recommends HBV vaccine followed by the confirmation of vaccine response in all HCWs.^[10] However, despite the high risk of contracting the disease among HCWs and medical professional students, the vaccination is only voluntary. Even though admissions to medical professional colleges in Kerala mandate hepatitis B vaccination, the vaccination status is not followed up, leading to incomplete vaccination, amounting to an unprotected status. This study was conducted with objectives to assess the hepatitis B vaccination rates in the study population, to evaluate the immune response to hepatitis B vaccine in students and HCWs, to determine the duration of persistence of antibody to hepatitis B surface antigen (anti-HBs) after vaccination, and to find the association of titer <10 mIU/ml by enzyme linked

immunosorbent assay (ELISA) method with independent variables.

MATERIALS AND METHODS

This was a cross-sectional study conducted in the Department of Microbiology at Government TD Medical College, Alappuzha, for a period of 1½ years (January 1, 2016–June 30, 2017) after getting clearance from the Ethics Committee (EC) (EC/02/2016 dated December 26, 2015, registered with the Central Drugs Standard Control Organisation). The participants were requested to fill the proforma after obtaining the informed consent from them. Inclusion criteria for titer estimation included completion of full course of hepatitis B vaccine (0, 1, and 6 months). Exclusion criteria included unvaccinated and partially vaccinated individuals, those with a past history of hepatitis B infection, or those on prolonged steroid therapy. A sample size of 567 was calculated based on the failure of seroconversion to hepatitis B vaccine in previous studies.^[8] Five milliliters of blood was collected aseptically from each participant and stored at -20°C until anti-HBs assay was done using quantitative ELISA (direct antibody sandwich enzyme immunoassay using Microlisa, BIO-RAD Laboratories, Redmond, WA 98052, USA). For each assay, anti-HB-negative control and calibrators corresponding to 10, 100, 400, and 1000 mIU/ml of anti-HBs were used. The correlate of protection (CoP) was defined as the presence of anti-HBs ≥ 10 mIU/ml.^[11] For quantitative interpretation, a graph was plotted with the optical density of controls against their assigned concentrations, using a linear regression with Microsoft Excel 2010 and equation formulated. The participants having inadequate titer values <10 mIU/ml were tested for HBsAg, and HBsAg-negative individuals

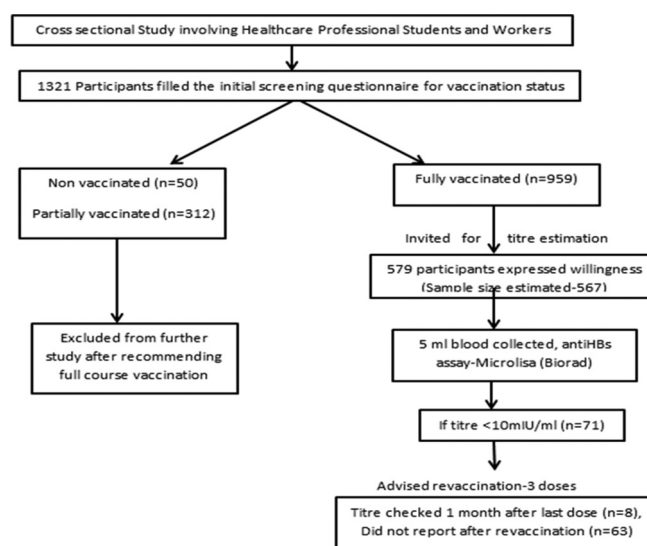


Figure 1: Schematic representation of methodology

were advised to take three doses of hepatitis B vaccine and report after 6 weeks after the third dose for rechecking the anti-HBs titre as shown in Figure 1. The data were analyzed using the Statistical Package for the Social Science SPSS for Windows, version 16.0. (SPSS Inc., Chicago, IL, USA) (trial version). Descriptive data were expressed using frequencies and percentages, and Chi-square test was applied to find the association between antibody titer <10 mIU/ml with variables such as age >35 years, female gender, body mass index (BMI) ≥25, smoking status, alcoholism, booster dose status, years elapsed after the last dose, and presence of chronic disease.

