Original article

Hepatitis B vaccination coverage rate and immune response among primary health care workers in Sarajevo Canton, Bosnia and Herzegovina

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ABSTRACT

Background: Immunization is a key step in preventing the occupational risk of acquiring hepatitis B infection for healthcare workers (HCWs). The aim of the study was determination of hepatitis B vaccine (HepB) coverage rate among HCWs and support staff and immune response 10 years after primary vaccination. Methods: A retrospective study was conducted in the Public Institution Health Centre of Sarajevo Canton in Bosnia and Herzegovina during 2005-2017. Second-generation vaccines Euvax (Sanofi Pasteur, Thailand/LG Life Sciences Ltd, Korea) and Engerix B (GlaxoSmithKline, Belgium) were applied. For quantification of antibody response to hepatitis B virus surface antigen three laboratory methods were used. A level of ≥ 10 IU/L anti-HBs was set as a cut-off value indicating the presence of protective immunity against new HBV infections and successful vaccination. Results: In total, 1541 (75.80%) were fully vaccinated, out of 1126 (73.07%) were females. The median age of participants was 50.5 ± 9.4 years. Control measurement of the anti-HBs level was performed for 409 (26.54%) HCWs, and the presence of protective antibodies was confirmed in 304 (74.33%). During the research, 37 booster doses were administered. Of the 23 retested participants, anti-HBs ≥10 IU/L were observed in 19 (82.16%). Three non-reactors subject were revealed. Conclusion: A satisfying HepB coverage rate and a high protective rate against hepatitis B infection among HCWs and support staff was achieved, although vaccination is voluntary in Bosnia and Herzegovina. These results indicate the active engagement of the institution in the implementation of preventive measures and the high level of awareness regarding the significance of immunization. Our results demonstrated the effectiveness of booster doses. A low prevalence of non-reactors was revealed. Additional research with a focus on occupational risk factors in dental service is advised.
**Introduction**

Hepatitis B infection is caused by the hepatitis B virus (HBV), an enveloped DNA virus that affects the liver. Infection can be either acute or chronic, and the associated illness ranges in severity. It is estimated that out of 257 millions people infected with HBV, 887,000 worldwide die annually due to the progression of cirrhosis and hepatocellular carcinoma. HBV presents an important occupational hazard for health care workers (HCWs) and support staff. In healthcare settings, HBV is transmitted through percutaneous or mucosal exposure to infectious blood or body fluids. It is highly infectious, can be transmitted in the absence of visible blood, and remains viable on environmental surfaces for at least seven days [1,2]. Of three million accidental injuries among HCWs annually, tens of thousands of infections develop each year [3,4]. The virus is present in hospital environments, and it is additionally a risk for patients as a cause of nosocomial infections [5,6].

Major public health problems are chronic carriers of HBV, HBsAg positive individuals. It is estimated that worldwide, 240 million are chronic carriers of and age-specific HBsAg seroprevalence varies markedly by geographical region (>5% in sub-Saharan Africa, East Asia, parts of the Balkan regions, the Pacific Islands and the Amazon Basin of South America) [1]. According to Hope, HBsAg prevalence varied from 0,1% to 9% in Europe [7]. During the past three years, 288 newly infected with HBV, and 208 HBsAg carriers have been registered in Bosnia and Herzegovina. The incidence is thought to be significantly higher due to the nature of the disease and the lack of surveillance systems [8,9].

The occupational risk for HCWs correlate with the number of carriers in the general population, therefore disease surveillance is crucial. Hence, in controlling the global public health problem, epidemiological surveillance with early detection of the disease, strong laboratory potential for conducting serological and molecular testing, and clinical treatment with adequately applied therapy are of particular importance [10].

Laboratory testing of highly exposed HCWs to HBV, hepatitis C, and human immunodeficiency virus antibodies is mandatory in Bosnia and Herzegovina, while vaccination as the most effective preventive measure against HBV is voluntary [11]. Due to the lack of a national surveillance system, we aimed to determine the HepB coverage rate among HCWs and support staff and to evaluate their immune response 10 years after primary vaccination.

