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Zoe Roupa

Maria Noula

Evi A. Farazi

Antonis Stylianides

Christos Papaneophytou

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Vaccination Coverage and Awareness of Hepatitis B Virus Among Healthcare Students at a University in Cyprus

Zoe Roupa[1], Maria Noula[1], Evi Farazi[2], Antonis Stylianides[1], Christos Papaneophytou[1]

[1]Department of Life and Health Sciences, School of Sciences and Engineering, University of Nicosia, Nicosia, Cyprus

[2]Department of Epidemiology, University of Nebraska Medical Center, Omaha, Nebraska, USA

Corresponding author: C. Papaneophytou. Department of Life and Health Sciences, School of Sciences and Engineering, University of Nicosia, Nicosia, Cyprus. Tel: +357 22 841941. E-mail: papaneophytou.c@unic.ac.cy. ORCID ID: http://www.orcid.org: 0000-0000-0000-0000. C. Papaneophytou

ABSTRACT

Introduction: The risk for healthcare students to get infected by transmitting infectious viruses, including hepatitis B virus (HBV), in a hospital setting is extremely high through exposure to blood and/or body secretions. **Aim:** The aim of this work was to evaluate both the vaccination history of healthcare students at a University in Cyprus and their serologic immunity against HBV. In addition, we assessed their knowledge and behaviors towards the transmission and prevention of hepatitis B (HB). **Results:** Total amount of 168 students participated in this study and more than 50% of them provided complete documentation of vaccination history against HBV. Antibodies levels ⊠10 mIU/mL to HB surface antigen (HBsAg) were detected for the 98.8% of healthcare students while 1.2% of the participants tested positive for HBsAg and antibodies to HB core antigen indicating chronic infection. Our study also revealed significant gaps in the knowledge of healthcare students on the efficiency of the vaccine against HBV and in terms of the HBV transmission. **Conclusions:** More information needs to be provided to healthcare students in Cyprus regarding HBV transmission and vaccination. In addition, there is a need for intervention to provide a safer workplace environment.

Keywords: Hepatitis B, Students Health Occupations, Awareness, Vaccination, Prevention.

1. INTRODUCTION

Hepatitis B virus (HBV) infection, affects the liver and is a serious global health issue as chronic infection with the virus is associated with the development of hepatocellular carcinoma (1). HBV infection is ranked as the 15th cause of death worldwide, resulting in 0.5 to 1.2 million deaths annually (2). It is estimated that, globally, over 2 billion people have been infected with HBV while more than 240 million people are chronic carriers of HBV (3). HBV is transmitted mainly through exposure to infected blood and other body fluids including vaginal secretions and semen (4) whereas is able to survive for a long time outside the body (5). Even though HBV has been also detected in tears, sweat, breast milk, saliva, sweat, and urine, there is not any evidence of transmission through exposure to these body fluids when blood is not present (6).

A safe and effective vaccine against HBV has been introduced in 1982 (7). Though WHO's universal vaccination action, HB vaccine was widely used and had been extended to all infants in order to achieve protection against HBV infection (8). Usually, a single course of three doses of the vaccine is administered in different schedules (e.g., at 0, 1, and 6 months), whereas a booster dose is administrated in some cases (9). A recombinant HBsAg is used for vaccination against HBV, and a positive immune response to the vaccine is defined as the development of antibodies to HBsAg (anti-HBs) at a titer of > 10 mIU/mL. The vaccination efficiency is evaluated 1 to 3 months after the administration of the third (or fourth) dose of the vaccine (8). Vaccination against HBV has been proven as an effective strategy for the prevention of infection with the virus and at reducing chronic infections in both children and adults, especially in high-risk groups including health-care professionals (10, 11).

During their clinical work course, healthcare students (especially nursing students) are at high risk of acquiring infectious diseases, as

well as transmitting them to their patient and/or to their co-workers. The determination of the HB vaccination status among healthcare students is essential to protect their health and to plan health education programs. Thus, the aim of this study was to evaluate the serologic immunity against HBV as well as the awareness and knowledge regarding HBV infection of healthcare students at a University in Cyprus. Another aim of this study was to evaluate the reliability of the history of vaccination against HBV documented by their doctors or reported by participants, to identify susceptible healthcare students.

