

SEROLOGIC HEPATITIS B VIRUS IMMUNITY IN HEALTH CARE WORKERS

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Health care workers (HCWs) are at high risk of blood borne infections including Hepatitis B virus (HBV) infection. HBV vaccination is recommended for HCWs but post vaccination testing of immune response (anti-HBs) is not routinely performed. In our study information on immune response after the first immunization schedule of HCWs is not available. By reason of the questions regarding long lasting immunity, we decided to assess the anti-HBs of HCWs who wished to check immune response after different times of vaccination and also unvaccinated persons in St. Marina University Hospital, Varna, Bulgaria. After informed consent, 341 HCWs were investigated. They were divided into 3 groups according to their status: Group A had no history of vaccination against HBV, Group B had no complete vaccination schedule and Group C had complete vaccination data. Of Group C, 32 had been vaccinated more than 10 years previously, 111 – 10-5 years previously and 48 – < 5 years previously. Quantitative detection of antibody to HBsAg (anti-HBs) by commercial ELISA was carried out. A total, positive immune response was detected in 35.6% (group A), 66.2% (group B) and 80.1% (group C) of HCWs investigated. Of Group C positive immune response was detected in 68.7%, 81.1% and 85.4% respectively of the time of vaccination. Detectable anti-HB was found in HCWs without HBV immunization, probably after unknown exposure to HBV. The lack of information regarding immune response after the first immunization schedule makes the interpretation of no detectible anti-HBs level 5–10 years post-immunization difficult. For the HCWs with anti-HBs loss, counseling for booster vaccine dose and consequent testing is mandatory.

Hepatitis B virus (HBV) infection and its sequels are a major global health problem and represent an important hazard for healthcare workers (HCWs). About 350 million chronic carriers constitute the primary reservoir of infection. According to WHO reports, an estimated 3-5% of the world population are infected by HBV (1-3). HBV is an etiological agent for about 30% chronic liver diseases in North-Eastern Bulgaria and about 15% of the acute viral

hepatitis cases (4, 5). Accidental needle-stick injuries among HCWs are a well-known health hazard that causes transmission of viral infections, especially HBV. According to available data (6-9), the risk of infection after single exposure to HBV-infected blood and other body fluids ranges from 6%-30% in unvaccinated individuals. HCWs are at high risk of HBV infection due to occupational and repeated exposure. HBV vaccination is recommended for

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medical staff in Bulgaria and is the most effective way to prevent infection (2, 10-12). Serologic testing for anti-HBs 1 to 2 months after completion of the primary vaccination schedule is not routinely performed. Despite recommendation, compliance of these recommendations remains poor in various health-care settings in the world (13, 14). The lack of information regarding the immune response after the first immunization schedule makes interpretation of no detectable level of anti-HBs at one-year post-immunization difficult. The low- and non-responders are at high risk of HBV infection after occupational exposure and this finding is of great clinical significance. According to the literature data, there is a non-response rate of 5% to 32% (15-17) and unknown duration of immunity. In addition, knowledge of prior seroconversion status will influence the decision on whether to treat with immune globulin in the event of an exposure. By reason of the questions about long lasting immunity after different time of vaccine administration, our screening study was performed to assess the HBV serologic immune status in HCWs of the University Hospital St Marina Varna, North-Eastern Bulgaria, and to evaluate the duration of the immune protection.

MATERIALS AND METHODS

Study population

Our study group was composed of both HCWs with varied HBV vaccination history and unvaccinated persons. After informed consent, 341 individuals of both sexes (55 male and 286 female), aged 24–65 years (mean age 40.1) were tested by measuring the concentration of antibodies to HBV surface antigen (anti HBs) in single serum samples. The study population consisted of 95 physicians, 189 medical nurses, 57 exposed helping personnel. The collected data included vaccination date (year), number of doses of vaccine, job description, sex and age at the time of our study. The enrolled HCWs were divided into 3 groups:

Group A ($n = 73$) included HCWs without HBV vaccine.

Group B ($n = 77$) included HCWs who had unknown history of HBV vaccination or who had no complete vaccination schedule.