**Participants and Methods**

**Study design**

A retrospective study was conducted in the Public Institution Health Centre of Sarajevo Canton in Bosnia and Herzegovina, during 2005-2017. As the largest institution of primary care with 2031 employees, it is divided into 10 organizational units. On average, they provide 13,816,187 visits and services annually. Ethical approval for the study in line with the Declaration of Helsinki, was obtained from the Ethics committees of the Institution.

**Participants**

The study included Immunization Program participants (HCWs and support staff) that are voluntarily vaccinated with HepB after the primary screening of hepatitis markers. Ten years after the immunization, the level of anti-HBs antibodies was determined. The criteria for exclusion from the Immunization Program were set: conducted hepatitis B immunization during childhood, the laboratory-confirmed positive hepatitis markers, developed HBV infection, rejection of vaccination, as well as the presence of chronic conditions, contraindicated for vaccination.

**Types of vaccines, administration and laboratory testing**

During the research, second-generation vaccines Engerix B (GlaxoSmithKline, Belgium) and Euvax B (Sanofi Pasteur, Thailand/LG Life Sciences Ltd, Korea) with 20 µg of purified HBsAg in a single dose of 1 ml were used. In participants who fulfilled the criteria for inclusion in the Immunization Program, vaccines were administered intramuscularly, in the deltoid muscle, according to scheme 0, 1, and 6 months from zero dose [11]. Serological tests were performed in Sarajevo University Clinical Center, the Institute of Transfusion Medicine of the Federation Bosnia and Herzegovina, and the Institute of Occupational Medicine of the Sarajevo Canton. For quantification of antibody response to hepatitis B virus surface antigen three laboratory methods were used: enzyme-linked immunosorbent assay (ELISA), microparticle enzyme immunoassay (MEIA), and chemiluminescent microparticle immunoassay (CMIA). A level of ≥ 10 IU/L anti-HBs was set as a cut-off value indicating the presence of protective immunity against new HBV infections and successful vaccination. In participants with antibody values
under cut-off, a booster dose was administered to improve the quality of the immune response, and retesting was performed. Participants in whom no seroconversion occurred, double vaccination schedule was performed. After retesting, participants with undetectable antibodies and with the excluded acute or chronic form of infection were defined as non-reactors [12]. An epidemiological survey for examination the risk factors that adversely affect seroconversion was designed for them.

**Data management**

Basic standard methods of descriptive statistics were used. Values are presented in frequencies and percentage. Collected data were analyzed in the MS Excel, and results are presented in tables.

**Results**

Of 2033 employees, 1541 (75.80%) were fully vaccinated. The median age of individuals was 50.5 ± 9.4 years. Among them, 1126 (73.07%) were females and 415 (26.93%) males, respectively. Eligibility criteria for the Vaccination Program was unmet in 492 (24.20%) participants. Comparing the total number of employees and immunized by organizational units, the largest vaccination coverage rate (90.79%) was in the Stari Grad Municipality. No discrepancies were detected in the frequency of immunized HCWs and supports staff in the laboratory, dental and specialist departments (74.30%, 75%, and 79% respectively).

Measurement of the anti-HBs antibody control level 10 years after primary immunization was performed in 409 (26.54%) participants (Table 1). A value < 10 IU/L was detected in 105 (25.67%) and ≥ 10 IU/L anti-HBs antibody in 304 participants (74.33%). The presence of protective antibodies was confirmed in 256 (84.21%) female participants and 48 (15.79%) males.

Out of 105 participants with anti-HBs level below 10 IU/L, 37 gave a consent to receive a booster dose. Following to the schedule 30 (81.08%) in the dental and seven (18.92%) in the laboratory department. A total of 23 (62.16%) participants who underwent control testing, 19 (82.16%) showed an increase in the anti-HBs antibody titer to ≥ 10 IU/L.

Age distribution of retested participants after a booster dose is shown in Table (2).

Four participants (17.39%) with undetectable anti-HBs received a second series of vaccines. On retesting, three participants with undetectable anti-HBs antibody levels were categorized as non-reactors, and seroconversion was detected in one (37 IU/L). The results of the survey designed for non-reactors are presented in Table (3).

