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Original Research Article

Immunization status and immune response to HBV vaccine among HCWs: a report from tertiary care centre in India

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ABSTRACT

Background: Healthcare workers (HCWs) are at a high risk of acquiring hepatitis B virus (HBV) infection which is preventable through hepatitis B vaccination. Hepatitis B surface antibody (anti-HBs) titre (≥10 mIU/ml) is a marker for protective immune response. The aim of this study was to evaluate HBV vaccination status and study factors affecting anti- HBs titres among the HCWs.
Methods: This cross-sectional study was conducted over 18 months and 1000 HCWs were enrolled. Personal, demographic and detailed HBV vaccination history were collected using predesigned proforma. Anti-HBs titre, were assessed by ELISA irrespective of the vaccination status. The HCWs with non-protective titres were screened for prior infection (HBsAg and Anti- HBc). All data were analysed using SPSS v21.
Results: Majority of HCWs (606) were completely vaccinated, 279 partially vaccinated and 115 unvaccinated. Vaccination compliance was significantly higher among the doctors and female HCWs. Among fully vaccinated HCWs non protective titres were recorded in 6.3%. Incomplete vaccination, male gender, smoking, and alcohol consumption were predictors of nonprotective titres. There was a significant fall in anti-HBs titres with time (p value =0.04). None of the HCWs had acute or previous HBV infection.
Conclusions: Study highlights the poor compliance to HBV vaccination among HCWs. In health care setting vaccination must be made mandatory for all HCWs at induction and documented by vaccination card. As anti-HBs titter decline with time, evaluation must be performed 1-2 months after the third dose and documented for guiding therapy following occupational exposure.

Keywords: Anti-HBs titres, Health care workers, Hepatitis B, Hepatitis B surface antigen, Hepatitis B vaccination, Protective titre

INTRODUCTION

Hepatitis B virus (HBV) infection is a major global health problem that may lead to chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). WHO estimates that 254 million people were living with chronic hepatitis B infection in 2022, with 1.2 million new infections each year.[1] In India, HBsAg prevalence among general population ranges from 2% to 8%.[2] India has 10% to 15% of the global population of HBV and has 40 million HBV carriers.[3]

HBV infection is an occupational hazard among healthcare workers (HCWs). The HBV virus spreads through contact with infected blood or body fluids and injuries by contaminated sharps like needles. The risk of contracting HBV by HCWs is four times greater than that of the general population. Each year 5.9% of HCWs are

exposed to blood-borne HBV infections corresponding to about 66,000 HBV infections worldwide.[4]

HBV infection can be prevented by hepatitis B vaccine (HBV vaccine) and efficacy is attributed to development of antibodies to hepatitis B surface antigen (anti-HBs). Implementing standard precautions is most important for preventing HBV infection. Administration of hepatitis B immunoglobulin (HBIG) is useful to mitigate the risk following exposure. However, the most effective strategy is active immunization with HBV vaccine. Centres for Disease Control and Prevention (CDC) in 1997 recommended vaccination of all HCWs.[5] In India there are no national policies mandating the hepatitis B vaccination of HCWs, however National guidelines for infection prevention and control released by MoHFW (2020) and guidelines for implementation of 'Kayakalp' initiative recommend hepatitis B vaccination and postexposure evaluation among the HCWs.[6,7] Although HBV vaccine is recommended for HCWs, the coverage is unsatisfactory and varies geographically. HBV vaccination compliance among HCW is 18-39% and 67-79% in low- and middle-income countries and high-income countries respectively.[8]

Three doses of the recombinant vaccine (0, 1, 6 month) is generally administered intramuscularly in the deltoid region. About 5 to 10% of people who receive an HBV vaccine do not generate antibodies.[9] Further, anti-HBs titres are known to decrease over time. Host characteristics including age, smoking, obesity, gender, genetic predisposition and vaccination parameters like vaccine type, dose, injection site, may also contribute to a weak response to the HBV vaccine.[10] The Advisory Committee on Immunization Practices (ACIP) thus recommends HBV vaccination, followed by assessment of anti-HBs titres 1-2 months after completion of first 3 doses to confirm vaccine response in HCWs. Post vaccination anti-HBs titres ≥10 mIU/ml are considered to be protective.[11] HBV vaccine induced protection persists for at least 11 years and even up to 30 years.[11] Even if there is decline in antibody titres, vaccinated individuals are believed to be protected against HBV infection because of a memory immune response. Therefore, booster doses of the vaccine are not recommended, except for some high-risk individuals like patients on dialysis. HCWs with non-protective titres (<10 mIU/ml) after 1-2 months of first series of vaccination are advised to vaccinate again with a single dose (booster) followed by measurement of anti-HBs titres 1-2 month later. HCWs who are seronegative after the booster dose, a second vaccine series of two additional doses, can result in seroconversion in 50 to 60% of recipients.[12] An HBV vaccine 'non-responder' refers to a person who does not develop protective surface antibodies after completing two full series (6 doses) of the HBV vaccine and for whom an acute or chronic HBV infection has been ruled out.[9]

In our institute, all HCWs are advised to take HBV vaccine which is provided free of cost. HCWs who are not immunized or fail to develop immune response following vaccination, remain at a high risk of being infected following breach in infection prevention control (IPC) practices. This study was aimed to evaluate the HBV vaccination status, the immune status and the factors influencing the anti-HBs titres in vaccinated HCWs. These findings will be useful to identify susceptible HCW and provide guidance for a cost-effective post exposure prophylaxis following occupational exposure in health care settings.

