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Hepatitis B Immunity Status among Healthcare Sciences Students, 20 Years after the Infantile Vaccination: The Most Appropriate Policy to Confer Full Protection.

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Abstract:

Background. During recent years, an increasing number of previously vaccinated children against hepatitis B (HBV) may begin activities as healthcare sciences students (HSS), so, at the higher risk of HBV infection. Therefore, documenting their immunity at before training was recommended. To evaluate their immunity status, as well as measuring the presence of immunological memory and protection through administering 1-to-3 additional doses of HBV vaccine among HSS who have been immunized at childhood, this study was conducted.

Subjects and Methods. The vaccination status of the accepted HSS was documented by reviewing their vaccination record card. HBV infection markers at before, and following 1-to3 dose of HBV vaccine were measured using ELISA. Simple descriptive statistical methods were used to analyze collected data.

Results. Totally, 274 HSS, 59.1% female, with mean age 23.8 years were included. Of those, 228 in infancy, and 46 within last 12-years have been immunized. From 228 infantile immunized students,103 with 1-to-3 doses of HBV vaccine were vaccinated. Of 125 non-boosted HSS, 64 preserved their protective antibody titers. The proportion of protected students and their antibody levels were increased significantly and approached to 96.8% following 3-doses of booster injection.

Conclusion. Nearly half of the vaccinated students had lost their protective antibody titers, but, the majority of them preserved their immunological memory, detected through anamnestic response to booster vaccination. To provide appropriate protection, universal vaccination with one-doses of HBV vaccine followed by serological monitoring to identify non-protected students for further management seems reasonable.

Key words. Hepatitis B, Healthcare sciences students, Booster dose, Infant HB immunization, Long-term protection.

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Introduction

Hepatitis B virus (HBV) infection is an important public health concern in the world (1). According to the World Health Organization (WHO) estimation in the year 2019, nearly 296 million people were living with chronic HBV that resulted to 820,000 deaths (2). HBV is a highly contagious infection which is transmitted through percutaneous or mucosal exposures to the blood and infectious body fluids (B/IBF). Hepatitis B is a well-recognized occupational risk for Healthcare personnel's (HCPs), whose work related activities involve reasonably anticipated risk of exposure to B/IBF (3-5). This risk is much higher among healthcare sciences students (HSS), because of their lesser skills and experiences during training (6). General recommendations regarding the vaccination and protection of these occupational high-risk groups against HBV have been published (3-5, 7-9).

An increasing number of routinely vaccinated infants now are young adults, who may begin activities as HSS or HCP, so, at the higher risk of exposure to HBV infection. The main issue is that most of these newly accepted HSS/HCP did not have previous documentation of seroconversion following their initial course of HBV immunization (4). Because vaccine-induced antibody concentration decline over time, testing HSS/HCP for anti-HBs years after vaccination might not distinguish true vaccine non-responders from responders. This raised concern about their protection while exposed to B/IBF. Therefore, assessment of anti-HBs titers just before clinical training or contact with patient, to providing appropriate post-exposure management was suggested (7,8). However, the main questions raised are what program, and how many additional doses of HBV vaccine to confer proper protection and to identifying true non-responders for further management are appropriate. For this purpose, while the CDC guidelines suggest assessment of anti-HBs levels upon hire or matriculation, followed by one or more additional doses of HBV vaccine for those with antibody titers less than protective (10mIU/mL) against HBV surface antigen (anti-HBs) and retesting antibody, if necessary, help to ensure that HSS/HCP will be protected if they have exposure to B/IBF(8). In this regard, the Iranian Ministry of Health and Medical Education (IrMHME) recommends that if the risk of exposures is present, HCP who had been immunized years earlier, should be immunized with 3-additional doses of HBV vaccine, and followed by serological screening for both HBV surface antigen (HBsAg) and anti-HBs antibody (9).

To determine the vaccination status of the students accepted to the healthcare-related sectors who had been immunized in the past; to estimate the proportion of students who lost their protective antibody titers over time; and also to assess the immunological response to 1-to-3 additional doses of HBV vaccine and differentiate true non-responders to HBV immunization this study was conducted. Moreover, to find the most appropriate policy to providing appropriate protection against HBV while considering the cost, ease of performance, and the ability of program to identifying non-responders, the policies recommended by IrMHME, CDC, and other related expert groups was compared.