Group C ($n = 191$) included HCWs who had complete vaccination data.

Of HCWs in group C, 32 had been vaccinated more than 10 years previously, 111 – 10 – 5 years previously and

48 < 5 years previously.

Study analysis

Quantitative detection of anti-HBs by commercial ELISA (ClinPro International USA, BIOKIT Bioelisa anti-HBs Spane, DiaSorin ETI-AB-AUK-3 Italy, DIA PRO HBsAb Italy), according to the manufacturer's recommendations, were performed.

Antibody concentration to HBsAg were estimated in ranges ≥ 10 mIU/ml (IU/L) to > 100 mIU/ml (IU/L) (2). Although 10 mIU/ml is generally taken to be protective according to European recommendations (2), some countries adopt a higher reference level of ≥ 100 mIU/ml (18, 19) when vaccine is given for occupational protection. Individuals with < 10 mIU/ml (IU/L) serum anti-HB values are considered negative. Those with values of 10-99 mIU/ml (IU/L) are considered as individuals with insufficient proof of long term protection (20, 21). Those with value ≥ 100 mIU/ml (IU/L) are considered as HCWs with true protection.

Statistical methods

Alternative and variation analysis were carried out. Statistical processing was by SPSS v.17.

RESULTS

In group A ($n=73$), 26 (35.6%) positive immune responses were detected, 13 (50%) of whom had had anti-HBs > 100 mIU/ml (IU/L) (Fig. 1).

In group B ($n=77$), 51 (66.3%) positive immune responses were detected, and 30 (59%) of them had had anti-HBs > 100 mIU/ml (IU/L) (Fig. 1).

In group C ($n=191$), positive immune responses were detected in 153 (80.1%), and 96 (62.7%) of them had had anti-HBs > 100 mIU/ml (IU/L) (Fig. 1).

Of those who had received complete immunization more than 10 years previously ($n=32$), positive immune responses were detected in 22 (68.7%), 13 (59.9%) of whom had had anti-HBs > 100 mIU/ml (IU/L) (Fig. 2). Of those who had received immunization 10-5 years previously ($n=111$), positive immune responses were detected in 90 (81.1%), and 54 (60%) of these had had anti-HBs > 100 mIU/ml (IU/L) (Fig. 2).

Of those who had received immunization < 5 years previously ($n=48$), positive immune responses were detected in 41 (85.4%), 29 (70.7%) of whom had had anti-HBs > 100 mIU/ml (IU/L) (Fig. 2).

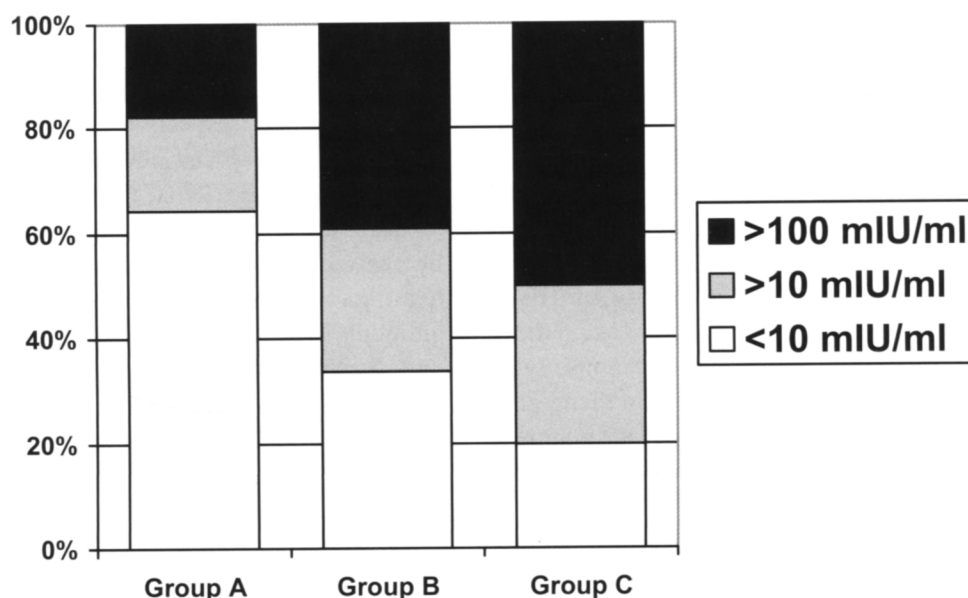


Fig. 1. Distribution of HCWs according to the vaccination status and immune response.