METHODS

Study design and venue

A hospital based cross sectional study was conducted in the department of microbiology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi.

Study period

Study was conducted over a period of 18 months (July 2022 to January 2024).

Ethical approval

The study was initiated after approval by the institutional ethics committee (IEC/VMMC/SJH/Thesis/06/2022/CC-139).

Sample size determination

The studies from India regarding hepatitis B immunization status and immune response among vaccine complaint HCWs were reviewed. Sample sizes were calculated based on previous Indian studies using Cochran's formula.[13]

Sample size based on prevalence of seroconversion post HBV vaccination

Based on Indian studies prevalence ranged from 61-97%.[14,15] Assuming average prevalence of 79%, a precision of 4 and with 10% nonresponse, minimum sample size was 442.

Sample size based on prevalence of vaccine complaint HCWs

Based on Indian studies, prevalence of vaccine complaint HCWs ranged from 37-90%.[15,16] Assuming the average prevalence of 63%, precision of 4 and with 10% nonresponse, minimum sample size was estimated to be 560.

Average of these prevalence values were calculated and minimal sample size of 600 was proposed. However,

1000 HCWs, were finally enrolled in the study after approval from ethics committee.

Data collection and investigation

A total of 1000 HCWs were enrolled in the study after a written consent. HCWs with known history of HBV infection were excluded from the study. A predesigned proforma was used to collect the personal and demographic history of participants including age, gender, weight, height, occupation, smoking, alcohol consumption habits and comorbidities. History of HBV vaccination including number of doses and time since last dose was collected. Details of type of vaccine were unavailable. Body mass index (BMI) was calculated using the formula weight (kg)/height ^{2} (m^2).

Five ml of blood was collected following standard precautions. Serological tests were performed in batches within 2-5 days of sample collection. Titres were evaluated using Monolisa™ Anti-HBs PLUS assay kit (BIORAD, France) All unvaccinated HCWs and completely vaccinated HCWs with non-protective titres were further investigated for acute or previous HBV infection by ELISA for HBsAg (Medsource Ozone Biomedical PVT LTD, India) and anti- HBc total (Biogenix anti -HBc ELISA). The workflow of the study is summarized in Figure 1.

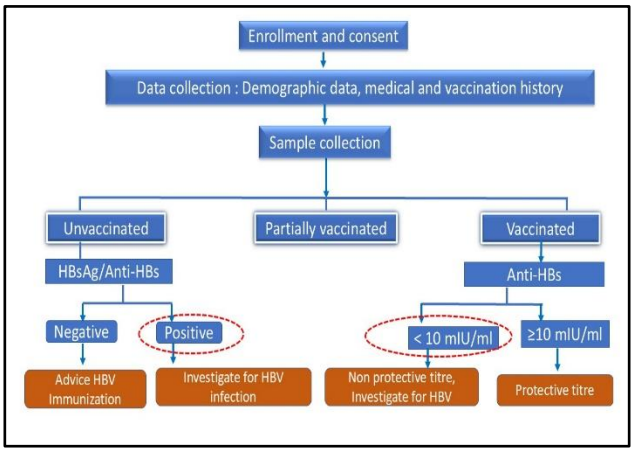

Figure 1: Workflow of the study.

Note: Vaccinated: HCW with history of receiving minimum three doses of HBV vaccine, at a schedule of 0, 1 and 6 months. Partially vaccinated: HCW with either single or 2 doses at 0 and 1 month. Unvaccinated: HCW who had not received any dose of HBV vaccination.

Definitions used in study

HCWs were defined as all persons, working in health care settings potentially exposed to patients and/or infectious materials. HCWs included doctors, nurses, other clinical workers (nursing assistants, therapists, technicians, emergency medical service personnel, pharmacists, students and trainees) and non-clinical workers (Multi task worker (MTW), house-keeping and laundry staff).[17] Based on the self-reported vaccination history, HCWs were grouped as completely vaccinated (minimum three doses of HBV vaccine, at a schedule of 0, 1 and 6 months), partially vaccinated (either single or 2 doses at 0 and 1 month) and unvaccinated (no dose).

HCW's who self-reported vaccination with one or more doses (0, 1, 6-month doses), anti-HBs titre ≥10 mIU/ml was considered as protective and titre <10 mIU/ml was considered as non-protective. Based on the quantitative analysis of anti-HBs titre, immune response was further categorized as 'good' (titre ≥100 mIU/ml), 'weak' (titre 10-100 mIU/ml).