RESULTS

A total of 1321 participants with a mean age of 24.98 ± 7.9 years filled up the screening proforma, of which 965 (73.1%) were female and 356 (26.9%) were male. The vaccination rate was 72.6% as 959 participants were fully vaccinated with 0, 1, and 6 doses of hepatitis B vaccine as shown in Figure 2, and they were invited for antibody titer estimation. Around 312 (23.6%) were partially vaccinated with 0 or 0 and 1 doses and 50 (3.8%) had not taken any dose of hepatitis B vaccine. Of the 50 participants who were not vaccinated, 15 (30%) were nurses, 16 (32%) were students, 18 (36%) were technicians, and 1 (2%) was a doctor. The vaccination rate was 60.7% among males and 70% among females. Of the 823 students screened, 614 were MBBS, 177 were BSc Nursing, and 32 were BDS students. Among them, 371 (45.08%) MBBS, 170 (20.65%) BSc Nursing, and 32 (3.8%) BDS students had taken primary series of vaccination. Of the 959 participants who were fully vaccinated, 222 (23.1%) had vaccination during childhood and 737 (76.9%) during adulthood. Only

21 (0.4%) participants reported developing adverse event following immunization in the form of pain at the site of injection, rashes, dizziness, and weakness of the whole body after primary vaccination in the screening proforma.

Five hundred and seventy-nine participants who completed primary vaccination with three dose series of hepatitis B vaccine were recruited for anti-HB assay. Their mean age was 25.5 ± 7.65 years, and the majority of participants fell in the 18–30 years' age group (81.5%) followed by 31–45 years (14.9%) and 3.6% were above 45 years. Among them, 479 (82.8%) were females and 17.2% were males. There were 307 students (145 [25%] MBBS, 133 [23%] BSc Nursing, and 29 [5%] BDS), 141 (24.4%) doctors, 124 (21.4%) nurses, and 7 (1.2%) lab technicians and Grade 4 assistants. After completing primary vaccination, 161 (27.8%) participants had taken at least one booster dose at the time of titer estimation. Majority of the boosters (124) were taken by participants who had childhood vaccination, of which 113 had taken revaccination, three had taken two booster doses, and the rest single dose of the booster.

The mean anti-HB antibody titer was 448.3 ± 284.97 mIU/ml ranging from 9.8 to 2000. Of the 579 participants, 71 (12.3%) had titer <10 mIU/ml, 36 (6.2%) had titer at 10–100 mIU/ml, 465 (80.3%) had titer at 100–1000 mIU/ml, and 7 (1.2%) had titer between 1000 and 2000 mIU/ml. Of the 71 participants with nonprotective titer, 9 had taken a single booster (8 after childhood and 1 after adult vaccination). All the 71 participants with nonprotective titer were advised revaccination with hepatitis B vaccine. Eight of them reported back after revaccination with 3 doses, after 1½ months of the third dose and had protective titers. We did not identify any nonresponder (who has titer <10 mIU/ml after revaccination with secondary three-dose series of hepatitis B vaccine).

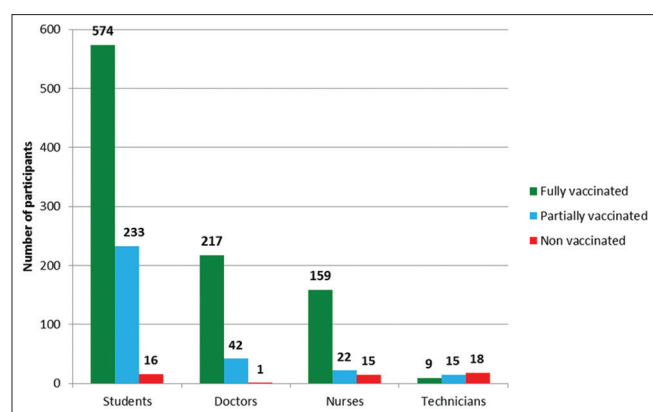


Figure 2: Vaccination among health-care students and professionals (fully vaccinated – those who completed all the three doses (0, 1, and 6) of primary vaccination with or without boosters or revaccination; partially vaccinated – those who had taken 0 or 0 and 1 doses; and nonvaccinated – those who had not taken any dose of hepatitis B vaccine)

On comparing the association of year of vaccination with titer, it was seen that out of the 71 participants with titer <10 mIU/ml, 31 (43.7%) had last vaccination more than 10 years ago (Chi-square 40.28, *P* < 0.001), as shown in Figure 3. There was a weak negative correlation (Pearson's *R* = -0.259, *P* < 0.001) with antibody titer and increasing years of vaccination, as shown in Figure 4. An antibody titer of 350 mIU/ml was seen in a participant who had taken the vaccine 25 years back.

