Original Article:

Hepatitis B Vaccinationstatus and Status of Vaccine Non-Responders among Healthcare Workers in a Tertiary Care Hospital of Western Uttar Pradesh

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Abstract

Background and Aims: Health care workers (HCWs) are at risk of acquiring Hepatitis B Virus infection (HBVI). Despite being a vaccine preventable disease, the vaccine "non-responders" are at a constant risk of acquiring infectiondue to lack of seroconversion. The current study aims to evaluate theHepatitis B vaccination coverage and status of vaccine non-responders among HCWs in a tertiary care hospital.

Methods: Among the 183 participating HCWs, 11(6.01%) who were Hepatitis B surface antigen (HBsAg) positive were excluded from the study. Estimation of anti-HBs titre was determined in HBsAg negative individuals. The HCWs with antibody titre <10mIU/ml (non-response) were identified and revaccinated. Post-vaccination titre in these individuals was reassessed 1-2 months after the last dose of both the vaccination series to look for sero-conversion and finally identify the vaccine non- responders.Individuals who did not seroconvert even after the 2nd series of vaccination were thus labelled as "non-responders".

Result: Overall, 72.67 % HCWs were immune (anti HBs titre ≥10mIU/ml). Male population, age ≥50 years, smokers, history of hospitalisation, previous operations and dental procedures in the past were the predisposing factors identified in non-response HCWs. Sero-conversion was seen in 96% of non- responsive HCWs. A total of 4% HCWs were vaccine "non-responders".

Conclusion: Complete vaccination coverage was low among health care workers. The vaccine non-responders were identified,counselled and posted at low risk area for their safety. Every health care organizationshould have a mandatory policy to vaccinateall the HCWsirrespective of their vaccination status at the commencement of their joband monitor their post vaccination antibody titre.

Keywords: *Health Care Worker, Hepatitis B Virus, anti- HBs titre, vaccine non-responders*

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Introduction

Hepatitis B virus (HBV) is a highly contagious blood-borne infection which can lead to the development of liver disease.[1] It is the most important occupational health hazard among the Health Care Workers (HCWs).[2] Due to frequent handling of blood and body fluids of patients,HCWs are four times more at risk of contracting

HBV infection as compared to the general population.[3] Immunization with Hepatitis B vaccine remains the most effective way of prevention of HBV infection (HBVI).[4] Following complete series of vaccination in an individual, an anti- HBs titre of ≥10mIU/ml is immune (protective antibody titre), titre between 10 and 100 mIU/ml is considered as hypo-response, titre of >100mIU/ml is high level of immunity and titre of < 10mIU/ml is considered as non-response.It has been shown that even after complete vaccination series (3 doses), the prevalence of non-response ranges between 10 - 15% , thus highlighting the importance of estimation of post-vaccination anti-HBs titres.[5]Some individuals fail to get protective antibody titre even after two complete series of vaccination and are labelled as "non-responder".[6] It has been shown that age, gender, obesity, smoking, immunity, and genetic predisposition might be factors responsible for reduced immune response to vaccination in some individuals. [7]

To the best of our knowledge this is the first study carried out from this geographical area which aims to evaluate the Hepatitis B vaccine statusand status of vaccine non-responders among the HCWs in a tertiary care hospital. An attempt has also been made to identify various factors responsible for reduced immune response.

Methods

A cross-sectional study was conducted among 183 participating HCWs in a tertiary care hospital. The participation was voluntary and informed consent was duly obtained from all the participants before conducting the study. The participants included doctors, post graduate (PG) students, nursing staff, technicians (OT & Lab technicians) and housekeeping staffs (cleaning staff and attendants). HCWs irrespective of age, both genders and Hepatitis B surface antigen (HBsAg) negative were included. Those with past history of jaundice or other chronic liver disease, pregnant women and who were HBsAg screen positive were excluded. The demographic data such as age, gender, designation, department, personal health information and vaccination detail was noted in a self-structured questionnaire (Table 1) distributed to all the participants.

According to the vaccination history given by the participants in the questionnairethey were grouped into 5 subgroups: i) completely vaccinated: participants who had received all 3 doses of HB vaccine. ii) incomplete/ partially vaccinated: participants who had received only one or two doses of vaccine. iii) non-vaccinated: participants who had not received any dose of vaccine. iv) unknown: participants who were unaware of neither their vaccination status nor the number of doses received. v) booster dose vaccinated: participants who had taken complete vaccination followed by booster dose after 5 years .