Statistical analysis

All data were coded and recorded anonymously in MS Excel spreadsheet program. SPSS v21 (IBM Corp) was used for data analysis. Descriptive statistics were elaborated in the form of means/standard deviations and medians/IQRs for continuous variables, and frequencies and percentages for categorical variables. Data found to be non-normally distributed, appropriate non-parametric tests: Kruskal Wallis test, Wilcoxon-Mann-Whitney U test were used. Chi-squared test was used for group comparisons for categorical data. In case the expected frequency in the contingency tables was found to be <5 for >20% of the cells, Fisher's Exact test was used. Statistical significance was kept at $p<0.05$.

RESULTS

Sociodemographic characteristics of participants

A total of 1000 HCWs without previous history of HBV infection were enrolled in the study. Based on the age and BMI, the participants were categorized into 5 and 7 groups respectively. The sociodemographic details of HCWs are summarized in the Table 1. The age of HCWs ranged from 22-63 years with mean age of 34.08±9.13. Majority of HCWs belonged to age group of 26-30 years (41.4%). Males and females were evenly distributed with 497 males (49.7%) and 503 females (50.3%). Majority of the HCWs were in the BMI range 25.0-29.9 kg/m^2. Based on occupational categories HCWs were grouped as doctors, nurses, laboratory technicians and 'others' which included MTW, housekeeping and laundry staff. Majority of the HCWs were nurses (489, 48.9%), followed by doctors (285, 28.5%), laboratory technicians (196, 19.6%) and 'others' (30, 3%). Majority of the HCW (n=935) denied the history of any known comorbidities. Comorbidities reported were diabetes (27), hypertension (27), tuberculosis (12) and arthritis (4). Four patients reported more than one co-morbidity. Only 28 and 17 HCWs self-reported history of smoking and alcoholism respectively.

Table 1: Sociodemographic characteristics of HCWs (n=1000).

Parameters	N (%)
Age groups	
<25 years	71 (7.1)
26-30 years	414 (41.4)
31-35 years	220 (22)
36-40 years	102 (10.2)
>40 years	193 (19.3)
Sex	
Male	497 (49.7)
Female	503 (50.3)
Occupation	
Doctors	285 (28.5)
Nurses	489 (48.9)
Laboratory technician	196 (19.6)
Others*	30 (0.03)
Body mass index (BMI) (kg/m^2)	
<18.5	19 (1.9)
18.5-22.9	306 (30.6)
23.0-24.9	250 (25.0)
25.0-29.9	333 (33.3)
30.0-34.9	72 (7.2)
35.0-39.9	19 (1.9)
40.0-44.9	1 (0.1)
Comorbidities**	
None	935 (93.5)
Diabetes	27 (2.7)
Hypertension	27 (2.7)
Tuberculosis	12 (1.2)
Arthritis	4 (0.4)
SLE	0
Habits	
Smoking	28 (2.8)
Alcohol	17 (1.7)

Note: * 'Other' included Multi Task Worker, security and laundry staff. **4 Health Care Workers had more than 1 comorbidity. BMI: Body Mass Index; SLE: systemic lupus erythematosus

Table 2: Status of hepatitis B vaccination among HCWs.

Parameters	N (%)
Vaccination status (n=1000)	
Unvaccinated	115 (11.5)
Incomplete	279 (27.9)
Complete	606 (60.6)
Booster dose among completely vaccinated*	36 (5.9)
Time since last dose (n=885)**	
0-6 months	15 (1.7)
6-12 months	73 (8.3)
1-5 years	392 (44.6)
>5 years	399 (45.4)
Not recalled	6 (0.006)
Self-evaluation of response following vaccination after 1 full series reported by HCWs * (n=606)	29 (4.8)

Note: *Booster doses and evaluation of response to complete vaccination reported by HCWs among completely vaccinated. **Time since last dose among HCWs who received complete (606) or partial vaccination (279). HCWs: Health care workers.

Table 3: Demographic data of vaccinated and unvaccinated HCWs.

Category	Unvaccinated N (%)	Incomplete N (%)	Complete N (%)	Total N (%)	P value
Age group (years)					
<25	15 (21.1)	21 (29.6)	35 (49.3)	71	
26-30	51 (12.3)	107 (25.9)	256 (61.8)	414	0.074[1]
31-35	24 (10.9)	63 (28.6)	133 (60.5)	220	
36-40	12 (11.8)	25 (24.9)	65 (63.7)	102	
>40	13 (6.7)	63 (32.6)	117 (60.6)	193	
Sex* **					
Male	76 (15.3)	148 (29.8)	273 (54.9)	497	<0.001[1]
Female	39 (7.8)	131 (26)	333 (66.2)	503	
Occupation* **					
Doctors	13 (4.6)	59 (20.7)	213 (74.7)	285	
Nursing staff	56 (11.5)	145 (29.7)	288 (58.9)	489	0.001[1]
Laboratory technicians	35 (17.9)	67 (34.2)	94 (48.0)	196	
Other	11 (36.7)	8 (26.7)	11 (36.7)	30	

Note: ***Significant at p <0.05, Statistical method 1: Chi-squared test

Table 4: Association of various factors with mean anti-HBs titres, protective titres and immune response.