As summarized in Table 1, the nonprotective titer <10 mIU/ml was found to be associated with age >35 years, last dose taken >10 years ago, no boosters/revaccination, and BMI ≥25. Gender, smoking, alcoholism, and chronic illness such as diabetes mellitus were not associated with titer <10 mIU/ml.

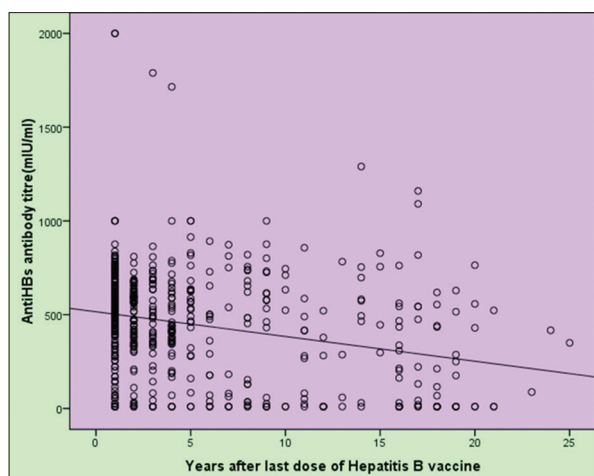


Figure 3: Association of antibody titer and years of vaccination

Table 1: Association of hepatitis B surface antigen titer <10 mIU/ml with risk factors

Variable	n (%)	χ^2, P	OR (95% CI)
Gender			
Female	55 (77.5)	1.57, 0.210	0.68 (0.37-1.25)
Male	16 (22.5)		1.46 (0.80-2.68)
Age >35 years	20 (28.2)	21.79, <0.001	3.85 (2.12-6.99)
Last dose was taken before 10 years	31 (43.7)	40.28, <0.001	5.01 (2.94-8.55)
No boosters/revaccination	62 (87.3)	9.23, 0.002	2.94 (1.42-6.07)
Body mass index >25	22 (31)	11.01, 0.001	2.51 (1.44-4.39)
Smoking	1 (1.4)	0.104, 0.74	1.43 (0.16-12.48)
Alcoholism	1 (1.4)	0.00, 0.98	1.02 (0.12-8.44)
Chronic illness such as diabetes	9 (12.7)	2.26, 0.13	1.76 (0.83-3.89)

CI=Confidence interval, OR=Odds ratio

DISCUSSION

The occupational risk associated with hepatitis B among health-care professionals has been identified long back. Vaccine-induced seroprotection is a useful surrogate of its efficacy, and we estimated the anti-HBs antibody titers to check the protection status of the health-care students and professionals at our institution. The nonresponders of vaccine are unprotected and are at a threat to develop the disease after accidental exposure to hepatitis B. In HCWs, early identification of nonresponders is a must by checking the titer levels so that they adopt better personal protective measures rather than being in a state of false sense of security.^[8,12] The Centers for Disease Control and Prevention (CDC) guidelines recommend anti-HBs titer measurement after 1–2 months of the last vaccine.^[13] A health-care professional is considered immune to hepatitis B only if the person has completed the three doses of vaccine and has anti-HB titer >10 mIU/ml.^[13]

Of the 1321 health-care professionals screened, 959 who had completed single series of vaccination with or without

