Clin. Lab. 2020;66:XXX-XXX

ORIGINAL ARTICLE

Hepatitis B Vaccine: Assessment of Immunologic Response, Coverage Rate, and Factors Influencing Seroreactivity

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SUMMARY

Background: **Hepatitis B infection and resulting health sequela is a worldwide health problem. Adults at increased risk of infection are recommended to receive hepatitis B vaccine for protection, followed by postvaccination titer testing to confirm immunity. The aim of this study is to assess coverage rate and immunologic response to hepatitis B vaccine and factors influencing seroreactivity.**
Methods: **This was a cross-sectional study carried out among medical doctors of Makkah city, medical interns, and medical students of Umm Al-Qura University, Saudi Arabia. A self-administered questionnaire was used to collect data for evaluation of hepatitis B vaccination coverage, immune status, and associated risk factors.**
Results: **Three hundred twenty-one (79.9%) out of 402 participants received the vaccination. Of those vaccinated 159 (48.3%) had subsequent testing for anti-HBs. One hundred thirty-nine (87.4%) had an appropriate immunologic response to the vaccine (titer ≥ 10 mIU/mL). Factors negatively influencing seroreactivity were male gender, high BMI, smoking, incomplete vaccination series, vaccination schedule non-adherence, and long elapsed time since last vaccination; with p-values of 0.001, 0.000, 0.002, 0.001, 0.037, and 0.000, respectively.**
Conclusions: **Hep B vaccination coverage in our study is considered insufficient. Smoking and obesity were modifiable and preventable risk factors negatively affecting the immunologic response. The development and enforcement of better health policies aimed at increasing access and coverage of the HBV vaccination of at-risk populations like medical students, with increased awareness, is recommended.**
(Clin. Lab. 2020;66:xx-xx. DOI: 10.7754/Clin.Lab.2019.191202)

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Manuscript accepted December 18, 2019

KEY WORDS

hepatitis B, vaccination, response, coverage, risk factors

INTRODUCTION

Hepatitis B virus (HBV) is a double-stranded DNA virus. In 2015, The Centers for Disease Control and Prevention (CDC) estimated that there were 21,900 cases of acute hepatitis B worldwide [1]. Nearly 25% of children and 15% of adults suffering from chronic hepatitis B infection die prematurely from liver cirrhosis or cancer [2].
The viral infection can be acquired through percutaneous or mucosal exposure to infected blood and/or body fluids. Health care personnel and medical students have a 4-times higher risk of exposure and infection of HBV

compared to general population [3].
The U.S. Preventive Services Task Force and The Advisory Committee on Immunization Practices recommend HBV vaccination for unvaccinated infants, children, unvaccinated adults requesting protection from HBV, and persons at increased risk of infection, and screening for hepatitis B in adolescents and adults with high risk of infection [4-6].
A follow-up postvaccination titer testing to confirm immunity is recommended. A responder is defined as a person with an anti-HBs level of 10 mIU per mL or more after completion of the vaccine series (2). If the anti-HBs level is less than 10 mIU per mL after the initial vaccine series, the person is considered a non-responder and revaccination is indicated [7]. In some countries a safe immunoprotection against HBV is considered anti-HBs level of ≥ 100 mIU/mL (e.g., in Germany).

MATERIALS AND METHODS

This was a cross-sectional study carried out among medical doctors of Makkah city, medical interns and medical students of Umm Al-Qura University, Saudi Arabia from September 2019 to November 2019. A self-administered questionnaire was used to collect data for evaluation of hepatitis B vaccination coverage, immune status, and associated risk factors.
After oral consent was taken from participants, all persons who accepted to share in the study, including participants who missed any of the vaccination doses were included in the study. While persons currently receiving the scheduled vaccine and those immunocompromised or known positive for hepatitis B surface Ag were excluded from the study.
The tool of this study was based on self-administered questionnaire divided into two sections; first section assessing sociodemographic information and potential factors influencing the immunological response (age, gender, marital status, medications, medical condition, smoking, and BMI) and second section assessing immunization status information (immunized or not, completed vaccination series or not, vaccination schedule adherence, time elapsed from last vaccination dose, anti HBSAG titer).
Since there is no enforced policy of mandatory vaccination and assessment of postvaccination immunological status across the study area and due to the difficulty of performing the testing to the participants ourselves due to lack of funding and difficult logistics of performing the testing for medical interns, students, and medical doctors across Makkah City, we based our assessment of immunization status on participant's reporting.
HBV vaccine status was defined as complete (3 doses at 0, 1, and 6 months), partial or incomplete (1 or 2 doses at any interval), and not vaccinated (zero dose). A responder to vaccination was defined as a person with an anti-HBs level of 10 mIU per mL or more [2]. The pilot study was done on 30 personnel to ensure validity of the questionnaire.
Data was analyzed using IBM advanced SPSS statistical package version 20. For quantitative data, *t*-test was used. Chi-square test (Fisher's exact test) was used to examine the relationship between qualitative variables, and $p < 0.05$ was considered statistically significant. Ethical approval was obtained from the Ethics and Research Review Committee of Umm Al Qura Faculty of Medicine. Confidentiality was ensured during the study. Participants were approached and an explanation of the nature and purpose of the study was given.