Parameters	Mean titre # mIU/ml	Protective status*		Immune response**			P value
		<10 mIU/ml N (%)	≥10 mIU/ml N (%)	10-100 mIU/ml N (%)	>100 mIU/ml N (%)	Total	
Gender							0.236[1]
Male	738.75±459.22	23 (8.4)	250 (91.6)	29 (10.6)	221 (81)	273	*0.048[2]
Female	698.17±455.77	15 (4.5)	318 (95.5)	54 (16.2)	264 (79.3)	333	**0.028[2]
Occupation							
Doctor	735.79±455.77	13 (6.1)	200 (93.9)	31 (14.6)	169 (79.3)	213	#0.006[3]
Nurse	746.31±449.14	17 (5.9)	271 (94.1)	33 (11.5)	238 (82.6)	288	0.930[2]
Laboratory technician	579.47±470.69	7 (7.4)	87 (92.6)	19 (20.2)	68 (72.3)	94	0.310[2]
Others	731.00±439.82	1 (9.1)	10 (90.9)	0	10 (90.9)	11	
BMI (kg/m^2)							
<18.5	948.66±400.42	0	7 (100)	1 (14.3)	6 (85.7)	7	
18.5-22.9	717.15±459.60	9 (4.8)	178 95.2)	25 (13.4)	153 (81.8)	187	0.358[3]
23.0-24.9	724.65±459.86	10 (6.5)	144 (93.5)	22 (14.3)	122 (79.2)	154	0.211[4]
25.0-29.9	710.20±454.11	13 (6.6)	184 (93.4)	30 (15.2)	154 (78.2)	197	0.086[2]
30.0-34.9	718.52±462.62	4 (8.5)	43 (91.5)	3 (6.4)	40 (85.1)	47	
35.0-39.9	626.62±473.50	1 (7.7)	12 (92.3)	2 (15.4)	10 (76.9)	13	
40.0-44.9	0.00±0	1 (100)	0 (0)	0	0	1	
Time since last dose							
0-6 months	857.00±472.54	0	5 (100)	1 (20)	4 (80)	5	0.046[3]
6-12 months	712.81±464.07	3 (6.4)	44 (93.6)	5 (10.6)	39 (83)	47	0.256[4]
1-5 years	778.53±430.55	11 (4.2)	249 (95.8)	31 (11.9)	218 (83.8)	260	0.334[2]
>5 years	659.86±473.70	24 (8.2)	268 (91.8)	46 (15.8)	222 (76)	292	

Note: #Significant association with mean titer, *Significant association with Protective status, **Significant association with immune response. Three p values given for each parameter, where each p value compares parameter versus titer/protective status/ immune response respectively. Significant at p<0.05, 1: Wilcoxon-Mann-Whitney U Test, 2: Chi-Squared Test, 3: Kruskal Wallis test, 4: Fisher's exact test. BMI: Body Mass Index; p value: probability value.

Status of HBV vaccination among HCWs

Majority of HCWs were completely vaccinated (606, 60.6%), 279 (27.9%) were partially vaccinated and 115 (11.5%) were unvaccinated. Only 885 HCWs recalled their last dose of vaccination and they were grouped based on time since last dose. Majority (399, 45.4%) of the HCWs reported administration of third dose >5 years back and 44.6% (392) reported last dose was received within past 1-5 years. Among the 606 completely

vaccinated HCWs, only 36 (5.9%) reported taking booster doses and 29 (4.8%) reported self-follow up after HBV vaccination by testing for anti-HBs titres (Table 2).

Demographic data of vaccinated and unvaccinated HCWs

Majority of completely vaccinated HCWs were in age group 36- 40 (63.7%). Majority of unvaccinated HCWs were in age group <25 years (21.1%) and were least in >40 years (6.7%) (p=0.074). The reported history of complete vaccination was significantly higher in female HCWs (66.2%) than males (54.9%) (p<0.001). Amongst various groups of HCWs, complete HBV vaccination with 3 doses was significantly higher among the doctors (213,74.7%), followed by nurses (288, 58.9%), laboratory technician (94,48%) and others (11, 36.7%) (Table 3).

