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SHORT REPORT

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"Titer of anti-HBs in health professions trainees: prevalence of antibody coverage in a University of Central Italy"

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ABSTRACT

Objective: This observational retrospective study aims at verifying hepatitis-B-virus (HBV) vaccination coverage in students vaccinated before and after 1992, in order to optimize health surveillance and vaccination recall.

Methods: Vaccination status was evaluated using the anti-HBs antibody titer (anti-HBs). Student t-test and the chi-square test were performed to identify the average age and the difference in antibody coverage between the two genders and in the two populations analyzed.

Results: Our study outlined a prevalence of 21.83% uncovered trainees among those vaccinated at age 12 and 45.03% among those vaccinated in neonatal age.

Conclusion: In conclusion, our data showed persistent protection against HBV infection in healthcare students.

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Antibodies; hepatitis B; Anti-HBs; vaccination; assessment risk; viral hepatitis vaccines; health students

Introduction

Hepatitis B virus (HBV) infection is the main cause of acute and chronic liver disease worldwide.[1] The World Health Organization (WHO) estimates that about 257 million people were infected with HBV[2] in 2015. The chronic sequelae of the infection, such as fulminant hepatitis, liver cirrhosis, and hepatocellular carcinoma led to 887,000 deaths.[3] According to the Epidemiological Service of the Italian National Institute of Health, HBV infection has reported a sustained and constant reduction in incidence over recent decades, mainly due to the introduction of the vaccination requirement in 1991. Infection rates decreased from 10 cases per 100,000 in 1984 to 0.6 cases per 100,000 inhabitants in 2015.[4,5]

Working age subjects are most at risk of contracting hepatitis B and, as a matter of fact, the highest incidence in Italy can be found in subjects aged over 30[6]. The strongest associations with acute HBV infections are due to percutaneous exposure during cosmetic treatments, dental therapy, and unprotected sexual intercourse. Over the last 5 years, 19% of acute HBV infections in Italy have involved non-Italian people immigrated from high endemic areas, especially Eastern Europe and Africa. HBV infection is the most prevalent work-related infectious disease, thus it can affect healthcare personnel and different risk areas including pediatric areas, emergency rooms, and ambulatory care facilities. HVB transmission may be quite easy through contact with infected patients and potentially infectious biological material like blood, saliva, semen, and feces.[5] Standard precautions are required for HBV prevention in healthcare workers. The use of personal protective equipment (PPE), as well as the disinfection and sterilization of medical devices, complies with the HBV prophylaxis program.[5–8]

Following the WHO recommendations, in 1991 the Italian law (n°165)[9] made anti-HBV vaccination mandatory for all the newborns during their first year of life (3 vaccine doses at 0, 2nd and 6th month of life) and for adolescents during their twelfth year of age.[10,11] Within 12 years after the introduction of the vaccination requirement, more than 12 million people were vaccinated. Consequently, a dramatic fall in hepatitis B infection was observed in subjects aged 15 to 24 without new hepatitis cases among the vaccinated.[12] Moreover, the current legislation (Ministerial Decree 149 of 11/20/2000) provides that it is advisable to carry out a qualitative test of anti-HBs antibodies as part of the health surveillance of workers exposed to biological risk before the start of any work activity.[13] In case of a positive test in a subject with a protective titer of anti-HBs (> 10UI/L) no hepatitis B vaccination booster dose and no further health status checks are necessary, independently of the primary vaccination cycle. On the other hand, in case of a negative test in a subject with a not-protective titer (anti-HBs <10 UI/L) a fourth dose of hepatitis B vaccine is recommended, together with a further evaluation of the antibody titer after two months.[14] Previous studies, reported that the anti-HBs antibody titer ≥10 IU/L can immunize from hepatits for up to 10 years even after 30 years from the last dose.[15,16] According to the World Health Association, even the vaccinated subjects presenting with an absent or <10 IU/L anti-HBs antibody titer have an immunological memory that protects them against HBV infection.[17]

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Furthermore, breakthrough infections (i.e. infections occurring in vaccinated individuals) seem to have no clinical significance. On the other hand, health professionals and students in health disciplines represent a category of people at high risk of HBV infection, thus a conservative strategy may be more appropriate. Several studies have shown that the anti-HBs antibody titer correlates with the number of vaccine doses administered, as well as with the subject gender and age at vaccine administration (in elderly vs age 12).[18,19]

In this study, we aim to evaluate the prevalence of trainees with a protective antibody titer, by assessing the difference in coverage rates between the subjects vaccinated in neonatal age and those vaccinated in adolescence in order to outline the evolution of the coverage rate over time.