RESULTS

Four hundred two participants responded to the questionnaire. The distribution of responders was 74 (18.4%) medical doctors, 61 (15.2%) medical interns, and 267 (66.4%) medical students. The study population comprised 214 (53.3%) males and 188 (46.7%) females. Out of the 402 participants, 310 (77.1%) were single, 123 (30.6%) were smokers, 70 (17.4%) had at least one chronic medical condition. Out of the 402 participants, 321 (79.9%) received HBV vaccination and 81 (20.1%) did not receive the vaccination at all. Of the total 321 vaccinated participants, 240 (74.8%) had received all three doses of vaccination and the rest had received two doses only. Additionally, out of the total 321 vaccinated persons, 159 (48.3%) were tested for anti-HBs and 162 (50.5%) did not. Of the 159 who tested for anti-HBs, 139 (87.4%) were responder (≥ 10 mIU/mL) and 20 (12.6%) were non-responder (Table 1).
Of the 159 who were tested for anti-HBs, 115 persons had received all three doses of vaccination while 44 persons either received one or two doses. When analyzing the data for participants who had anti-HBs, it was found that the immunologic response was similar in those with chronic medical conditions and those without chronic medical conditions ($p = 0.120$), across all marital statuses ($p = 0.317$), and across all participants' training and career levels ($p = 0.419$). There was a decline in immunological response in males ($p = 0.001$), smokers ($p = 0.002$), participants who did not follow the recommended 0, 1, 6 months schedule ($p = 0.037$) and participants with incomplete vaccination status ($p = 0.001$) (Table 2).
There was a decline in immune response as the time gap increased between the last dose of vaccination and the time of assessment of anti-HBs levels ($p = 0.000$). Additionally, lower BMI was associated with better immune response ($p = 0.000$). There was no effect of age on the immunological response ($p = 0.131$) (Table 3).

Table 1. General characteristics of the participants.

		n (%)
Participant's level	medical doctor	74 (18.4%)
	medical intern	61 (15.2%)
	medical student	267 (66.4%)
Gender	male	214 (53.3%)
	female	188 (46.7%)
Marital status	married	90 (22.4%)
	single	310 (77.1%)
	divorced	2 (0.4%)
Chronic medical problem(s)	yes	70 (17.4%)
	no	332 (82.6%)
Chronic medications' use	yes	64 (15.9%)
	no	338 (84.1%)
Smoker	yes	123 (30.6%)
	no	279 (69.4%)
Received vaccination	yes	321 (79.9%)
	no	81 (20.1%)
Vaccination series	completed (3 doses)	240 (74.8%)
	incomplete (1 or 2 doses)	81 (25.2%)
HBsAg ab test done	yes	159 (49.5%)
	no	162 (50.5%)
Response to Hepatitis B vaccination	responder (≥ 10 mIU/mL)	139 (87.4%)
	non-responder (< 10 mIU/mL)	20 (12.6%)

Table 2. Evaluation of various factors affecting response to hepatitis B vaccination.

		Response to hepatitis B vaccination		p-value
		Responder (≥ 10 mIU/mL)	Non-responder (< 10 mIU/mL)	
Participant's level	medical doctor	52 (37.4%)	6 (30.0%)	0.419
	medical intern	36 (25.9%)	8 (40.0%)	
	medical student	51 (36.7%)	6 (30.0%)	
Gender	male	58 (41.7%)	16 (80.0%)	0.001
	female	81 (58.3%)	4 (20.0%)	
Marital status	married	58 (41.7%)	6 (30.0%)	0.317
	single	81 (58.3%)	14 (70.0%)	
Chronic medical problem(s)	yes	22 (15.8%)	6 (30.0%)	0.120
	no	117 (84.2%)	14 (70.0%)	
Chronic medications' use	yes	20 (14.4%)	6 (30.0%)	0.078
	no	119 (85.6%)	14 (70.0%)	
Smoker	yes	26 (18.7%)	10 (50.0%)	0.002
	no	113 (81.3%)	10 (50.0%)	
Vaccination series	completed (3 doses)	107 (77.0%)	8 (40.0%)	0.001
	incomplete (1 or 2 doses)	32 (23.0%)	12 (60.0%)	
0, 1, and 6 schedule	yes	103 (98.1%)	8 (80.0%)	0.037
	no	2 (1.9%)	2 (20.0%)	