Vaccination status and anti-HBs titres

Protective titres (≥10 mIU/ml) among HCWs with complete vaccination were detected in (568, 93.7%) as compared to only 71.3% of partially vaccinated HCWs. The HCWs with non-protective titre (<10 mIU/ml) were significantly lower among completely vaccinated (38, 6.3%) (p<0.001). Protective anti-HBs titres were demonstrated in 3 HCWs without any prior exposure to vaccine. Good immune response (>100 mIU/ml) was significantly higher among the completely vaccinated (80%) compared to the partially vaccinated HCWs (52.7%) (p<0.001). The mean titres (mIU/ml) were significantly higher among completely vaccinated as compared to partially vaccinated (716.5 versus 411.9) (p<0.001). The HCWs who had received the booster dose after 3 doses, showed a higher mean titre (745.56±462.98) compared to those who had not received an additional dose (545.17±496.77) (p=0.008) (Figure 2).

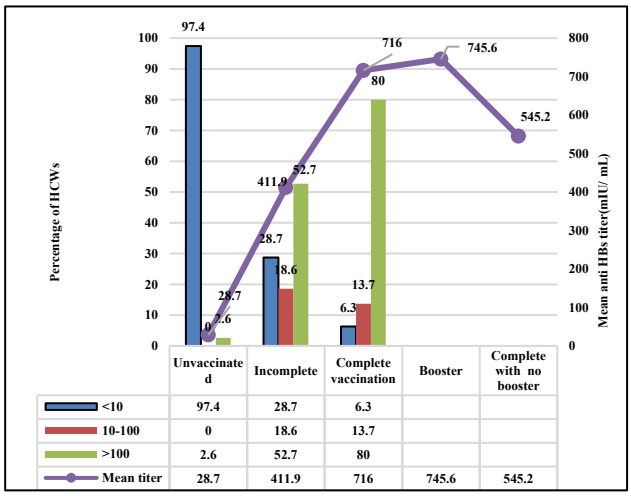

Figure 2: Association of vaccination status and anti-HBs titres among HCWs.

Note: Anti-HBs titres in terms of non-protective titre: <10 mIU/ml, 10-100 mIU/ml: weak immune response, >100 mIU/ml: good immune response.

Factors associated with anti-HBs titres among the completely vaccinated HCWs (N=606)

Age and time since last dose of vaccination

As demonstrated in the Figure 3, protective titres (≥10 mIU/ml) were highest in the age group 26-30 years (95.7%), followed by 95.5% in 31-35 years, 94.3% in <25 years, 91.5% in >40 years and 86.2% in 36-40 years (p=0.04). The weak immune response was significantly associated with higher age groups. Good immune response (titre ≥100 mIU/ml) was seen among participants below 35 years and the immune response reduced as the age advanced. The percentage of HCWs with good immune response (≥100 mIU/ml) were significantly higher among 26-30 years (84.4%) followed by age group 31-35 years (83.5%). Mean anti-HBs titre showed a trend to fall as the age advances. The mean titre was highest in the age group 26-30 years (p=0.03).

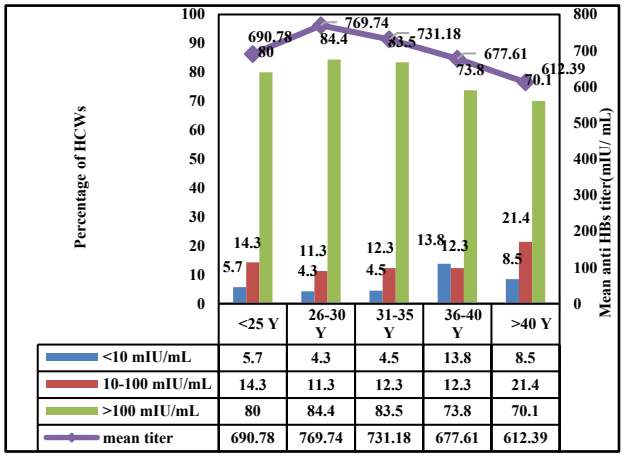

Figure 3: Association of age with anti-HBs titre among completely vaccinated HCWs.

Note: Y- age in years, anti-HBs titres in terms of non-protective titre: <10 mIU/ml, weak immune response: 10-100 mIU/ml, good immune response: >100 mIU/ml.

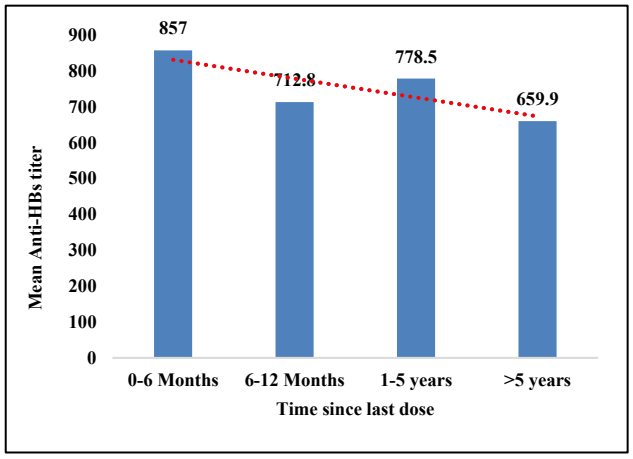

Figure 4: Time since last dose and mean anti-HBs titres among completely vaccinated HCWs.