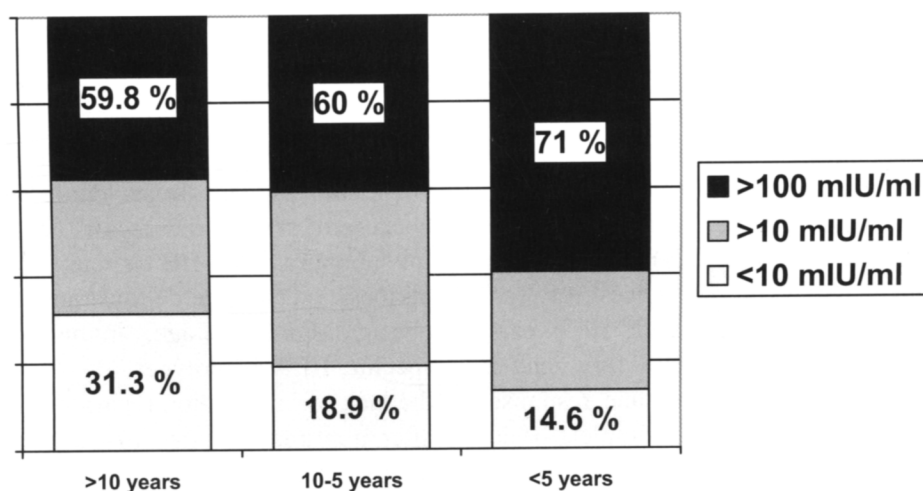


Fig. 2. Distribution of HCWs according to the immune response and depending on the time of vaccination in group C.

DISCUSSION

HBV infection has been recognized as a significant occupational hazard for HCWs after exposure to body fluids from patients with acute or chronic HBV infection and asymptomatic carriers. In our University Hospital, about 36% positive immune

responses were found in unvaccinated HCWs (Group A), half of them at concentration > 100 mIU/ml (IU/L). These HCWs were presumed to have had unknown exposure to HBV. It is not clear whether these individuals are also anti-HBc positive due to past infection. However, no clinically overt hepatitis had been reported. In previous studies (6–9, 22)

the risk of infection after single exposure to HBV-infected blood and other body fluids in unvaccinated individuals ranges from 6% to 30%, and following an occupational exposure - on average 18-30%, depending on the type of exposure and the infectivity of the patients. There is need for future investigations among positive HCWs on possible low level viremia and occult infection.

In the persons with unknown history of HBV vaccination or without complete vaccination schedule (Group B), positive immune response was detected in 66.3%, and in 30 (59%) of them, the level was > 100 mIU (IU/L). It is not clear whether these responses are because of vaccination or results of HBV exposure, or both. In the studies (18, 23), the first two vaccine doses usually suffice to initiate the production of anti-HBs, thereby priming the immune system for a second response. The third dose stimulates this secondary response, resulting in higher anti-HB concentrations. In our study there are statistically significant differences between the rate of positive immune response of HCWs after adequate completion of its courses (group C) and those without complete vaccination schedule (group B) ($p = 0.05$). We therefore believe that the completion of vaccination schedule is necessary to form sufficient immune answer.