Table 3. Assessment of age, BMI, and timed elapsed effect on response to Hepatitis B vaccination

		Mean ± SD	p-value
Age	**responder**	**27.80 ± 11.14**	**0.131**
	non - responder	**23.80 ± 9.91**	
BMI	**responder**	**26.92 ± 8.25**	**0.000**
	non - responder	**34.84 ± 7.02**	
Time elapsed (months)	**responder**	**22.42 ± 40.51**	**0.000**
	non - responder	**76.00 ± 106.21**	

DISCUSSION

In this study vaccination coverage was 79.9% only, which is a very low rate for vaccination coverage for our study population, who were healthcare personnel. They are at a higher risk of exposure to HBV and are recommended to take the vaccination for protection. Most likely this low coverage is due to the lack of application of policies enforcing the vaccination of this population against HBV, due to the unavailability of the vaccine in some hospitals and medical schools, and due to unawareness in the population about the importance of vaccination.

Out of 159 who tested for anti-HBs in our study, one hundred thirty-nine (87.4%) participants were hepatitis B vaccination responders, showing our results are closely consistent with studies by Chathuranga et al. [8], Thomas et al. [9], and Nashibi et al. [10] which showed 91.1%, 98.89%, and 94.1% have protective immunity, respectively, and were lower than Chakrabarthy et al. [11] and Nagamani et al. [12] which both showed 100% protective immunity. This difference may be due to inclusion of participants with incomplete vaccination in our study. Non-response rate was more in males in the current study which could be explained by the higher BMI of males compared to females (males: mean + SD 30.36 + 10.08 and females: 25.78 + 6.14). Other studies have shown that males have a lower response rate even after correcting the weight, which can be explained by the opposite effects of sex hormone androgen and estrogen [13]. Our results are similar to some authors who have found a poorer response in males than in females [14]. Other studies found no association between gender and the rate of seroconversion to anti-HBs [15].

Decreased anti-HBs response was noticed with increased BMI in the current study. In some studies, a significant association between response and BMI was found [16], while in a few other studies no significant association was found [10,15]. The negative effect of high BMI can be explained by the strong evidence that showed excess adiposity negatively impacts immune function and host defense in obese individuals [17]. The low response to vaccination in overweight individuals could be due to the main distribution of the vaccine in fat not in muscle. This could hinder absorption and enable denaturation of the vaccine antigen by enzymatic action. Another possible interpretation is damaged proliferation and function of the antibody-secreting plasma cells [18].

The time gap between the last dose of vaccination and the time of assessment of anti-HBs levels ranged from 6 months to 19 years. The mean months after the last dose of vaccination were 60.36 months. Our findings show that the anti-HBs level significantly declines with time as in previous studies [19]. Although antibody titer declines with time, it should be reasonable to the level of 10 mIU/mL at any time for ensuring immunoprotection among vaccinated individuals [20].

The current study showed that smoking is strongly associated with a poor response rate to hepatitis B vaccine as shown by other studies as well [10]. Smoking has been implicated in the production of many immune or inflammatory mediators, including both pro-inflammatory and anti-inflammatory cytokines [21] which hinder the immune system efficacy.

Our study showed that the participants who follow 0, 1- and 6-months schedules for vaccination have a higher seroprotection rate to hepatitis B vaccine than others which is consistent with results of other studies [10]. In our study, we included participants who did not complete vaccination series due to various causes as unavailability of the vaccine last dose on occasions or carelessness of the participant, and we found that incomplete vaccination is associated with nonresponse to HBV vaccine compared to those who completed the vaccine series.

Aside from those factors, our study showed that age has no significant effect on anti-HBs response, which is inconsistent with other studies, that showed that older age affects the response negatively [23]. This is most likely due to our participants being on the younger side of the age spectrum and did not include older individuals.

In addition to age in our study, having a chronic medical disease was not associated with increased nonresponse rates to HBV vaccine which is in agreement with some studies which found no association between comorbidity and seroprotection [24,25]. However, some studies found that comorbidity may be a significant ele-

ment decreasing the efficacy of hepatitis B vaccine from this analysis and others, which could bring immunity disturbance. However, the detailed mechanisms between the poor response to hepatitis B vaccine and adults suffering from concomitant disease are still incompletely understood [26,27].

In a word, our study showed that being a male, having a high BMI, being an active smoker, and not completing the vaccination series or not following the recommended 0, 1, 6 months vaccination schedule are factors associated with reducing the immune response to HBV vaccination. Those who are more likely to have non-response should be checked for seroprotection level and offered additional booster vaccinations if they had anti-HBs titers below 10 mIU per mL following vaccination. Finding those without immunization and improving overall immunization rates across the population should be emphasized.

The limitation of our study is that it depended on self-reporting of the participants.

Financial Support and Sponsorship:
None.

Declaration of Interest:
No conflicts.

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