### Table 1. Anti-HBs antibody level by department 10 years after primary immunization.

<table>
<thead>
<tr>
<th>Departments</th>
<th>anti-HBs ≥ 10 IU/L</th>
<th>anti-HBs &lt; 10 IU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (n)</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>Dental</td>
<td>171</td>
<td>70.37</td>
</tr>
<tr>
<td>Laboratory</td>
<td>56</td>
<td>74.67</td>
</tr>
<tr>
<td>Family medicine</td>
<td>77</td>
<td>84.62</td>
</tr>
<tr>
<td>Total</td>
<td>304</td>
<td>74.33</td>
</tr>
</tbody>
</table>

### Table 2. Age distribution and level of anti-HBs antibodies in a group of participants after a booster dose.

<table>
<thead>
<tr>
<th>anti-HBs level</th>
<th>Age groups</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21-30</td>
<td>31-40</td>
</tr>
<tr>
<td>≥ 10 mIU/mL</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>&lt; 10 mIU/mL</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>
Table 3. Epidemiological data of non-reactors.

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organizational unit</td>
<td>Ilidža</td>
<td>Ilidža</td>
<td>Ilidža</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>39</td>
<td>61</td>
<td>54</td>
</tr>
<tr>
<td>Occupation</td>
<td>Charwoman</td>
<td>Dentist</td>
<td>Dental nurse</td>
</tr>
<tr>
<td>Length of service</td>
<td>13</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28.1 kg/m²</td>
<td>18.4 kg/m²</td>
<td>25.5 kg/m²</td>
</tr>
<tr>
<td>Active smoker (number of cigarettes)</td>
<td>Yes (20)</td>
<td>Yes (20)</td>
<td>Yes (30)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hereditary and chronic diseases</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Blood type and Rh factor</td>
<td>0 (+)</td>
<td>0 (+)</td>
<td>B (+)</td>
</tr>
<tr>
<td>Recorded needle-stick injury</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Uses personal protective equipment</td>
<td>Yes</td>
<td>Occasionally</td>
<td>Occasionally</td>
</tr>
</tbody>
</table>

Discussion

Vaccination coverage rate varies from 76% in Africa to 90% in Western Pacific Region [13]. Conferring to Rapiti et al., Bosnia and Herzegovina was classified in Europe B region with 29% HepB coverage rate among HCWs [14]. At the contrary, present study reveals 75.80% vaccination coverage rate among HCWs and support staff in primary health care. The similar study was conducted in Brazil among the aforementioned population, with vaccination coverage rate of 64.61% [15]. In Bosnia and Herzegovina's surrounding countries, vaccination of HCWs workers and support staff is mandatory, but vaccination coverage rate is lower. Depending on the region in Serbia vaccination coverage rate ranges from 31.1% to 66.2% [16,17], while in Croatia is 49.2% [18]. Results of our study correlate with studies conducted in highly developed countries like Italy (77.3%) [19], Sweden (79%) [20], and the USA with 80.7% of immunized HCWs [21]. Our findings are not in line with studies among same population in Pakistan and India, the countries with high HBV prevalence (40% and 49.6% respectively) [22,23]. Difference in obtained results from abovementioned studies can not be explained by regional connectivity or legislative proceedings, but it can be related to significant level of immunization awareness and its importance as a universal preventive measure.

Maintaining a high vaccination coverage rate among HCWs in our country is important, particularly nowadays since the current epidemiological situation is affected by the migrant crisis. Most migrants come from endemic areas for HBV infection. The Organization for Security and Co-operation (OSCE) in Europe states that since the beginning of 2018, Bosnia and Herzegovina has experienced a drastic increase in the number of migrants and refugees. The biggest refugee center is located in the Sarajevo Canton [24]. Coppola et al. have tested 882 migrants in Italy in less than two years and recorded 9% HBsAg-positive individuals [25]. The prevalence of HBsAg outside the European Union (EU)/European Free Trade Association (EFTA) area is about three times higher than in EU countries, and Hope et al. estimated about 8.8 million virus chronic carriers [7]. The above indicates the need for the active involvement of health authorities in the detection of chronic carriers of the virus among migrants, as they are a significant occupational risk for Bosnian HCWs and support staff.