Note: Trendline of the titer is shown in red dotted line.

Figure 4 shows association of time since last dose of vaccination on anti-HBs titres. HCWs reporting last dose within 1-6 months, had the highest mean anti-HBs titres (857) while those with >5 years had lowest (659.86). Mean anti-HBs titre declined significantly with increasing time period since last dose of vaccination as demonstrated in Figure 4 (p value =0.04). Non protective titres and immune response did not vary significantly with the time since last dose of vaccination.

Gender and occupation

Among the completely vaccinated HCWs, protective titres were significantly higher among females than males (p=0.048) and no variation in mean titres was observed (Table 4). The mean anti-HBs titre were higher among nurses and lowest among laboratory technicians. Protective titres and good immune response were also higher among nurses however; this difference was not statistically significant (Table 4).

BMI and comorbidities

Mean anti-HBs titres and protective titres showed a trend to decline with increasing BMI, however the difference was not statistically significant (Table 4). Similarly, comorbidities like diabetes, hypertension, tuberculosis and arthritis did not demonstrate any association with the anti-HBs titres (Table 5).

Smoking and alcoholism

Significantly higher percentage of non-smokers (479, 80.8%) and non-alcoholics (481,80.6%) had good immune response with titre ≥100 mIU/ml as compared to smokers (6, 46.2%) and HCWs with history of alcoholism respectively (4, 44.4%) (p value =0.05). HCWs with history of smoking and alcohol consumption showed significantly lower titres compared to their counterparts (Table 5). There was no significant association between protective titres and smoking and alcoholism.

Table 5: Association of habits and comorbidities with anti-HBs titre.

Parameters	Titre # (mIU/ml)	Protective status*		Immune response**		Total N	P value
		<10 mIU/ml N (%)	≥10 mIU/ml N (%)	10-100 mIU/ml N (%)	>100 mIU/ml N (%)		
Smoking							#0.004[1]
Yes	92.4 (25.6-291)	1 (7.7)	12 (92.3)	6 (46.2)	6 (46.2)	13	0.573
No	1100 206.1-1100)	37 (6.2)	556 (93.8)	77 (13)	479 (80.8)	593	** 0.004[2]
Alcohol							#0.005[1]
Yes	89.4 (20-683)	2 (22.2)	7 (77.8)	3 (33.3)	4 (44.4)	9	0.104[2]
No	1100 (201-1100)	36 (6)	561 (94)	80 (13.4)	481 (80.6)	597	**0.014[2]
Diabetes							0.710[1]
Yes	1100 (605-1100)	0	13 (100)	2 (15.4)	11 (84.6)	13	1.000[2]
No	1100 (180.85-1100)	38 (6.4)	555 (93.6)	81 (13.7)	474 (79.9)	593	1.000[2]
Hypertension							0.814[1]
Yes	3 (3-3)	1 (5.6)	17 (94.4)	2 (11.1)	15 (83.3)	188	1.000[2]
No	3 (3-3)	37 (6.3)	551 (93.7)	81 (13.8)	470 (79.9)	588	1.000[2]
Tuberculosis							0.177[1]
Yes	139 (78.62-1100)	2 (25)	6 (75)	0	6 (75)	8	0.084[2]
No	1100 (192-1100)	36 (6)	479 (80.1)	83 (13.9)	479 (80.1)	598	0.088[2]
Arthritis							0.205[1]
Yes	1100 (1100-1100)	0	2 (100)	0	2 (100)	2	1.000[2]
No	1100 (1100-1100)	38 (6.3)	566 (93.7)	83 (13.7)	483 (80)	604	1.000[2]

Note: Titre (mIU/ml) is expressed as median and inter quartile range. Three p values given for each parameter, each p value compares comorbidity versus titre/protective status/immune response respectively. #Significant association with titer, *Significant association with protective status, **Significant association with immune response, Significant at p<0.05, 1: Wilcoxon-Mann-Whitney U test, 2: Fisher's Exact test.

Evaluation of HBsAg and anti-HBc total

In this study, 115 unvaccinated HCWs and 38 completely vaccinated HCWs with non-protective titres were further investigated for acute or previous HBV infection. All were non-reactive for both HBsAg and anti-HBc total indicating no prior exposure to HBV. These HCWs are susceptible to hepatitis B in case of any occupational exposure.

DISCUSSION

Hepatitis B infection is a global health problem and HCWs are at increased risk of acquiring the infection. It is important to estimate the vaccine coverage and immune status post vaccination (responders or non-responders) for optimal management following occupational exposure.

ACIP has recommended that unvaccinated and incompletely vaccinated HCW should receive HBV

vaccination, followed by postvaccination serologic testing 1-2 months after completion of the vaccine series and this was reaffirmed in 2011.[18] Although HBV vaccine is recommended, many developing countries like India lack government policies that mandate HBV vaccination followed by serologic testing for HCWs. This study evaluates the vaccination status, anti-HBs titres and the factors influencing the anti-HBs titres in vaccinated HCWs. Status of anti-HBs titre is important to guide optimal and early post exposure management following occupational exposure.