2. AIM

The aim of this study was to evaluate the serologic immunity against HBV as well as the awareness and knowledge regarding HBV infection of healthcare students at a University in Cyprus. Another aim of this study was to evaluate the reliability of the history of vaccination against HBV documented by their doctors or reported by participants, to identify susceptible healthcare students.

3. MATERIALS AND METHODS

3.1 Study population

The study was conducted from July 2016 to July 2017 at the University of Nicosia, Nicosia Cyprus. Overall, 168 healthcare students between 18 and 38 years of age (mean 23.6 ± 4.3) participated in the study. The information obtained from these students during personal interviews (after written informed consent was provided) included name, sex, date, and place of birth, nationality, place of residence marital status and whether there was a history of hepatitis virus infection. Vaccination history was abstracted from each student's vaccination records when available. The Cyprus National Bioethics Committee approved the study protocol.

3.2 Assessing HBV awareness and knowledge

The questionnaire consisted of three parts and was delivered in the Greek language. The first section focused on the demographic background of the participants including, their gender, nationality, date of birth, marital status, place of birth and residence. The second part asked about previous vaccination against HBV. The third part was composed of a set of nine questions exploring knowledge on HBV vaccination, HBV transmission modes and protective measures, their source of knowledge about HB and attitude towards people infected with HBV.

3.3 Serologic studies

Blood samples were obtained from consented students and subsequently, serum was recovered by centrifugation (2000g, 10 min, 4oC) and stored at -20oC. Measurements of antibodies against i) hepatitis B surface antigen (anti-HBs) and ii) hepatitis B core antigen (HBc) and of hepatitis surface antigen (HBsAg) were performed with the commercially available enzyme-linked immunosorbent assay (ELISA) monolisaTM kits (anti-HBs Ultra, anti-HBc PLUS and HBsAg Ultra, respectively) (Bio-Rad; catalog numb: 72566, 72315, and 72346, respectively). All assays were performed according to the manufacturers' instructions. All reactions were directly monitored using a temperature-control microplate reader (Victor X3; Perkin-Elmer). The levels of anti-HBs were calculated using a standard curve using the anti-HBs standard calibrators (Bio-Rad). An anti-HBs level ⩾10 mIU/mL was considered protective. The presence or absence of antibodies against HB core antigen (anti-HBc) and of the HBsAg was determined by comparing for each sample the recorded absorbance with that of the calculated cut-off value. The cut-off value for the detection of anti-HBs and HBsAg in serum samples was calculated as the mean negative control (MNC) value and the MNC value plus 0.050, respectively. Samples with a signal/cutoff ratio of ⩾1.0 were considered to be positive, and those with a signal/cutoff ratio of <0.9 were considered to be are negative (12). Students found to be positive HBsAg were referred to Nicosia's general hospital for further tests.

3.4. Statistical analysis

SPSS 23.0 for Window package (SPSS Inc. Chicago, USA) was used for data entry and analysis Tables showing the frequency of certain variables were created and the statistical significance of the variables analyzed was assessed using the w2 Pearson test using SPSS program. Quantitative anti-HBs levels are also presented as geometric mean concentrations (GMC). Anti-HBs levels were log-transformed and were compared by analysis of variance (ANOVA) (13). The level of statistical significance was set at $p<0.05$.

4. RESULTS

4.1 Demographic data

Out of 200 questionnaires sent out, 168 valid questionnaires were recovered (31.0% males, 69.0% females) giving a response rate of 84 %, while 87 (51.7%) provided complete documentation of vaccination history. The characteristics of the sample used in this study are summarized in Table 1. Nearly two-thirds (66.1 %) of participants were aged 20–24 years while most of them (84.5%) were not- married. In addition, most of the participants were Cypriots (85.1%) followed by Greek (9.5%) whereas only 5.4% were from other countries including (Russia, Philippines, Croatia, and Moldavia). The place of birth and residence of the participants are also summarized in Table 1.