In this study, 75% of dental staff were covered with three doses of the vaccine. Higher vaccinal coverage rate was reported in Iran (87.90% and 85.40%, respectively) [26,27]. Our results are not in line with studies of Chathuranga et al. (65%) in Sri Lanka [28] and Basireddy et al. (32.90%) in India [29], conducted among HCWs.

Control testing for the detection of protective antibodies 10 years after primary vaccination was performed in 409 (26.54%) participants. The satisfactory level of antibodies was confirmed in 304 (74.33%). After dividing
The mechanism that determines the strength of the immune response to the vaccine has yet been unelucidated, but factors affecting its quality are the length of the post-vaccination period, age, increased body mass index (BMI), smoking, gender, chronic metabolic disorders, immune suppression and genetic factors. According to the Centers for Disease Control and Prevention (CDC), seroprotection after immunization is achieved in 84% of HCWs over the age of 40 and 92% under 40 [32]. This framework can be related to our results (50.5 ± 9.4 years). Averrhof et al. suggest that HCWs should receive the vaccine younger age so body can respond adequately [33]. Opposite to these findings, research of Argentina scientists did not prove influence of subjects age to immune response [34]. In this study, 25.67% of participants obtained a reduced immune response 10 years after vaccination, and three non-reactors were recorded. According to Nejad et al., 17.9% of HCWs in Iran obtain a reduced immune response after seven years [35]. Insufficient levels of anti-HBs antibodies were detected in 29% of HCWs in Philadelphia, five years after vaccination [36]. These results support the relationship between the length of the post-vaccination period and the strength of the immune response. Absence of immune response and BMI can not be related since all three non-reactors had different BMI values. On the other hand, it can be associated with female gender and smoking status.

It is indicative that non-reactors in our study are employees of the dental service, therefore it is necessary to investigate influence of the working environment conditions and the possible influence the occupational risk factors on immune response. The quality of the immune response can also be affected by the type of vaccine. The immune response in plasma-derived vaccines, which were, besides, the first generation of vaccines, is expectedly low, given the mode of production and origin. Also, reduced seroconversion occurs with the polyvalent vaccine [37]. The results of our study and the other researchers suggest a decrease of immune response [35,36]. Therefore, the third generation of vaccines is of prime importance for the high-risk group of HCWs and non-reactors. According to Shouval et al., new vaccine leads to more successful seroconversion and more efficient in the treatment of persons with persistent HBV infection [38].

The World Health Organization does not recommend the usage of "booster" doses in healthy individuals [39], nevertheless their application has become part of practice around the world. During our research, 37 "booster" doses were applied, and subsequent laboratory testing was performed for 23 (62.16%) participants. An increase in anti-HBs antibody titer to ≥ 10 IU/L was observed in 19 (82.16%). Similar results were obtained by Zamani et al. on a sample of Tehran Hospital staff (85.5%) [27], and Barash et al. reported 100% seroconversion among healthcare professionals in Presbyterian Medical Center, Philadelphia [36]. Since the results of studies suggest that single booster dose lead to a successful seroconversion, their application can be considered justified.

Conclusions

A study demonstrates a satisfying coverage rate of hepatitis B vaccine and a high protective rate against hepatitis B infection among health care workers in primary care, although vaccination is voluntary in Bosnia and Herzegovina. Additionally, the results indicate the active engagement of the institution in the implementation of preventive measures and the high level of awareness about the significance of immunization. Screening for hepatitis B markers and monitoring of protective antibody levels ensures the safety of health care workers in primary health care and prevents possible nosocomial hepatitis B virus transmission. Our results demonstrated the effectiveness of booster doses. A low prevalence of non-reactors was revealed in the study. Additional research with a focus on occupational risk factors in dental service is advised.

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Conflict of interest: The authors declare they have no conflict of interest.

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