In developing countries 40-65% of HBV infections in HCWs are attributable to percutaneous occupational exposure as compared a 10% in developed countries.[9] These differences are attributed to poor compliance to immunization and postexposure prophylaxis policies in developing countries. The HBV vaccination was introduced in India in 2002 and incorporated in national immunization schedule from 2011.[19] In this study among 1000 HCWs there were important observations regarding HBV vaccine compliance and factors associated with poor compliance. The study identified that 39.4% of the enrolled HCWs (partially, 279 and non-vaccinated, 115) which were still at risk of acquiring the HBV infection following an exposure. Vaccine compliance reported in this study was similar to the study by Paul et al.[4] Other studies from India have reported higher vaccination coverage of 82.5-89.4%.[16,20] The vaccination compliance may vary due to the lack of awareness regarding efficacy of HBV vaccine or vaccine hesitancy among the HCWs.

In this study complete vaccination was highest among the age group of 36- 40 years followed by 26-30 years and the unvaccinated HCWs were highest in the age group <25 years (Table 3). Similar observation was reported by a study from northern India.[4] Although HBV vaccination is available free of cost, the lack of awareness about HBV vaccination during the initial years of their career might also contribute to low vaccination rates in this group. Awareness and educational sessions regarding occupational hazards, strategies to contain them and vaccine safety should be conducted for all HCW at the time of induction to service. Following this study, the unvaccinated HCWs were sensitised about the efficacy of HBV vaccination for prevention HBV infection. All the partially vaccinated HCWs were advised regarding the completion of the vaccination schedule as per the recommendations. These HCWs at risk were also counselled to seek immediate post exposure prophylaxis following any exposure.

Vaccination coverage was significantly higher ($p<0.001$) among the females HCWs (66.2%) than males (54.9%). Similar findings have also been reported by various Indian studies.[4,21] Women in general are known to engage in more health-seeking behaviours which could account for the increased vaccine compliance seen in female HCWs. Female HCWs may adhere to proper vaccination guidelines as a reflection of their awareness about chances of mother to child transmission of hepatitis B. It is common for males to be reluctant to seek medical advice, and there have been reports of inadequate use of healthcare services by men.[22]

The highest rate of complete vaccination coverage was observed in doctors (74.7%), followed by nurses (58.9%) (Table 3). Noncompliance was significantly higher among the 'other' HCWs which included MTW, housekeeping and laundry staff. In a study conducted by Batra et al, 92.4% doctors, 41.7% nursing staff, 24.2% laboratory technicians and none of the grade 4 staff were vaccinated.[23] In contrast, a study conducted by Sharma et al, vaccination rate was highest among nursing staff.[24] Likely cause of this kind of variation in vaccination coverage among HCWs can be attributed to lack of awareness about the significance of vaccination among the 'others' group of HCWs as they may not have direct patient contact. It may also be attributed to their socioeconomic status, level of education and knowledge regarding vaccination and risk of infection.

This study highlighted the factors associated with immune response following vaccination which include number of doses, age, time since last dose and smoking and alcohol use. According to MMWR reports, postvaccination seroprotection is related to age of vaccination and is achieved in approximately 95% of healthy infants, 92% of HCWs aged <40 years, and 4% of HCWs aged ≥40 years.[18] The mean antibody titre was significantly higher among HCWs of 26-30 year followed by 31-35 years (Figure 3). Similarly protective titres (≥10 mIU/ml) were significantly higher among HCWs in the age group 26-30 years and non-protective titres were highest among 36-40 years (Figure 3). The good immune response (>100 mIU/ml) also was higher among age group of 26-30 years which reduced in the higher age groups. Further this study demonstrated a trend of declining immune response following HBV vaccination after the age of 35 years. Studies by Shashikala et al and Zeeshan et al have also reported declining antibody titres with age.[25] Decline in immune response with age is attributed to the decreased lymphocyte proliferation activity in older age groups.[15] Early age of adult vaccination also enhances the efficacy of vaccination. The lower titres in older groups may also be attributed to decline in titres with increasing time since last dose.

It is reported that following HBV vaccination 5 to 10% do not generate antibodies.[9] Among the 606 completely vaccinated HCWs in this study, protective anti-HBs titre ≥10 mIU/ml were present in 93.7% HCWs and 6.3% did not demonstrate protective anti-HBs titre. Various studies from India have reported protective titre among completely vaccinated HCWs ranging from 90.2% to 98.89%.[24,26]

In our study, only the 604 completely vaccinated HCWs recalled the time since last dose. Mean anti-HBs titres decreased significantly with increasing time period since

last dose of vaccination. Mean titre was highest among the HCWs vaccinated within 6 months of enrolment and lowest in those vaccinated more than 5 years back. A study by Sahana et al reported declining mean anti-HBs titres with time since vaccination.[27] The authors therefore recommend anti-HBs titre should be measured periodically after completing the three-dose vaccination. In the current study, titres were measured irrespective of the duration since last dose. The non-protective titres in vaccinated HCWs in our study may thus be attributed to declining titres or lack of seroconversion following vaccination. This highlights the importance of post vaccination follow up with anti-HBs evaluation to differentiate between seroconversion or fall in titres. CDC also recommends evaluation of response following vaccination among high-risk group such as HCWs by evaluating anti-HBs titre 1-2 months after the third dose. In this study, among the 606 completely vaccinated HCWs, only 29 HCWs (4.78%) reported self-follow up after hepatitis B vaccination by testing anti-HBs.