4.2 Immunization level for hepatitis B virus

To achieve protection against HBV it is mandatory to have anti-HBs levels ⩾10 mIU/mL whereas three doses of the vaccine are usually administered in order to achieve full protection. Overall, 72 of 168 (42.8%) participants did not provide any vaccination records regarding HBV while 9 provided vaccination records that were incomplete (the age at first vaccination and/or the number of doses were not recorded). The vaccination status against HBV of 87 (51.7 %) students provided complete documentation of vaccination history since childhood by age group of vaccination is summarized in Supplementary Table 1. The number of doses and the age of vaccination varies among the healthcare students of our study. The majority of the participants (48 individuals, 28.6%) received the first dose against HBV at 0-1 years of age, 16 (9.5%) received the first dose between 2 and 10 years of age, 17 (10.1%) received the first dose between 11-20 years of age and the rest 10 participants received the first dose between 21 and 30 years of age. As far as dosage compliance, 20 participants (11.9%) of the participants received the full series (4 doses), 48 (28.6%) had had three

	n	%
Sex		
Male	52	31.0
Female	116	69.0
Age group		
<20	15	8.9
20-24	111	66.1
25-29	24	14.3
30-34	13	7.7
>35	5	3.0
Marital Status		
Non-married	142	84.5
Married	16	9.5
Other	9	5.4
Unknown*	1	0.6
Nationality		
Cypriot	143	85.1
Greek	16	9.5
Other	9	5.4
Place of birth		
Nicosia	82	48.8
Limassol	22	13.1
Famagusta	2	1.2
Larnaca	23	13.7
Paphos	14	8.3
Greece	17	10.1
Other	8	4.8
Place of residence		
Nicosia	90	53.6
Limassol	21	12.5
Famagusta	4	2.4
Larnaca	25	14.9
Paphos	16	9.5
Other	12	7.1

* Did not answer the question

Table 1. Demographic data

doses, 3 (1.8%) had had 2 doses and 21 (12.5%) had had only one dosage dose administrated.

Immunization with three doses of HBV vaccine was statistically different between male and female participants (17 [32.7%] of 52 male vs 31 [26.7%] of 116 of females; p=0.043) (Supplementary Figure 1). In contrast, immunization with the full series (4 doses) of HBV vaccine was significantly higher among female participants than among male participants (16 [13.8%] of 116 females vs 4 [7.7%] of 52 males; p=0.007) (Supplementary Figure 1).

4.3. HBV serological markers

Anti-HBs Levels

In this study, blood samples from all participants were analyzed to assess their serologic immunity against HBV. Data on the levels of IgG antibody against HBsAg (anti-HBs) among 168 participants are illustrated in Table 2. Overall, 2

Characteristic	Participants (No)	Anti-HBs GMC, mIU/mL	Anti-HBs ⩾10 mIU/mL No (%)	*p*-value
Sex				>0.05**
Male	52	206.82	50 (96.1)	
Female	116	288.54	116 (100)	
Age of vaccination				>0.05
0-1	48	116.47	48 (100)	
2-10	16	260.44	16 (100)	
11-20	17	558.50	17 (100)	
21-30	10	261.00	9 (90)	
Unknown*	77	295.96	76 (98.7)	
Number of Doses				>0.05
1	21	250.23	20 (95.2)	
2	3	55.33	3 (100)	
3	48	231.56	48 (100)	
4	20	241.13	20 (100)	
Unknown*	76	307.26	75 (98.7)	
Anti-HBs level				<0.001***
<10	2	3.91	-	
10-99	52	41.21	-	
100-999	64	321.28	-	
1000-1999	37	1313.10	-	
⩾2000	13	2798.13	-	

GMC: geometric mean concentration. *Missing or incomplete vaccination records,**Student's t-test,***Chi-square test

Table 2. Serum levels of antibody to Hepatitis B surface antibody (anti-HBs) of the 168 participants in correlation to the vaccination scheme

(3.8%) male (n=52) participants (one Cypriot and one Greek) had an anti-HBs level <10 mIU/mL while 116 of 116 female (100%) participants had an anti-HBs level ⩾10 mIU/mL. One of the two students that had anti-HBs level <10 mIU/mL, received only one dose of the vaccine while the other one had missing vaccination records. The GMC for male participants was slightly lower than that of female participants (206.82 vs 288.54 mIU/mL respectively; p>0.05). Even though 112 (66.7 %) of the participants were shown to have antibody titers >100 mIU/mL, no correlation was found between the number of doses administrated and the levels of anti-HBs (Supplementary Figure 2).