All the serum samples collected were first screened for HBsAg by rapid immune-chromatographic test (Standard Q HBsAg test, SD Biosensor Healthcare Pvt. Ltd). The HBsAgscreen negative serum samples were then subjected for estimation of anti-HBs titre by ELISA (DIA.PRO, Diagnostic BioprobesSrl; San Giovanni, Milano Italy) as per manufacturer's instructions to look for presence of protective immunity (titre ≥10mIU/ml). The non-immune (non-response) individuals (titre <10mIU/ml) were identified and motivated for complete 3-dose series vaccine irrespective of their previous vaccination status. These non-response HCWs were subjected for serologic testing 1–2 months after the last dose of vaccine to look for sero-conversion as per the recommendation of Advisory Committee on Immunization Practices (ACIP).[4] Those who did not sero-convert after the first dose were given the second vaccine series to finally identify the vaccine non-responders. However after 2 series no further routine doses or testing wasindicated in these individuals.[6]

Statistical Analysis

SPSS software version 25 (IBM, SPSS statistics) was used for statistical analysis. Chi-square test was performed for data analysis. The p values below 0.005 were considered to be significant.

Results

A total of 49.72% HCWs gave history of being completely vaccinatedfollowed by (15.84%) who were partially vaccinated and (10.38%) who had taken

a booster dose vaccination. However, a significant number of HCWs (16.93%) were unaware about their vaccination status and 7.10% disclosed that they were non-vaccinated (Table2)]. Among the different groups of HCWs ,maximum (75%) of OT technicians were completely vaccinated followed by doctors (66.66%), attendants (63.33%), nurses' (62.5 %) and cleaning staff (54.55%). However, 18.18 % of the cleaning staff, 15% of the PG students and 6.67% attendants were non-vaccinated. (χ^2-value=103.5214,p-value=0.000). Among the participants, 58% were males and 42% were females.

A fairly high number (6.01%) of HCWs, were HBsAg positive.An estimation of anti-HBs titres in negative group showed high level of immunity (titre of > 100mIU/ml) in 52.32%, hypo-response (titre 10-100mIU/ml) in 20.35% and non-response (titre <10mIU/ml) in 27.33%. (Table 3) On correlation of level of immunity with age**,** non- response to vaccination was seen in ≥50 year's (64 %)age group. (χ^2-value=8.315,p-value=0.015). The non- response to vaccination was maximum (91.66%) in the non-vaccinated category followed by unknown status category (35.5%), showing the direct relation between vaccination and production of antibodies. (Table 4) High level of immunity (100%) was seen in booster dose vaccinated individuals followed by completely vaccinated (56.47%) and partially vaccinated (40%) individuals. However, 38.70% of the unknown status category individuals and 8.33% of the non-vaccinated individuals also had presence of high level of immunity. The latter may have been due to the presence of natural immunity in these HCWs. The association was statistically significant (χ^2-value=48.6991, p-value=0.000).

Overall in our setup, 125 (72.67%) HCWs had a protective antibody titres (10-100mIU/ml) as compared to 47 (27.32%) with non-protective titres (<10mIU/ml). Smoking, alcoholism, history of hospitalisation, previous operation, dental procedure, and obesity were the major associated factors identified comparatively more in HCWs with non-protective titres (non-response) as compared to those with protective anti HBs titres (Table 5) .(χ^2- value=4.338, p-value=0.888). Among the 27.34% non-responsive individuals, 96% seroconverted (titre >10mIU/ml) after 2nd complete series of vaccination. However, 4% showed non-response. As these non-response individuals belonged to the completely vaccinated category, as per the CDC definition they were termed as vaccine "non-responders".[6]

Table 1: Structured questionnaire distributed among the HCWs for demographic, personal and vaccination details

Name: Age/Sex:, Designation :Department:, Relevant details:

S.No.	History	Yes	No
1.	Received Hepatitis B vaccination		
2.	Received all three doses of Hepatitis B vaccination		
3.	Received single or two doses of Hepatitis B vaccination		
4.	Do not know the status/ dose of vaccination received		
5.	Received booster dose of Hepatitis B vaccination in the last 5 years		
6.	Known HBs antigen positive status		
7.	Jaundice or any other chronic liver disease		
8.	Prolonged steroid therapy/ immunosuppressive drugs		
9.	Smoker		
10.	Diabetic		

Cont... **Table 1: Structured questionnaire distributed among the HCWs for demographic, personal and vaccination details**

11.	Alcoholic			
12.	Family history of hepatitis B			
13.	History of hospitalization			
14.	History of previous operation			
15.	History of blood transfusion			
16.	History of any dental procedure			
17.	Current Pregnancy status			
18.	Obesity			

Table 2: Overall assessment of vaccination status among the participating groups of Health Care Workers as per the questionnaire (n=183)