Protective anti-HBs titre (≥10 mIU/ml) following first, second, and third doses of the recombinant vaccine have been reported to be 20-30%, 75-80%, and 90-95% respectively in previous studies.[9] Protective titres were significantly higher among the completely vaccinated (93.7%) compared to the partially vaccinated (71.3%) (Table 4). The mean anti-HBs titres were also seen to increase with number of doses. These findings emphasize the need of compliance to complete 3 dose vaccination schedules especially in high-risk groups like HCWs.

Among completely vaccinated HCWs, 36 (5.9%) reported history of receiving additional booster doses in this study. Booster doses are not routinely recommended in completely vaccinated HCWs with documented protective titres (>10 mIU/ml) post vaccination. The majority of vaccinated individuals who demonstrated protective titre post vaccination and current anti-HBs titre of <10 mIU/ml will mount an anamnestic response when they receive a booster dose or are exposed to HBV, indicating that they are protected by memory B and T cells.[28] Therefore, based on currently available scientific evidence, different advisory groups do not recommend routine booster doses of the HBV vaccine in immunologically competent persons who have received a full primary course and demonstrated protective titre post vaccination.[28] Booster doses of HBV vaccine is recommended in patients on haemodialysis, with immunodeficiency or HCW with risk of HBV infection.

This study also demonstrates other factors that have an impact on immune response following vaccination. Significantly higher percentage of female HCWs (95.5%) had protective titres (≥10 mIU/ml) than male HCWs (91.6%) (Table 4) following vaccination. Similarly, Tanmay M et al protective titres were detected in 41.5% females and 33.3% males.[16] The poor immune response among the males might be due to higher weight of men and influence of habits like smoking which can alter the immune system.[29]

In this study, among the 115 unvaccinated HCWs, 3 (2.6%) HCWs had a protective titre. These 3 HCWs were female nurses of ages 29,32 and 60 years. To rule out the possibility of prior infection, they were further investigated and found negative for HBsAg and antibodies to hepatitis B core antigen (anti-HBc total). The disparity in the unvaccinated status and protective antibody titres in this study might be due to error in recall about hepatitis B vaccination status, as our study depended on self-reported vaccination status of HCWs.

This study demonstrates a negative impact of smoking and alcohol consumption on anti-HBs titres following complete vaccination. Cigarette smoke exposure and alcohol weakens the immune system, making it more challenging for the body to produce memory cells, which are essential for maintaining the protective immunological response following vaccinations. Similar observation has also been reported by Basireddy et al.[23]

In this study no significant correlation was observed between anti-HBs titres and comorbidities like diabetes, hypertension, arthritis, tuberculosis. This may be attributed to relatively small no of HCWs with co-morbidities.

All the unvaccinated HCWs (n=115) and the completely vaccinated HCWs with non-protective titres (≤10 mIU/ml) (n=38) were non-reactive for HBsAg and anti-HBc indicating absence of active or previous infection. These unvaccinated HCWs were sensitised about vaccine safety and need of 3 doses of HBV vaccine followed by post vaccination testing for anti-HBs titres. The completely vaccinated HCWs with non-protective titres were advised to receive 1 booster dose followed by anti-HBs evaluation. This strategy of post vaccination testing helps to identify non-responders.

In this study, vaccination status of HCWs were assessed through the self-reported proforma as there was no vaccination record available resulting in possible recall bias. Due to the short time period and cross-sectional nature of study, follow-up of the HCWs after the vaccination was not possible and non-responder status were not analysed. Even though, CDC recommends evaluation of anti-HBs titre post primary vaccination after 1-2 months of last dose, in our study we evaluated the anti-HBs titre of HCWs at the time of enrolment. Evaluation of certain genetic factors like HLA types which is known to affect the immune response was not undertaken due to resource constrains.

CONCLUSION

This study highlights poor compliance to HBV vaccination among HCWs. National recommendations regarding mandatory hepatitis B vaccination of HCWs at

recruitment or training period would assist in filling the gap in vaccination coverage. As anti-HBs titres decline with time, post-vaccination anti-HBs testing, 1-2 months after primary vaccination series should be undertaken, to detect non-responders without which, may lead to false sense of protection. It also reduces the costs of post-exposure management related to HBV thereby optimizing scarce public resources in our country.

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