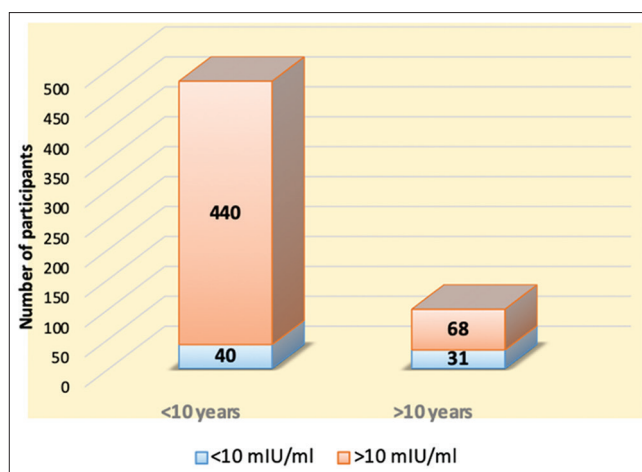


Figure 4: Antibody titer in participants with last dose > or <10 years

booster doses were eligible to be enrolled for titer assay. The percentage of HCWs who satisfied the inclusion criteria and considered immunized were 83.5% of doctors, 81.1% of nurses, 69.7% of students, and 21.4% of laboratory technicians. Studies have shown variable vaccination rates from 33% to 83% among HCWs in various states in India.^[14-16] Abidi *et al.* in a study found that the overall vaccination rate was higher among doctors than nurses.^[17] In the present study, higher vaccination rate was seen in females as 70% of them were vaccinated compared to 60.7% of males. In the study by Patil *et al.*, the vaccination rate among the doctors was lowest as only 72% of them were fully vaccinated as compared to 93% of nurses and 82% of other staff.^[16]

Studies show that vaccine is effective in 90%–95% of adults by protecting against HBV infection.^[18] Globally, immune response following primary vaccination against hepatitis B has been found to be 55%–100%.^[8] In this study, titers of 579 participants were checked after primary vaccination, of which 161 (27.8%) had taken boosters/revaccination. The immune response was 87.7% as compared to 96.4% by Purvi *et al.* and 97.5% by Kollathodi *et al.*^[8,19] Of the 71 (12.3%) participants who had titer <10 mIU/ml, only 8 reported back after revaccination and had 100% seroconversion. Hence, we could not identify any nonresponders. Studies elsewhere have shown seroconversion of 89.24%–100% after revaccination.^[8,19,20] Booster doses are dose of hepatitis B vaccine administered after primary vaccination series to provide rapid protective immunity against significant infection. However, there is no point in taking booster doses without checking the anti-HBs titer as the responders to boosters vary by population and age at receiving the primary hepatitis B vaccine.^[13] In 2016, the World Health Organization has done away with the concept of booster doses.^[5] It is recommended that in those with anti-HBs

titer <10 mIU/ml after primary vaccination, a secondary vaccine series of three doses has to be given. Those with titer >10 mIU/ml following revaccination are protected for life.^[5]

In our study, we found that nonprotective titer <10 mIU/ml was found to be associated with age >35 years, last dose taken >10 years ago, no boosters/revaccination, and BMI \geq 25. We could not associate gender, smoking, alcoholism, and chronic illnesses such as diabetes mellitus with titer <10 mIU/ml. Several studies have shown that there is an inverse relation of age with vaccine immunogenicity and as found in our study, age more than 35 years had 3.85 times chance to develop poor response to vaccine.^[19,21] This is in contrast to that reported by Purvi *et al.*, in whom patients of all age groups under the study had a seroconversion of 95%–97%.^[8] In tune with the inverse relation of immunogenicity with age goes the statement of decline in immunogenicity of vaccine as years run by after vaccination. We could establish a weak negative correlation of years after vaccination with that of the anti-HBs antibody titer, which is similar to the results observed elsewhere.^[8,19,22] When time since vaccination was considered, the protection rate declined and there is statistically significant reduction in anti-HBs titers beyond 10 years of postvaccination. Despite this, we could find a titer of 350 mIU/ml in a participant who had taken the last dose of vaccine 25 years back. This is in line with Gilca *et al.* who reported a persistent protective level of anti-HBs antibodies after 22 years of primary doses.^[23]