In group C of our study, positive immune responses were retained in 153 (80.1%) HCWs. There are no statistically significant differences between complete vaccinated HCWs >10 years, 10-5 years and <5 years previous to testing ($p > 0.05$), gender and sex. That is why the initial immune response to hepatitis B vaccine following the complete basic immunization series is an important determinant of the duration of immunity. According to the data (24, 25) the post-immunization anti-HB titer was the strongest predictor of antibody loss during follow-up: the high responders had the lowest risk of anti-HB loss at 18 years (76.5%) and 15 years (66.7%) after vaccination. In our study 69% of the completely vaccinated HCWs retained immune response > 10 years after immunization and 60% of them were with anti-HBs >100 mIU/ml, themselves with long lasting protective post-vaccine immunity.

Of a total of 191 completely vaccinated HCWs in our study, approximately 20% had no detectable immune response (Fig. 1). The same negative results

were detected approximately in one-third of those vaccinated more than 10 years previously, and in 19% and 15% of those immunized 10-5 and less than 5 years before, respectively (Fig. 2). Statistically significant differences between these three groups were not found. It is not clear whether these subjects are non-responders or their anti-HB titers decrease over time. A previous study (26) favors the hypothesis that with increasing age, seroprotective antibody formation after vaccination is decreased, and the most significant decrease occurred 5-8 years post-vaccination. According to other data (23, 27, 28), strong immunologic memory persists more than 12 years after immunization and there is evidence of a large, rapid increase in antibody titer after booster immunization, even in individuals who have lost their antibodies. The number of memory B lymphocytes able to produce anti-HBs does not diminish as the level of antibody decreases. The proportion of protection 6.5 years after vaccination is 85%, as observed in our study for the relevant group. In some studies (23, 29), primary course of vaccination in infancy or adolescence might confer life-long protection and anamnestic response present in 96-97% of subjects who had received booster doses of vaccine. Of the adult population, 5-14% does not respond to standard HBV vaccination because of several risk factors (9, 30). Risk factors for suboptimal anti-HB response are injection in the buttocks (versus the deltoid muscle), male gender, obesity, smoking, age, immunosuppression and specific HLA haplotypes (31). For these reasons, the lack of information regarding immune response after a primary course of vaccination makes the interpretation of no detectable level of anti-HBs 5-10 and more years post-immunization difficult.

There is need for future investigation among HCWs who have been completely vaccinated but with low or no detectable anti-HB titer, on possible low level viremia and other causes of lower vaccine efficacy.

The decision whether to document seroconversion is primarily based on the reason why the individual is being vaccinated and the expected risk of future exposure. According to the European recommendations (2) and recommendations of the Bulgarian Ministry of Health (11, 12), due to their nature of work, HCWs should be vaccinated against

HBV before entering nursery and medical schools and before employment in healthcare settings. In many countries, anti-HBs should be assessed 4–8 weeks after completion of a 3-dose vaccination series by serological control of successful response to vaccination (19), but in Bulgaria there are no recommendations for this to be carried out. Usually, individuals with <10 mIU/ml (IU/L) serum antibody values are considered “non-responders” and those with values 10–99 mIU/ml (IU/L) are considered “low responders”, i.e., with insufficient proof of long term protection (20). Among issues related to HBV vaccination in HCWs, there is no unanimous consensus regarding the post-vaccinal anti-HB level to be considered as protective. Although 10mIU/ml is generally taken to be protective, according to the European recommendation (2), some countries adopt a higher reference level, if vaccine is given for occupational protection (18, 19, 28), because the infectivity of sources can vary considerably. According to the data in literature (20, 28, 32, 33), the level should be greater than 100 mIU/ml.

We do not have information about immune response after the primary course of vaccination of the HCWs in our study, because post-vaccination serologic testing was not routinely performed in the past in Bulgaria and there is no strong recommendation for this purpose. Our data indicated that it is extremely important to check the post-vaccination status after 6–8 weeks of vaccination as this not only ensures safety of employees but also reduces the rate of transmission (2, 29). The initial immune response to hepatitis B vaccine following the basic immunization series is an important determinant of the duration of immunity and correlates with protection after infection. A booster dose of vaccine was proposed for these HCWs with antibody loss and then testing again. If they are again seronegative, they will be offered a second or continuous series of vaccine (19). Periodic testing or boosting is not needed for the HCWs who were anti-HB positive after a first immunization schedule and have a protective value.

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