We subsequently analyzed results from the 87 students that had records regarding the age-group of vaccination and as shown in Table 2, even though there were differences in the anti-HBs GMC level by group, these differences were not statistically significant (p>0.05). Interestingly, similar anti-HBs GMC levels were detected between the 0-1 (n=16) and 21-30 (n=10) group. In addition, we analyzed results from 92 students that had records regarding the number of doses (Table 2). However, the anti-HBs GMC levels did not statistically differ between the students that had had 1 (n=1), 3 (n=48) or 4 (n=20) doses of HBV vaccine, but the group that had had only 2 doses of the vaccine had 4-6 times lower anti-HBs GMC compared with the other groups. It should be noted that this group consisted only of three participants; one of them had an anti-HB level equal to 13 mIU/mL and the other equal to 35 mIU/mL. The anti-HBs

	n	%
Does the HBV vaccine protect you against HBV infection?		
Yes	150	89.3
No	8	4.8
N.A.*	10	6.0
If you have answered YES in above question then at what percentage does it protect you?		
40-50	13	8.7
60-80	44	29.3
80-90	51	34.0
90-100	34	22.7
N.A.*	8	5.3
Are there any side effects of HBV vaccine?		
Yes	83	49.4
NO	73	43.5
N.A.*	12	7.1
If you have answered YES, in the previous question then what types of side effects are there?		
Transmission of diseases	3	3.6
Usual side effects	70	84.3
Other	6	7.3
N.A.*	4	4.8
*N.A.: did not provide an answer		

Table 3. Knowledge regarding HBV vaccine

	n	%
How is HBV spread?		
Sexual contact (true)	130	77
From mother to child (true)	84	50
Contact with infected blood (true)	123	73
Breath (false)	2	1
Saliva (false)	29	17
Feces (false)	21	13
Insects (false)	17	10
Food (false)	2	1
Sweat (false)	11	7
W.C. (false)	29	17
Social life (false)	6	4
After an accident with a needle contaminated by HBV what you have to do in the case are not vaccinated		
Vaccination	26	15.5
Injection with hyperimmune globulin γ	42	25.0
Report to supervisor	62	36.9
I do not know	61	36.3

Table 4. Knowledge regarding the transmission of HBV

GMC levels for students with unknown vaccination status was equal to 295 mIU/mL. Table 2 also summarizes the anti-HBs levels of study participants and as already mentioned only two students had anti-HBs levels <10 mIU/mL, and their GMC of anti-HBs was 3.91 mIU/mL.

	n	%
What is your source of HBV information?		
Ministry of Health	29	17.3
Nursing Departments	91	54.2
Hospital infection control committee	7	4.2
Social media	27	16.1
Personal environment	59	35.1
Do you think that you are well informed regarding HBV?		
Yes	109	64.9
No	50	29.8
N.A.*	9	5.4
Do you consider nursing patients with HBV being an issue?		
Yes	39	23.2
No	121	72.0
N.A.*	8	4.8
If you have answered YES in the previous question please clarify why		
Personal safety	24	14.3
Insufficient knowledge	9	5.4
Insufficient safety measures	15	8.9
High risk to contaminate other people	4	2.4
Where do you think that nursing patients with HBV should be?		
Specific Hospitals	17	10.1
Specific Hospital wings	77	45.8
Isolation wards	46	27.4
Common wards	19	11.3
Patients' home	10	6.0
*N.A.: did not provide an answer		

Table 5. General knowledge regarding HBV

Detection of anti-HBc and HBsAg

During the testing for the presence of HBV serological markers in blood samples, 66 participants were tested positive for anti-HBc indicating previous infection. In addition, two participants (both Cypriots), were tested positive for HBsAg, a serological evidence of acute or chronic HBV infection. The presence of anti-HBc in the blood samples of the two participants indicated a chronic HBV infection. One of these students had anti-HBs levels equal to 13.10 mIU/mL and received one dose of the vaccine while the second one had anti-HBs levels equal to 11.5 mIU/mL and did not provide any vaccination records. Usually, in chronic HBV infection patients have HBsAg in the blood circulation but not anti-HBs (14). However, the presence of HBsAg along with anti-HBs has been reported in many cases (15-19).