We found that the risk for having titer <10 mIU/ml was 2.9 times higher in those who were immunized with primary vaccination alone without a booster. However, this may be viewed skeptically as the current recommendation is to take a second series of vaccination if the titer is <10 mIU/ml and blanket boosters are no longer advocated. In this study, majority of the participants had taken booster doses or revaccination without checking the titer after primary vaccination. The CDC recommends booster vaccine only for hemodialysis patients and immunocompromised patients with HIV, hematopoietic stem-cell transplant recipients, and patients receiving chemotherapy.^[24] For nonresponders, the current recommendation is a full-course revaccination.^[5] A vaccination course is said to be complete only if three doses of the vaccine have been taken and the antibody titer is checked and documented. This has to be made a mandatory requirement for all health-care professionals. In government medical colleges in Kerala, it is recommended to take hepatitis B vaccine at the time of admission to medical, dental, and paramedical courses. Yet, it is a sad fact that there is no proper follow-up of the actual

protection status on whether the student has completed the course of vaccine and developed protective titers. Instead of asking vaccination certificate against hepatitis B, the anti-HBs titer assay should be made mandatory for students being enrolled as health-care professionals to prevent inadvertent revaccination among those students who had taken childhood vaccination.

We found that overweight participants with BMI >25 had a higher risk of developing nonprotective titer. This is in concurrence with several studies published so far which stated that obesity was a predictor of poor response to the vaccine.^[3,25-28] This may be attributed to the effect of deposition of HBV vaccine in adipose tissue rather than in muscle, leading to the denaturation of antigen by enzymatic action and hormonal effects in overweight individuals.^[3,25-27] Yang *et al.* stated that in overweight persons, there can be damaged proliferation and function of the antibody-secreting plasma cells.^[3] Liu *et al.* stated that the mechanism responsible for decreased immunization responses in obesity included leptin-induced systemic and B cell intrinsic inflammation, impaired T cell responses, and lymphocyte division and proliferation.^[29] However, recent studies done by Purvi *et al.* and Kollathodi *et al.* did not find any association of BMI with that of nonresponse to hepatitis B vaccine.^[8,19]

We could not find any relation of gender with nonprotective titers, which is comparable to those published elsewhere.^[8,19,25] There are contrasting results regarding the association of gender with titer <10 mIU/ml as some studies show that it is males^[3] who have decreased response, while others show that it is females.^[10,26] Yang *et al.* stated that only few immunological genes are expressed on the Y chromosome unlike the X chromosome and testosterone damages the production of immunoglobulin (Ig) IgG and IgM from B-lymphocytes and restrains the production of interleukin-6 from monocytes as opposed to estrogen which activates them, which influences the vaccine response.^[30] Although some studies have shown that smoking and chronic diseases result in negative response with no-protective titers, we could not establish any association.^[3,6,19,25] In line with Kollathodi *et al.*, we could not establish an association of alcoholism with anti-HB titer <10 mIU/ml.^[19] This may be attributed to the participation of low number of participants with smoking, alcoholism, and chronic disease as in the case of Purvi *et al.*^[8] Alcohol due to its ability to cause cirrhosis has been incriminated to be an independent risk factor of poor immune response. Literature shows that nicotine and persistent alcohol can alter immune response by affecting the antigen-mediated T cell pathway and intracellular calcium response.^[3]

Antigenic subtypes of HBV exist, but immunization provides immunity to all subtypes because of the presence of a common antigen. When immune memory cells are present, the anti-HBs responses are immediate within 7–10 days following an exposure, and those with titer >10 mIU/ml 1 month after a dose of vaccine may be a primary immune response or it can be an anamnestic response.^[31] T helper cell responses that mediate the memory of B cells have been induced with a titer >10 mIU/ml. Anamnestic response that prevents disease and infection is initiated when a vaccinated person is exposed to HBV.^[11] Hence, we have to revaccinate persons who have titer <10 mIU/ml following primary vaccination. We found that all the eight patients who had revaccination had seroconverted with good titers. Sixty-three out of the 71 participants (88.7%) who had titer <10 mIU/ml and advised revaccination did not report back for titer estimation. This shows the lack of awareness, lackadaisical attitude, or busy professional commitment, which requires intervention. Following this, the Hospital Infection Control Committee of our institute drafted policies for compulsory immunization followed by titer checking in new recruits of HCWs.