Subjects and Methods.

A cross-sectional study between 1-November 2018 and 28-February 2019 was performed. Target population include first year healthcare sciences students,who were accepted to different faculties of the Mazandaran University of Medical Sciences (MAZUMS), Sari, North of Iran, before their hospital training on a voluntary basis. In every faculty except pharmacy, an oral presentation about the scopes of the study was made and all students were invited to participate in the study. Students with acute or chronic illnesses, malignancies and Immunodeficiency's, those who received blood and/or blood products during recent 12 months were excluded. The study protocol was approved by the Ethic Committee of the University [IR.MAZUMS.Rec.3082) and informed written consent from each student was obtained. Information was gathered via personal interview and self-administered questionnaire. In addition to the age, gender, and type of faculty, the history of vaccination against HBV during infancy or later years were sought. For history of HBV vaccination, postulation was made on the

age of the HSS and the National Immunization Program, and was confirmed by examining their vaccination records card. Blood samples were obtained and sera were stored at -20°C to testing. HBV infection markers were measured using ELISA kits according to the manufacturer's instructions. HBV surface antigen (HBsAg), antibody against HBV Core antigen (anti- HBc) and antibody against HBsAg (anti-HBs) concentrations were measured using specific Kits. Anti-HBs concentrations was measured quantitatively up to maximum 250 mIU/mL, HBsAg conversion Ultra, and anti-HBc levels were measured qualitatively, all kits from Diapro: Diagnostic Bioprobes Srl, Milano-Italy. Anti-HBs titer > 10 mIU/mL was considered protective and <10 as non-protective (susceptible). Anti-HBs titer <10 was categorized as titer 2-<10(detectable) and <2 mIU/mL(non-detectable). Sera sample positive for HBsAg was rechecked and if positive, considered as possible chronic HB infection. The presence of anti-HBc antibody was considered as marker of HBV infection, and if associated with protective anti-HBs titers, as subclinical resolved natural HBV infection. Mean concentrations of anti-HBs antibodies (MCA) among seroprotected students was calculated. To investigate the presence of immunological memory and to find true non-responders to initial HBV immunization, students vaccinated at childhood, with 1-to 3-doses of HBV vaccine were boosted (true non-responder was defined as: the proportion of the students with a history of complete primary vaccination series that remained non-protected following three additional doses of HBV vaccine). Finally, the most appropriate policy to confer full protection, and can find the students who are non-responders to second courses of vaccination, the costs of each guidelines raised by the Ir MHME, CDC, and 2 other related experts was determined. Costs estimation was made on the current costs of ELISA serological testing for different marker; each 35.000 Toman, and the HBV vaccine price (WHO, EPI vaccine price for year 2019; one dose: 0.3264 USD) and the USD currency rate to Toman: one USD equals to 30.000 Toman as the follow:

Policy A (as recommended by IrMHME (9)): universal vaccination with 3- doses, followed by serological testing both for HBsAg and anti-HBs.

Policy B: universal vaccination with 3-doses, followed only for anti-HBs testing to find non-responders

Policy C: universal one-dose booster injection followed by serological testing and vaccination of the susceptible students with 2 additional doses of HBV vaccine and screening for anti-HBs to find non-responders.

Policy D (as recommended by CDC (8)); universal serological testing followed by vaccination of susceptible students with 1- doses of HBV vaccine, and screening for antibody to find seronegative subjects for further vaccination to complete second course.

The collected data were analyzed using SPSS version 16.0. The descriptive statistical method was used in the form of mean and range for age and percentile for proportion of the protected subjects. The Chi-Square, Fischer Exact test, and Student t-test were used to find differences between groups. Results were considered to be statistically significant when the P-value was less than 0.05.

Results. For the first trimester academic year of 2018-2019, nearly 390 students were accepted. Of those,40 HSS from the pharmacy faculty were excluded. From the 350 recruited students, 274(78.3%) agreed to participate and completed the study. The demographic characteristics and the relative contribution of students related to each faculty are presented in the Table 1.

Table 1. Demographic characteristics of the studied healthcare sciences students, Mazandaran University of Medical Sciences, Sari-Iran, 2019.