4.4. Basic knowledge about HBV transmission and prevention

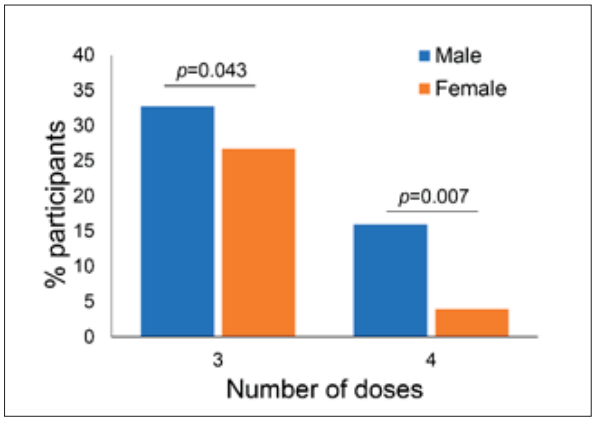
HBV vaccine awareness

Basic knowledge about HBV transmission and prevention was assessed by questions focusing on protection, side effects, transmission, and prevention. In the begging, participants have been asked to answer questions regarding the

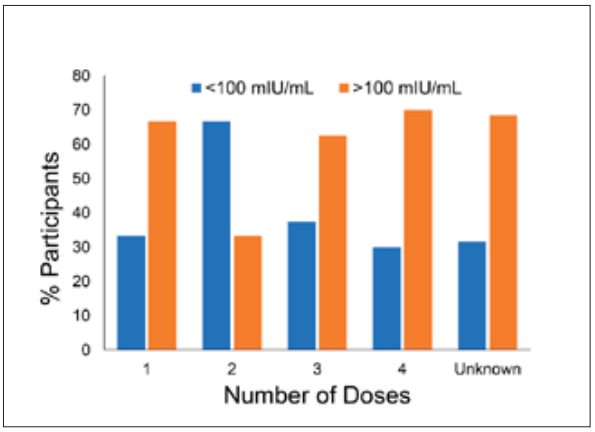
Age of Vaccination	n (%)	Number of Doses				
		1	2	3	4	Unknown*
0-1	48 (28.6)	4	1	25	17	1
2-10	16 (9.5)	0	1	12	3	0
11-20	17 (10.1)	9	1	5	0	2
21-30	10 (6.0)	7	0	2	0	1
Unknown*	5 (2.9)	1	0	4	0	0
No-records**	72 (42.9)	-	-	-	-	-
TOTAL	168 (100)	21	3	48	20	4

*incomplete vaccination records, ** missing vaccination records

Supplementary Table 1 Immunization level against HBV of 168 healthcare students



Supplementary Figure 1 Percentages of male and female participants that received either 3 or 4 doses of vaccine against HBV



Supplementary Figure 2 Correlation of % of participants that developed antibodies to hepatitis B surface antigen (HBsAg) at lower or at higher levels than the recommended titer of 100 mIU/mL, for the healthcare workers, with the number of doses of vaccine against HBV.

vaccine against HBV (Table 3). Overall, 150 (89.3%) students knew that HBV could be prevented through vaccination, but only 22.7% (34/150) of the participants were aware regarding the efficiency of the vaccine. In addition, 83 of 168 students (49.4%) replied that vaccination against HBV causes some side effects, including the common side effects of any vaccine (70/83), transmission of diseases (3/83) or other side effects (6/83), while 4 participants did not know if there are any side effects from vaccination.