Limitations

Majority of the persons who had titer <10 mIU/ml who were advised revaccination did not report back for titer estimation. We could not get proper data on the brand of vaccine used. We could not get any authentic data on the vaccination status of the participants through health cards or previous antibody titer reports and had to believe what the participants had written in the screening proforma.

CONCLUSION

More than a quarter (362) were unvaccinated or partially vaccinated among the screened participants (1321), and they were at high risk of exposure. Even after taking a full course of hepatitis B vaccine, 12.3% had lower than CoP (<10 mIU/ml). Nonprotective titer was found to be associated with age >35 years, last dose taken >10 years ago, no boosters/revaccination, and BMI \geq 25. We could not find any association of gender, smoking, alcoholism, and chronic illness with nonprotective titer in this study. This study brings forth the need for initiating awareness program regarding the need for immunization against HBV in health-care professionals and students. Vaccine should be made available free of cost for all HCWs and students and they should be followed up by checking and documenting anti-HBs antibody titer. Records should be maintained regarding their hepatitis B vaccination status.

Acknowledgment

We would like to thank all the participants who were involved in this study, Mrs. Aiswarya, Lab Technician, Department of Microbiology, Government TD Medical College, Alappuzha, and all other staff of Department of Microbiology for their support in this study. We thank the State Board of Medical Research, Government of Kerala, through Government TD Medical College, Alappuzha, for funding the study.

Financial support and sponsorship

This study was funded by the State Board of Medical Research, Government of Kerala.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Ray G. Current scenario of hepatitis B and its treatment in India. *J Clin Transl Hepatol* 2017;5:277-96.
2. Antony J, Celine T. A hospital-based retrospective study on frequency and distribution of viral hepatitis. *J Glob Infect Dis* 2014;6:99-104.
3. Yang S, Tian G, Cui Y, Ding C, Deng M, Yu C, et al. Factors influencing immunologic response to hepatitis B vaccine in adults. *Sci Rep* 2016;6:27251.
4. Kuriakose M, Ittyachen AM. An investigation into the high prevalence of hepatitis B in a rural area of Kerala state, India: Hypothesis on *Chrysops* sp. (*Diptera: Tabanidae*) Transmission. *Biomed Res Int* 2018;2018:4612472.
5. World Health Organization. Global Health Sector Strategy on Viral Hepatitis 2016–2021. Available from: <https://apps.who.int/iris/bitstream/handle/10665/246177/who-hiv-2016.06-eng.pdf;jsessionid=fc387a4f48a114579c882b84cd2191e5?sequence=1>. [Last accessed on 2019 July 18].
6. Aaron D, Nagu TJ, Rwegasha J, Komba E. Hepatitis B vaccination coverage among healthcare workers at national hospital in Tanzania: How much, who and why? *BMC Infect Dis* 2017;17:786.
7. Sastry AS, Bhat SK. *Essentials of Medical Microbiology*. 2nd ed. New Delhi: Jaypee Brothers Medical Publisher; 2019. p. 554.
8. Purvi K, Rupal P, Chirag M. Hepatitis B immunization on status of health care personnel. *Natl J Integr Res Med* 2018;9:37-42.
9. Lahariya C, Subramanya BP, Sosler S. An assessment of hepatitis B vaccine introduction in India: Lessons for roll out and scale up of new vaccines in immunization programs. *Indian J Public Health* 2013;57:8-14.
10. OSHA Factsheet. Hepatitis B Vaccination Prevention. Available from: https://www.osha.gov/OshDoc/data_BloodborneFacts/bbfact05.pdf. [Last accessed on 2019 Jul 18].
11. Plotkin SA. Correlates of protection induced by vaccination. *Clin Vaccine Immunol* 2010;17:1055-65.
12. Lin CS, Xie SB, Liu J, Zhao ZX, Chong YT, Gao ZL. Effect of revaccination using different schemes among adults with low or undetectable anti-HBs titers after hepatitis B virus vaccination. *Clin Vaccine Immunol* 2010;17:1548-51.
13. Schillie S, Murphy TV, Sawyer M, Ly K, Hughes E, Jiles R, et al. CDC guidance for evaluating health-care personnel for hepatitis B virus protection and for administering postexposure management. *MMWR Recomm Rep* 2013;62:1-9.
14. Gopalakrishnan R, Ramamurthy S. Seroprevalence of hepatitis B infection among health care workers and the importance of anti HBs