Characteristics of HSS groups	female	Male	Mean age (years)	Age range (years)
Nursing, n=138	70(50.7%)	68(49.3%)	22.3	19-28
Midwives, n=35	35(100%)	0	27.8	20-47

Paramedical, n=42	26(61.9%)	16(38.1%)	22.6	18-31
Medical, n=27	12(44.4%)	15(55.6%)	23.2	19-27
Dentistry, n=32	19(59.3%)	14(40.7%)	23.2	18-26
Total, n=274	162(59.1%)	112(40.9%)	23.8	18-47

After registration, based on the university policy, a medical file including the demographic characteristics, past medical history status and a copy of the vaccination record card at the student medical health center affiliated to university were made. All students declared that they had been vaccinated against HBV in the past that was verified by examining their vaccination recording card. Of 274 included HSS, 228(83.2%) have been immunized since birth, and 46(16.8%) within recent 12 years (most of these students were accepted as a new student to complete their previous education). After acceptance, according to the IrMHME recommendations, HBV re-vaccination of the students, who had been immunized since birth was begun. In this regard, 103 out of 228 students with 1-to 3-doses of the HBV vaccine were vaccinated. Based on the initial and the booster vaccination status; HSS were categorized as the following; G1: including 125 students who had been vaccinated since birth, and no history of further vaccination; G2: consist of 72 students from infant immunized group; who by one dose of HBV vaccine were boosted; G3: includes 31 infantile immunized students who received 3-additional doses of HBV vaccine; and G4: consist of 46 students; who received their primary vaccination series during recent 12 years. The HBV infection markers detected among students in relation to their vaccination status are presented in the table 2.

Table 2. Hepatitis B immunity seromarkers patterns of the Healthcare sciences students, based on their initial and booster vaccination status, Mazandaran University of Medical Sciences, Sari-Iran, 2019.

	Anti-HBs antibody status(a)			MCA level mIU/mL(a)	anti-HBc positive
	>10, n=195(a)	2-<10 n= 55	<2, n=24		
Vaccinated in infancy n= 228					
G1: non-boosted n=125	61 (48.8%)	45	19	94.81±90. 90	3
G2: 1-dose boosted, n=72	63 (87.5%)	6	3	151.93±92.70	2
G3:3 doses boosted: n=31	30 (96.8%)	0	1	205.75±71.98	1
G4:Vaccinated later years: n=46	41 (89.1%)	4	1	151.48±98.27	2
Total=274	95(71.1%)	55	24	107.37±104.05	8

a) P values for proportion of sero-protected HSS and MCA levels between groups were as follow: G1 Vs three other groups; p=0.000 and P=0. 000, G2 Vs G3; P=0.000 and P=0. 027, G3 Vs G4; p=1 and P=1, respectively.

As are shown, from 274 studied HSS,195 (71.1%) showed protective anti-HBs antibody titers. Also,8 (2.9%) students were anti-HBc positive; all cases were associated with protective titers of anti- HBs (resolved natural HBV infection). However, the relative proportion of protected students and their related MCAs levels were varied significantly between groups. As are presented in the table 2, only 61/125(48.8%) of the HSS including in the G1, with the lowest MCA levels showed protective antibody titers. The seroprotection rates are increased to 87.5% following one booster dose, and approached to 96.8% after completion of the second vaccination course. In this study, overall, 3.2% of HSS who had been vaccinated as infant, following two cycles of HBV vaccination remained non-protected, possibly non-responder to HBV vaccination (susceptible). While

comparison was made between G1 and two other boosted groups, and those immunized during recent years, the proportion of protected students and their related MCAs levels were increased significantly following booster administration (Table 2). In this study, the frequency of protected students and the MCAs levels detected among those, who were vaccinated during past 12 years (G4) were similar to the rates observed among one-dose boosted students (G2). In this study, among 64 out of 125 infantile vaccinated students with antibody titers less than 10 mIU/mL ,45(70.3%) showed detectable (2-to <10) and 19 (29.7%) undetectable anti-HBs antibody titers <2 mIU/mL. Regarding the most appropriate policy to provide adequate protection against HBV infection, and possibly to find non-responders to second vaccination cycle, while considering the vaccine and laboratory testing prices in Iran: as are seen in Table 3, the policy A, as was recommended by the Ir MHME was the highest and the policy 3, least expensive methods.