HBV transmission knowledge

Subsequently, participants were asked to answer questions regarding HBV transmission (Table 4). The majority of students demonstrated an acceptable level of knowledge about HBV transmission. Sexual, perinatal, and blood transmission of HBV were recognized by 77%, 50% and 73% of students respectively; however, a small proportion (1-4%) of participants did not know that HBV is not transmitted by breath, food, sweat, and social life. Interestingly, most students knew that HBV is not transmitted by saliva, feces, toilet, and insects. When students were asked what they have to do if they accidentally were injured with a needle contaminated by HBV (and they are not vaccinated against HBV), only 36.9 % replied that they have to report the accident to their supervisor while 36.3% reply that they do not know what they have to do. It should be noted that after accidental exposure to blood contaminated with HBV unvaccinated persons should receive immediately the first dose of the vaccine along with hepatitis B immune globulin (HBIg) (20).

General questions about HBV and attitude towards HBV carriers

In the last part of the questionnaire, students were asked to answer some general questions about HBV and general attitude towards patients with HB (Table 5). More than one-half of the participants (54.2 %) obtain information about HBV from the nursing department of University of Nicosia, 29 (17.3%) from the Cyprus ministry of health, 7 (4.2%) from the Hospital infection control committee, 27 (16.1%) from the social media and 59 (35.1%) from their personal environment. Overall, 109 students (64.9%) believe that are well informed about HBV, 50 (29.8%) believe that their knowledge about HBV is insufficient while 9 did not give an answer.

Overall, 121 (72%) students reported that they believe that it is safe for nursing patients with HBV while eight (4.8%), did not answer the question. 39 (23.2%) students replied that it is dangerous to treat HBV carriers while the majority of them (24/39) had some concerns about their personal safety. In addition, 9 replied that they are not well informed about the transmission of the disease, 15 reported that there are insufficient safety measures in hospital, while 4 replied that there is a high risk to contaminate other patients and/or medical staff. When students were asked where they believe that it is safe to hospitalize HBV carriers, 10.1% (17/168) and 45.8% (77/168) replied in specific

hospitals or in specific hospital wings respectively, 27.4 % (46/168) in isolation wards, 11.3% (19/168) reported that is save to keep HBV carriers in common hospital wards, while 6% (10/168) replied that HBV patients should stay in their houses.

5. DISCUSSION

The risk of infection with HBV for HCW in their workplace (and it is higher during training), is extremely high due to their potential contact with infected body fluids, including blood or vaginal fluid (21). Administration of vaccine against HBV is the most common vaccination among HCWs in several countries, e.g., Greece, Turkey, and Austria (22). Unfortunately, in Cyprus, there aren't sufficient data on the immunization status and seroprevalence of antibodies to vaccine-preventable diseases, including HBV, among healthcare students and professionals, while a comprehensive vaccination program in healthcare students has not been implemented.

This study revealed several interesting findings of healthcare students' vaccination status against HBV and their awareness of HBV infection. Specifically, the vaccination coverage of 168 healthcare students was examined by determining the anti-HBs levels in blood serum samples. Results regarding records for vaccination against HBV are not satisfying; 48.2% of the students had incomplete vaccination status. Of those students, two had levels of antibody to HBsAg that were lower than 10 mIUm/L. According to European recommendations, the protective cutoff level of anti-HBs antibodies was set at ⩾ 10 mIU/mL (10). In our study, 52 participants had anti-HBs levels from 10 to 99 mIU/ml (Table 2) and we advised them to receive a booster dose of vaccine against HBV. An interesting observation during our serological HBV markers examination was that the group of participants aged 11-20 years when they received their primary vaccine series had the highest protective antibody levels (anti-HBs ⩾10 mIU/mL) compared with those aged <10 or >20 years at primary vaccination. It has previously demonstrated that children vaccinated through catch-up programs or young adults vaccinated for occupational safety reasons have a high probability of being protected for several years (>20) (11). A high percentage of participants had incomplete vaccination records, and therefore it was difficult to find a correlation between the anti-HBs levels and the number of doses. In addition, no correlation was detected between gender and anti-HBs levels.