Methods

Study population and design

A retrospective observational study was conducted by the Occupational Medicine Department at the G. d'Annunzio University of Chieti (Italy). The study targeted the students enrolled in 12 health degree courses of the Faculty of Medicine (Medicine and Surgery, Nursing, Physiotherapy, Dentistry, Dental care, Dental Practice Assistants, Laboratory Techniques, Cardiovascular Physiopathology and Cardiovascular Perfusion Techniques, Dietetics, Obstetrics, Health care, Occupational Therapy) exposed to biological risk during their internship. A total of 1052 students were enrolled in the study over the mandatory health surveillance period between 2015 and 2018, pursuant to the Legislative Decree 81/08 and the subsequent amendments. The University Health Protocol provides a preventive medical examination and first-level exams such as blood chemistry exams (hemochrome with leucocytary formula, erythrocyte sedimentation rate, epatic and renal function, blood sugar, cholesterol, surface antigen of HBV (HBsAg), anti-HBs, anti- Hepatitis C Virus (HCV), and anti- Human Immunodeficiency Virus (HIV) exam subject to informed consent from the trainee), Mantoux intradermal test, and any other specific risk tests, performed at the Clinical Analysis Laboratory of the "SS.Annunziata" Hospital of Chieti, Italy. Informed consent to the processing of personal data (EU Regulation 2016/679-GDPR Privacy) and the privacy statement (EU Regulation 2016/679-GDPR Privacy) were provided from all the students. During the medical examination, a copy of the vaccination diary was collected for each trainee, in order to asses the vaccination coverage against HBV, HAV, tetanus, and measles-mumps-rubella (MMR). Vaccination schedules consisted of three pediatric doses (10ug) of either Engerix B or HBV AxPro vaccine. According to the Italian guidelines, the subjects had received three adult doses (20ug) of the same vaccine in adolescence. Exclusion criteria were: confirmed immunodepression-immunosuppression, failure to present the vaccination diary, birth from HBsAg positive mothers. Pursuant of the D.Lgs 165/1991 introducing mandatory vaccination against viral hepatitis B, we arbitrary classified the subject into two groups, i.e., the subjects vaccinated in the first year of life (post-1992 group) and the subjects vaccinated in the course of their twelfth year of age (pre-1992 group). For all the subjects we considered the anti-HBs titer as protective when the value was anti-HBs>10UI/L (Covered). Conversely, we considered the anti-HB<10UI/L as not protective (Not Covered).

Statistical methods

According to the scientific literature, ~20% was the expected prevalence of subjects with HBsAg titer lower than 10 UI/L.[5] Assuming a 5% of type I error, the minimum number of students involved in our study was estimated to be 246 with a power (1 – β error) of 80%. Continuous variables were summarized as mean and standard deviation or median and interquartile range (IQR) [25th – 75th percentile] according to their distribution. Normality was tested by using the Shapiro-Wilk's test. The categorical variables were reported as frequencies and column percentages. $\chi 2$ test was used to evaluate the independence. Between groups differences were assessed by using the Mann U Whitney test and the t-test. All the tests were two-sided, and a level of statistical significance was set at $p < .05$. All the statistical analyses were performed using the R software environment for statistical computing and graphics version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

Results

Among the 1052 trainees included in the study, 965 (91.7%) had received HBV vaccination in the neonatal period (post-1992 group), whereas 87 (8.3%) at the twelfth year of age (pre-1992 group). The Shapiro-Wilk's test shows a normal distribution for the Age variable, but not for anti-HBs.

Within the post-1992 group, the average age at the medical examination was 20.71 ± 1.5; the distribution of males/females were 33.13% and 66.87%, respectively. We found a protective antibody titer (covered) only in 54.97% of the students, whereas 45% presented a titer <10UI/L (not covered).

On the other hand, within the pre-1992 group, the average age of the subjects was 27.14 ± 4.38, with a male/female distribution of 41.38% and 58.62%, respectively. As reported in Table 1, antibody coverage (anti-HBs>10 UI/L) was found in 78.17% of the students vaccinated at the twelfth year of age.

The χ^2 -test indicated a significant p-value ($p < .001$) and a 5% difference between covered and not convered subjects in the post-1992 group. Conversely, the difference in coverage was up to 56% in the pre-1992 group. The median difference for antibody titer (anti-HBs) resulted to be statistically

Table 1. Summary statistics between the pre-1992 and the post-1992 group. Frequency (Column percentage) for categorical variables, mean±SD for normally distributed Age variable and median (IQR) for anti-HBs. Covered and not covered indicate an antibody titer >; <10UI/L, respectively. *P*-values result from Chi-squared test, t-test, and Mann U Whitney test.

Statistical variable	Pre-1992	Post-1992	*p-value*
Students; *n (%)*	87 (8.3%)	965 (91.7%)	
Age; *mean ± SD*	27.1 ± 4.4	20.71 ± 1.5	<0.001
Males; n (%)	36 (41.4%)	320 (33.13%)	0.160
Females; n (%)	51 (58.6%)	646 (66.9%)	
Covered; n (%)	68 (78.2%)	530 (54.%)	<0.001
Not Covered; n (%)	19 (21.8%)	435 (45%)	
Anti-HBs; median (IQR)	69 (14.5–476.5)	13 (0.5–50.0)	<0.001

significant ($p < .001$); the median value in the pre-1992 group was 13 (0–50), whereas in the post-1992 group was 69 (14.5–476.5).