Designation	Completely vaccinated	Partially vaccinated	Booster dose vaccinated	Non-vaccinated	Unknown status of Vaccination	Total	χ2-value, p-value
PG students (n=60)	19 (31.66%)	12(20%)	4(6.66%)	9(15%)	16(26.66%)	60	χ2-value=103.5214, p-value=0.000
Doctors (n=12)	8(66.66%)	1(1.66%)	2(3.33%)	0(0%)	1(1.66%)	12	
Nurses (n=48)	30(62.5%)	7(14.58%)	2(4.17%)	0(0%)	9(18.75%)	48	
Lab technicians (n=10)	0(0%)	1(10%)	9(90%)	0(0%)	0(0%)	10	
OT technicians (n=12)	9(75%)	1(8.33%)	0(0%)	0(0%)	2(16.67%)	12	
Attendants (n=30)	19(63.33%)	5(16.67%)	2(6.67%)	2(6.67%)	2(6.67%)	30	
Cleaning staff (n=11)	6(54.55%)	2(18.18%)	0(0%)	2(18.18%)	1(9.09%)	11	
Total	91 (49.72%)	29 (15.84)	19 (10.38%)	13 (7.10)	31 (16.93%)	183	

Table 3 : Correlation of level of immunity of HCWs with age (n=172)

Age group (in years)	Anti HBs Titre : <10mIU/ml (non-response)	Anti HBs Titre : 10-100mIU/ml (hypo-response)	Anti HBs Titre : >100mIU/ml (high level immunity)	Total	χ2-value, p-value
18-49 (n=161)	40 (25%)	33 (20%)	88 (55%)	161 (93.60%)	χ2-value=8.315, p-value=0.015
≥50 (n=11)	7 (64%)	2 (18%)	2 (18%)	11 (6.40%)	
Total	47 (27.33%)	35 (20.34 %)	90 (52.32%)	172 (100%)	

Table 4: Correlation of vaccination status with immune response (n=172)

Vaccination status	<10mIU/ml (non-response)	10-100mIU/ml (hypo-response)	>100mIU/ml (high level of immunity)	Total	χ^2-value, p-value
Completely vaccinated (n=85)	18 (21.17%)	19 (22.35%)	**48 (56.47%)**	85	χ^2-value=48.6991, p-value=0.000
Partially vaccinated (n=25)	7 (28%)	**8 (32%)**	10 (40%)	25	
Booster dose vaccinated (n=19)	0 (0%)	0 (0%)	**19 (100%)**	19	
Non vaccinated (n=12)	**11 (91.66%)**	0 (0%)	1 (8.33%)	12	
Unknown status (n=31)	**11 (35.5%)**	8 (25.80%)	12 (38.70%)	31	
Total	47 (27.32%)	35 (20.34%)	90 (52.32%)	172	

Table 5: Comparison of the associated factors affecting immune response identified in HCWs with protective and non-protective antibody titre (n=172)

Factor	HCWs with protective titres (10-100mIU/ml) (n=125)	HCWs with non-protective titres. (<10mIU/ml) (n=47)	Total n=172	χ2-value, p-value
History of hospitalisation	32 (25.6%)	19 (40.42%)	51 (29.65%)	χ2- value=4.338, p-value=0.888
History of previous operation	20 (16%)	16 (34.04%)	36 (20.93%)	
History of dental procedure	21 (16.8%)	8 (17.02%)	29 (16.86%)	
Alcoholic	16 (12.8%)	8 (17.02%)	24 (13.95%)	
Smoker	15 (12%)	7 (14.89%)	22 (12.79%)	
Obesity	8 (6.4%)	5 (10.64%)	13 (7.56%)	
Prolonged steroid therapy	8 (6.4%)	3 (6.38%)	11 (6.39%)	
Diabetic	1 (0.8%)	2 (4.26%)	3 (1.74%)	
History of blood transfusion	6 (4.8%)	2 (4.25%)	8 (4.65%)	
Family history of Hepatitis B	2 (1.6%)	1 (2.12%)	3 (1.74%)	

Discussion

HCWs are always at risk of contracting hepatitis B infection due to frequent handling of blood and body fluids of patients.[3]Vaccination against HBV is the most effective way to prevent HBVI.[4] Despite being a vaccine preventable disease, due to lack of sero-conversion, some individuals fail to develop protective level of antibody even after two complete series of vaccination. The vaccine "non-responders" have a false sense of security and are at a constant risk of acquiring infection. Therefore along with immunization of HCWs, testing for evidence of protective immunity becomes essential in any health care setting.