During the HBV serological markers examination, 66 participants were tested positive for anti-HBc. In general, the total antibody to HBV core antigen rises approximately 2-3 months after exposure to HBV and is a marker of natural infection (23). Following primary infection with HB, IgM anti-HBc antibodies are produced and are present in the bloodstream for 4 to 6 months. During recovery, HBsAg is cleared and the long-lived IgG anti-HBc antibodies are produced and then antibodies to HBsAg (anti-HBs) are developed (24). In several cases, serum samples have been found positive for total anti-HBc, but negative for both anti-HBs and HBsAg, a phenomenon that is called "anti-HBc alone". This serological response is compatible with resolved, acute, HBV infection but might also signify occult HBV infection (25). In our study, of 66 students, tested positive to anti-HBc, 4 had anti-HBs levels from 50 to 99 mIU/mL while the rest 62 had anti-HBs levels > 100 mIU/mL, indicating resolved HBV infection and that students have developed immunity against HBV. Surprisingly during the HBV serological markers tests, the HBsAg was detected in blood serum samples of 2 participants, whereas total anti-HBc antibodies also detected, indicating a chronic HBV infection (26). These students were referred to Nicosia's general hospital for further tests.

Moreover, in this study, we examined the awareness of healthcare students about HBV, its transmission modes as well as the behavior of participant towards people with HB. The majority (89.3%) of the participants were aware that HBV vaccine provides protection against HBV infection, however awareness may not reflect knowledge since only 20.2% replied that the vaccine provides (after administration of the three doses) > 90% protection to infants, children, and adults immunized before being exposed to the virus. This contradicts the results in the research of Yasobant et al. (27) which two thirds of the population in Gujarat was found to be unaware about Hepatitis B and its vaccine, as well as, the results of a research done in Mumbai that showed that only less than 5% of the participants stated that they were aware of the disease (28). In addition, only 43.5% replied that vaccine is safe and does not cause any side effects and that the HB vaccine is not only one of the most effective but also one of the safest vaccine ever developed while side-effected have rarely been reported (Saridi et al., 2011).

In this study, a misconception regarding the transmission modes of HBV was observed among the participants and only 12 of 168 replied that HBV is transmitted by unprotected sex, from mother to child during pregnancy and by contact with infected blood. A significant proportion (36.3%) of our participant replied that they do not know what they have to do if they get injured with a contaminated by-HBV needle (in the case they are not vaccinated) while only 62 (36.9%) participant replied that they have to report their supervisor.

Inadequate knowledge is probably an important factor in HBV infection. The majority of the participants believed that are well informed regarding HBV infection, while the most common source of HBV information reported by our participants was universities' nursing departments. Of our 168 participants, 121 replied that is safe to take care of people infected with HBV. On the other hand, while 39 believed that is it not safe because they mainly worry about their personal safety, while 49 (of 168) participant replied that HB patients should be hospitalized in isolated wards.

Limitations of the Study

A limitation of the study was that almost 50% of the participants had incomplete vaccination records against HBV. Additionally, according to Loftin et al. (29) when students are used as participants in a study there is a high possibility of bias. Another limitation of our study was usage of a questionnaire that was not previously tested in a separate patient sample for reliability and validity; therefore results of the study should be interpreted with caution. However, the results are indicative of certain tendencies and could be considered as a pilot.

6. CONCLUSION

This study provides important information regarding vaccination status and serologic immunity against HBV among healthcare students in Cyprus and revealed that is an urgent need to raise awareness and knowledge of HBV among healthcare students. HBV education should mainly focus on modes of transmission and precautions to avoid infecting others. In addition, to ensure the adequate protection of healthcare students, we propose blind immunization of students that have missing or incomplete vaccine records or selective vaccination after serologic evaluation of susceptibility.

- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms.
- **Author contributions:** All the authors contributed to the preparation of this paper: Z.R., M.N., and E.F. collected and managed data; A.S., E.F., and C.P have performed final processing and analyzing of collected information and data; Z.R., A.S., and C.P prepared the article for drafting or revising it critically for important intellectual content. All author gave final approval of the version to be published.
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