Table 2 shows the distribution of the students according to their protection status by gender for both groups. In the pre-1992 group, the proportion rate of protection among males and females subjects was 88.9% (32/36) and 70.6% (36/51), respectively. Our results showed independence between gender and protection rate in the pre-1992 group ($p = .076$). The Mann U Whitney test assessed not significant difference in the median values of anti-HBs, both in males and females (0.532). In addition, no differences resulted between the gender means for Age ($p = .643$).

In the post-1992 group, the protection rate of anti-HBs was 57.2% (183/320) for males and 53.9% (346/646) for females. Our results showed independence between gender and protection rate in the post-1992 group ($p = .385$). The Mann U Whitney test assessed a not significant difference in the median values of anti-HBs both in males and females ($p = .264$). Conversely, the T-test for unbalanced samples defined a difference for Age ($p < .001$) between males and females in the post-1992 group.

Discussion

According to the National Prevention Vaccination Plan 2017–2019 and subsequently to the high biological risk, HBV vaccination is widely recommended for health-care workers and medical students in Italy. Although vaccines are carefully controlled and safe, vaccine coverage appears to be significantly variable over time due to immunity decline.[17] Despite a large population has been vaccinated since 1980, limited data are available on the anti-HBs antibody titer in relation to the age of vaccination.[20] In our study, a prevalence of 21,8% of the students vaccinated at 12 (pre-1992) and 45% of the students vaccinated in the neonatal age (post-1992) shows a not covered anti-HBs titer. The difference is significant ($p < .001$). Conversely, in the pre-1992 group the levels of anti-HBs are significantly higher than in the post-1992 group ($p < .001$). As hypothesized in other studies, this result may be due to a greater response of the immune system in adolescents than in newborns. This is probably related, in turn, to a greater maturation of the immune system in the pre-1992 group.[21]

Other findings of the present study demonstrate that the duration of vaccine efficacy is not affected by gender. In our study population there are actually not significant differences among males and females both in the pre- and post-1992 groups. This stratification between males and females further highlights the difference between the anti-HBs levels in the two study groups, in accordance with the independence between gender and antibody titer previously outlined by other studies.[22]

On the other hand, the assessment of the duration of immunity led to conflicting results. Some researchers have reported a progressive decline with age of the protective anti-HBs titer rate, actually pointing out the need for a vaccination booster.[23] However, according to several studies, after an initial antibody response to the vaccine, the immunological memory still provides an adequate level of protection even if the antibody titer results as not-protective (anti-HBs <10 UI/L). Thus, a booster dose is unnecessary.[17,20]

In conclusion, our findings outline a good persistence of protection against HBV in 78.2% of healthcare students during the training programs within a period of 18–25 years after vaccination.

According to the current ministerial guidelines, healthcare professionals with a not-protective antibody titer should be recalled for a booster dose.

However, the number of future health workers and the incidence of adverse events to the vaccine (1 per 10,000 doses administered) it is necessary to define a preventive strategy in order to monitor and protect workers. Further studies are needed to assess the difference in protective anti-HBs antibody titer between vaccinated 12 year old subjects and newborns, in order to determine the duration of the immunological memory. Although the study reaches its aim, there were some limitation. First, the sample study uses student sampling, which provides the advantage of being readily available, but also limiting due to the great heterogeneity of the subjects. Furthermore, the study can be improved by evaluating others HBV markers in order to provide data analysis on the positive rates of HBsAg, anti-HBs, and anti-HBc in the subjects.

Table 2. Summary statistics in pre- and post-1992 groups divided by gender. Frequency (Column percentage) for categorical variables, mean±SD for normally distributed Age variable, and median (IQR) for anti-HBs. *P*-values result from Chi-squared test, t-test, and Mann U Whitney test.

pre-1992 group	Males	Females	*p-value*
Covered; n (%)	32 (88.9%)	36 (70.6%)	0.076
Not covered; n (%)	4 (11.1%)	15 (29.4%)	
Anti-HBs; median (IQR)	71.5 (24.7–481.5)	69 (0.5–415.0)	0.532
Age; *mean ± SD*	27.4 ± 3.5	26.9 ± 4.9	0.643
post-1992 group			
Covered; n (%)	183 (57.2%)	346 (53.9%)	0.358
Not covered; n (%)	137 (42.8%)	296 (46.1%)	
Anti-HBs; median (IQR)	13.5 (0.5–65.0)	12 (0.5–48.0)	0.264
Age; *mean ± SD*	21.1 ± 1.5	20.5 ± 1.5	<0.001

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Author contributions

Conceptualization, DGL and MR; methodology and statistical analysis, DNM and PA; investigation, CL and DGL; resources, DGL and MR; writing original draft preparation, DGL, CE and CL; writing—review and editing, CE and DGL; supervision MR. All authors have read and agreed to the published version of the manuscript.

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