A study conducted by Singhal*et al.*,[8]from AIIMS New Delhi, showed only 50.2% of HCWs was completely vaccinated, 6.3% were partially vaccinated and 43.5% were non-vaccinated. The vaccination coverage in our institution was coherent to apex institute like AIIMS. Another similar study from G.B. Pant Hospital, Delhi, also showed only 55.4% of HCWs being completely vaccinated against Hepatitis B.[9] The percentage of completely vaccinated HCWs ranged from 40% to 49.6% across various Hospitals in India.[10-12]

Two groups of HCWs were identified, first were those who were either partially vaccinated, non-vaccinated or had unknown status thus emphasizing an urgent need to implement a proactive Hepatitis B immunisation programme to improve protection against this infection and to achieve target of 90% vaccination coverage.[13] The second group included significant numbers of HCWs in booster dose vaccination category showing

relatively good vaccination awareness and vaccination coverage in our hospital. (p-value<0.05) Overall the vaccination coverage rate among the doctors, nurses, OT technicians, attendants and housekeeping staffs was fairly good in our hospital as compared to other institutions. Previous studies carried out by Batra*et al*.,[10] and Singhal*et al*.[8] showed highest vaccination coverage rate in doctors and lowest among grade IV/laundry staff/ housekeeping staff. We observed the lowest vaccination coverage among the PG residents. This emphasizes a need of a mandatory policy to vaccinate all the residents & HCWs irrespective of their vaccination status at the commencement of their course or job in an organization. Simultaneously, regular screening for HBsAg should be part of immunization programme to prevent the spread and transmission of this infection.

As per CDC criteria(titre ≥10mIU/ml), [4] 72.67% HCWs were immune and 27.33% were non-immune in our hospital (p-value=0.000). However, some researchers have identified anti-HBs titre of >100mIU/ml as protective for sero-conversion to immune status.[14] Taking this latter criteria, 52.32% in our setup had high level of immunity (titer>100mIU/ml) and 20.35% had hypo-response (titer of 10-100mIU/ml). Different levels of antibody response in HCWs have been shown by various workers in the past.[15,16]

The non–response was observed maximum in the non- vaccinated category (91.66%) of individuals. Similar findings have been reported.[15] The non-response was also seen in (35.5%) unknown status category and 21.17% incompletely vaccinated category, showing the direct relation between Hepatitis B vaccination and production of antibody in vivo. (p-value=0.000) High level of immunity was seen in the booster dose vaccinated category individuals followed by completely vaccinated category. However, protective level of antibody titres was also seen in unknown status category and non-vaccinated category individuals. This may be due to the presence of natural immunity through previous contact with HBV. Similar observations have been reported previously by other workers.[8]

Increase in age (≥50 years) was identified as a major factor responsible for low immune response irrespective of the vaccination status (p-value=0.015). Similar observation has been reported. [2] It maybe because advancing age proves to be a big factor for low antibody response and could be due to a decrease in lymphocyte proliferation activity. The other factors identified for non-response was male gender (56%) as compared to the females (44%) which is coherent to a previous study.[17] The effect of gender could be explained by the greater weight of men.[18]Smoking was another factors identified in non-responsive HCWs, which is in concurrence with study done in the past.[19] This may be because of 1st lower number of immunoglobulin in smokers than in non-smokers [20] and 2nd impaired dendritic cell function in smokers.[21] History of hospitalisation, previous operation, dental procedure in the past, alcoholism and obesity were other associated factors identified more in non-responsive HCWs. (p-value=0.888)

Sero-conversion was seen in 96% of non- responsive HCWs however, 4% were vaccine "non-responders"[6](no seroconversion).The **"non-responders"**are at a constant risk for being infected as they tend to have a false sense of security of being immune but are not. There are no regulations and guidelines that demand removal of these non-responders from the job; moreover each organization needs to develop a policy concerning non-responders. Infact, the vaccine non-responders should first be identified then counselled as to what non-response to the vaccination series means for him/her that is, they are susceptible to HBVI and the treatment modality for post exposure prophylaxis for any known or likely exposure to a positive sourceis to use HBIG.[22]

There are limited literatures that address the issue of non-responsive HCWs. An old study involving about 2000 HCWs, showed cumulative response rate to three re-vaccination doses of 69%.[23] Another study showed 85.7% sero-conversion rate after 3 repeat dose of HBV vaccination in non- responsive HCWs and 73.2% sero-conversion rate with a single booster dose of the same vaccination.[24]

The Occupational Safety and Health Administration (OSHA) mandate that employers offer Hepatitis B vaccination to all employees who are at occupational risk, [25] along with provision of adequate personal protective equipment . Adequate documentation in the employee record regarding nonresponse to vaccination is required. Simultaneously, HBsAg testing should be recommended in these individuals as it is possible that these employees maybe chronically infected with HBV.[6]

Conclusion

Complete vaccination coverage was low among health care workers. We could identify the vaccine non-responders in our setting thus emphasizing the importance of this study. However , the study has few limitations like not able to enrol all the HCWs in a setup plus those on long leave and maternity leave were missed. In future studies may be carried out by following up the non-responders to determine the long term outcome.Finally, we recommend that every health care organization should have a mandatory policy to vaccinate all the HCWs irrespective of their vaccination status at the commencement of their job and monitor their post vaccination antibody titreto identify these HBV vaccine non-responders, counsel them and post them at low risk area for their safety.

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