Table 3. Cost- estimation based on 4-different policies to provide full protection against HBV among healthcare sciences students vaccinated as infant, more than 20 years earlier.

Vaccination policies	How the policy costs was calculate	Final estimation to toman (USD)
Policy A: universal 3-doses vaccination followed by HBsAg and anti-HBs monitoring (Ir MHME recommendation).	274×3×0.3264 USD × 30.000+ 274×35.000×2=27.229.024 Tmn (907.64 USD)	27.229.024 Tmn (907.64 USD).
Policy B: universal 3-doses immunization followed by anti-HBs screening.	274×3×0.3264 (USD)×30.000 + 274×35.000= 17.639.024 Tmn (587.97 USD)	17.639.024 Tmn (587.97 USD).
Policy C: one-dose boosting followed by anti-HBs monitoring, and vaccination of susceptible students with 2-additional doses.	274×0.3264×30.000+ 274×35000 + 40[a]×0.3264×30.000×2-doses + 40×35000 =14.456.368 Tmn (481.88 USD)	14.456.368 Tmn; (481.88 USD).
Policy D: Serological screening followed by 1-3 doses vaccination (CDC recommendation).	274×35000 + 150[b]×0.3264×30.000 ×35.000[c] + 22[d]×0.3264×2×30.000 +22×35000= 17.509.648 Tmn (583.65 USD).	16.739.648 Tmn (583.65 USD).

a: (susceptible students based on 85% response rate to boosting)
b: (no of susceptible students)
c: (re- screening cost of the susceptible students)
d: (non-responders to first booster dose)

Discussion.

The present study showed that the National Immunization Program of the newborn infant against HBV was implemented successfully. Two decades after the primary course of vaccination, 51.2% of the HSS had lost their protective antibody titers (antibody titers less than 10 mIU/mL). However, the majority of the vaccinated subjects preserved their immunological memory, detected through anamnestic response to one challenge dose of HBV vaccine; the proportion of protected students from 48.8%, increased to 87.5%. The study results showed that to achieve a proper protection, and to identify true non-responders, 2-additional dose of HBV vaccine to complete the second course of vaccination was required. After completion of the second vaccination course, protection rate was increased to 96.8%, and 3.2% of the students remained susceptible to HBV infection (true non-responder to HBV vaccination).

Following the primary 3-doses of vaccination against HBV, nearly 80%-100% of the healthy vaccinated infants, children, and subjects younger than 40 years, induce a protective anti-HBs antibody response (5,7,8). Long-term follow-up studies results among vaccinated infant showed that vaccine-induced antibodies decline, and even may became undetectable over time, therefore, the serologic testing of HSS/HCP years after initial vaccination might not accurately distinguish responders from non-responders to vaccination. However, the majority of those who responded initially will show an anamnestic response to a challenge dose of HBV vaccine, indicating the presence of immunological memory and long-term protection (5,8). HSS and HCP are at the higher risk of exposure to HBV infection, therefore, the cornerstone of primary prevention of those completed their initial vaccination series several years earlier enacted by the occupational services in many countries is to assess anti-HBs titers prior to work or training (5,7,8,9). In order to provide adequate protection, and to determine the possible necessity for booster vaccination among HSS/HCP, who had been immunized during childhood, several studies were conducted, worldwide. However, the results of these studies were not uniform and conclusive (10-13). While some studies results indicated the presence of long-iasting protection detected through strong anamnestic response to a challenge dose of HBV vaccine (10,11), others showed waning of vaccine-induced protection in some vaccinated subjects over time and to provide an appropriate protection, 1-to3-additional doses of HBV vaccine were recommended (12,13). For example, to determine the persistence of protective antibody titers, and the presence of immunological memory among 717 HSS (age 24.8±4.6 years), who had received their primary vaccination course during first year of life (74.6%) or at adolescence, a study by Dini, et al, was conducted (10). Overall, 29.3% of the students (33.1% vs 18.1% among infant vaccinated) had lost their protective antibody titers. After administering one booster dose to non-protected students, a 95% anamnestic response was found. Researchers concluded that optimal anamnestic response provide an evidence of a strong immunological memory and persistence of protection for more than 20 years (10). Conversely, similar to our study findings, in a similar study by Bini etal(12),the persistence of protection and immunological memory among Italian HSS was investigated. Of 1051 included students vaccinated as infant, 51.1% showed non-protective antibody titers. One month after boosting of the students with antibody titer less than 10, still 11.2% remained non-protected. They concluded that it is necessary to protect all HSS against HBV infection, and to achieve full protection, administering up to 3 doses of HBV vaccine may be required (12).