- testing among the health care workers. *Int J Curr Microbiol App Sci* 2017;6:2280-5.
15. Taishete S, Chowdhary A. Seroepidemiological survey of health care workers in Maharashtra. *Indian J Med Microbiol* 2016;34:237-40.
 16. Patil S, Nair HR, Krishna S, Kumar A, Pillai B, Venu RP, *et al.* Prevalence of HBV and HCV Infection and Adequacy of HBV Vaccination among Healthcare Workers – A sero epidemiological survey and knowledge, Attitude and Practice (KAP) study. *Kerala Med J* 2016;9:1-5.
 17. Abidi TF, Ahsan SJ, Fatima N. Hepatitis B vaccination coverage and immunization status among health care workers in Punjab and Islamabad, Pakistan. *South Asian J Emerg Med* 2014;8:67-76.
 18. Batra V, Goswami A, Dadhich S, Kothari D, Bhargava N. Hepatitis B immunization in healthcare workers. *Ann Gastroenterol* 2015;28:276-80.
 19. Kollathodi N, Moorkoth AP, George K, Narayanan MP, Balakrishnan SM, Lelitha Bai SD. Hepatitis B vaccination-immune response and persistence of protection in susceptible population. *J Acad Clin Microbiol* 2017;19:42-6.
 20. Zhang L, Liu J, Lu J, Yan B, Song L, Li L, *et al.* Antibody response to revaccination among adult non-responders to primary hepatitis B vaccination in China. *Hum Vaccin Immunother* 2015;11:2716-22.
 21. 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.
 22. Chen YS, Chu CH, Wang JH, Lin JS, Chang YC. Predictors of booster response to hepatitis B vaccine at 15 years of age: A cross-sectional school-based study. *Pediatr Neonatol* 2016;57:302-9.
 23. Gilca V, De Serres G, Boulianne N, Murphy D, De Wals P, Ouakki M, *et al.* Antibody persistence and the effect of a booster dose given 5, 10 or 15 years after vaccinating preadolescents with a recombinant hepatitis B vaccine. *Vaccine* 2013;31:448-51.
 24. Centre for Disease Control and Prevention. Hepatitis B: Questions and Answers for Health Professional. Available from: <https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#ref19>. [Last accessed on 2019 Dec 04].
 25. El Bahnasy RE, Salem ME, El Shazly HM, Morad WS, Moaz EM. Predictors of poor response to the hepatitis B vaccine among healthcare workers at the national liver institute hospital. *Menoufia Med J* 2016;29:131-5.
 26. Weber DJ, Rutala WA, Samsa GP, Santimaw JE, Lemon SM. Obesity as a predictor of poor antibody response to hepatitis B plasma vaccine. *JAMA* 1985;254:3187-9.
 27. Ingardia CJ, Kelley L, Steinfeld JD, Wax JR. Hepatitis B vaccination in pregnancy: Factors influencing efficacy. *Obstet Gynecol* 1999;93:983-6.
 28. Abdolsamadi HR, Vaziri BP, Abdollahzadeh SH, Kashani KH, Vahedi M. Immune response to hepatitis B vaccine among dental students. *Iran J Publ Health* 2009;38:113-8.
 29. Liu F, Guo Z, Dong C. Influences of obesity on the immunogenicity of hepatitis B vaccine. *Hum Vaccin Immunother* 2017;13:1014-7.
 30. Klein SL, Marriott I, Fish EN. Sex-based differences in immune function and responses to vaccination. *Trans R Soc Trop Med Hyg* 2015;109:9-15.
 31. Jan CF, Huang KC, Chien YC, Greydanus DE, Davies HD, Chiu TY, *et al.* Determination of immune memory to hepatitis B vaccination through early booster response in college students. *Hepatology* 2010;51:1547-54.