The presence of immunological memory and resultant immunological response to challenge dose administration are directly correlated to the pre-booster anti HBs concentrations; more cases with undetectable antibody titer; lower response rate (14). In this study, following administration of one booster dose, the proportion of seroprotected students from 48.8% increased to 87.5%. The rate was increased to 96.8% after two-additional doses of HBV vaccine boosting. In our survey, of 64 non-protected and non-boosted students, 29.7% showed titer less than 2 mIU/mL. This possibly have influenced the number of HBV vaccine doses that was required to provide more than 95% protection rate in our HSS. Similarly, Posuwan, et al, (13) in their study on 271 Thai HSS, found that immunological response rates to booster injection was correlated directly with pre-booster anti-HBs titers, and concluded that to achieve full protection in students with undetectable anti-HBs titer, a regimen including 3-doses of HBV vaccine was required (13). This assumption was confirmed through a recent systematic review and meta-analysis. In this review, the long-term effectiveness of HBV vaccination among HSS, who have been vaccinated at childhood was evaluated. Results indicated that majority of the vaccinated students maintained their humoral immunity for more than 20 years, and nearly 5% of HSS remained non-protected following a full second course of HBV immunization (true non-responders to HBV vaccine) (15). Based on this study findings, and other similarly studies, to ensure proper protection among these high-risk groups, while considering these studies findings, for a minority of vaccinated students, more than one booster doses of HBV vaccine may be required (12-14).

Breakthrough HBV infection among properly vaccinated infants detected through the presence of anti-HBc or HBsAg/HBV-DNA have occurred in a minority of immunized subjects, but these infections typically are transient and asymptomatic (16). In this study, none of the HSS was HBsAg positive, but, 2.9% of students showed evidence of resolved HBV infection. In a similar study reported by Dowran et al (17), from Shiraz, Iran; none of the studied HSS was HBsAg positive, but 1.1% were anti-HBc positive. As was reported in the world (1,2,5,7), well planned vaccination strategy implemented during the last 3 decades in the Iran, largely contributed to the control of HBV infection both in the community and in the several occupational settings, especially among healthcare personnel's/trainees (18-20).

According to the WHO (7), and the CDC (8) guidelines and recommendations, the HBV immunity status of the HSS/HCP in the healthcare sectors should be documented before their work. In this regard, for those students who had been immunized years earlier without previous serological monitoring, regarding the National Policy(9), the most suitable approach to confer appropriate protection while considering the recent epidemiology of HBV infection in the country and in the world, a regimen consists of universal one additional dose of HB vaccine, followed by serological screening only for anti-HBs antibody(policy C) seems to be the most appropriate method: because of the least cost, program can be conducted easily with the least possibility of losing follow-up, could enhance the immunity status of those with low protective antibody titers, and the most important, its ability to identifying those students who did not respond properly to re-immunization(non-responders to HB immunization), and providing an opportunity to be managed accordingly seems reasonable.

For this study some limitations did exist. The main limitation is the relatively small sample size, and single center sampling. The other one is revaccination of the students before serological monitoring, and lastly, the possibility of recall bias for history of vaccination among a minority of the students.

Conclusion. This study showed that universal HBV immunization of the infants was implemented successfully in the country, and provide additional evidence to the available information that despite loss of protective antibody over time, the protection and immunological memory persist longer in the majority of the vaccinated subjects. Results indicated to ensure suitable protection against HBV infection among newly accepted HSS who have been immunized at birth, a regimen consist of universal immunization with one dose of HB vaccine followed by serological screening for anti-HBs antibody to find non-protected subjects for further management seems the most appropriate approach. However, further studies with larger sample size from other parts of the country and the world, to define the most appropriate policy to provide adequate protection in this special group are recommended.

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Authors Contribution and Details: HnS and HvS: both involved in study design, literature search, and laboratory testing and writing the paper.JM: data collection and statistical analysis and interpretation. HSj, recruiting, selection, and interview, MsR, in study design, journal search and writing the paper, MS all phases of the study.

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