



Twenty years after the implementation of HBV vaccination: Epidemiology and risk factors for hepatitis B infection in the south of Bosnia and Herzegovina

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Keywords

Epidemiology • Hepatitis B • Vaccination • Risk factors • Bosnia and Herzegovina

Summary

Introduction. According to the World Health Organization, Global hepatitis report 2024, there were 254 million people living with HBV. Vaccination, testing and antiviral treatment are currently available tools to prevent transmission of HBV infection, but also to prevent the progression of infection. The aim of this research was to identify epidemiological data and risky behaviors for infection twenty years after the implementation of vaccination.

Methodology. We performed a case-control study including 63 respondents that were in contact with HBV (HBsAg positive or anti-HBs and anti-HBc IgG positive) and 62 control respondents matched by gender and age. All of them completed a questionnaire focusing on sociodemographic characteristics and potential risk factors for HBV-infection.

Results. Out of a total of 63 respondents in the study group, 39 (61.9%) were male and 24 (38.1%) were female. The mean age was 56.90 ± 15.576 years. There were no statistically significant

differences between HBV cases and control participants with respect to employment status, educational level, or marital/intimate status.

Contact with other people's blood was identified as a key risk factor for HBV infection, with blood transfusion being the most commonly reported route of exposure in this study.

Conclusion. Twenty years after the introduction of mandatory vaccination against hepatitis B in Bosnia and Herzegovina, the dominant risk factor for the hepatitis B is contact with other people's blood, and the most common way of coming into contact with other people's blood is transfusion. On the other hand, the data obtained, that 20 years after the introduction of the hepatitis B vaccine, we see hepatitis B most often in older people speaks in favor of the favorable impact of vaccination on the movement of HBV.

Introduction

HBV (hepatitis B virus) is a hepatotropic DNA (deoxyribonucleic acid) virus belonging to the *Hepadnaviridae* family. The virus has a lipid envelope with the viral surface antigen (Hepatitis B surface antigen, HBsAg) that surrounds the nucleocapsid, which contains the core protein (Hepatitis B core antigen, HBcAg), polymerase and the viral DNA [1]. According to the World Health Organization (WHO), Global hepatitis report 2024 there were 254 million people living with HBV [2]. The prevalence of HBV varies worldwide. There are high, medium and low endemicity areas according to HBsAg prevalence. Southeast Asia, sub-Saharan Africa, China, Indonesia and Nigeria are considered highly endemic areas with more than 8% of the population living with chronic hepatitis B. South America and countries of Central America, Southeast Europe and Southwest Asia belong to countries of medium endemicity with a prevalence of 2 to 7%, while countries of Western Europe and North America are areas of low endemicity [3]. The route of transmission varies according to the prevalence. In high-prevalence countries, the dominant route of transmission

is vertical, from mother to child, while in low-prevalence countries, the dominant route of transmission is contact with the blood of intravenous drug users and the sexual route [4]. The latest data on the prevalence of HBsAg in Bosnia and Herzegovina are presented in 2022, showing a strong effect of the introduction of mandatory vaccination on HBsAg seroprevalence and a statistically significant decrease from 0.345% in 1998 to 0.028% in 2019 among voluntary blood donors [5]. The dominant route of transmission in high-prevalence countries is vertical from mother to child or horizontal through close family contact. In low-prevalence countries, HBV is transmitted mainly through intravenous drug usage, sexual contact and "piercing". HBV is still a risk in transfusion therapy. However, with the introduction and improvement of blood testing, today, the final risk of HBV transmission through transfusion in European countries ranges from 1 to 10 per million transfusions. Although transmission of HBV is also possible through a stabbing incident among health care workers, studies from Denmark, Germany, Turkey, and Albania have shown the same prevalence among health care workers as in the general population [6]. Vaccination, testing and antiviral treatment are currently available tools to

prevent the transmission of HBV infection, but also to prevent the progression of HBV infection [7]. Since 1980, HBV infection can be prevented with an effective vaccine [4]. According to WHO data, the percentage of chronically infected children under the age of five fell to 1% in 2019 compared to 5% before the introduction of vaccination [8]. Vaccination against HBV in Bosnia and Herzegovina was introduced in 1999 for first-graders, and in 2004, vaccination of newborns after birth was introduced according to the scheme 0, 1, 6 months. This research aimed to identify risky behaviors and risk groups for HBV infection with the goal of directing prevention measures, more mass vaccination and testing, and possibly treatment in Bosnia and Herzegovina.

Methods

We performed the case control study on 63 subjects, which were serologically diagnosed with HBV infection in the period 2017-2021 (HBsAg positive or anti-HBs and anti-HBc IgG positive). The study included subjects who were diagnosed with current or past HBV infection during the specified period through serological testing for HBV markers, and who agreed to participate in the surveillance. Each subject from the examined group was assigned a control subject matched by gender and age. The research plan, purpose, and possible risks were explained in detail to all research participants from the experimental and control groups. The participants signed a consent form to participate in the research. After informed consent was obtained for every HBV-positive and control case, respondents filled out self-administered questionnaire. The questionnaire focused on sociodemographic status (gender, age, educational level and marital status) and potential risk factors for HBV infection (tattoo, piercing, transfusion, contact with blood, receiving clotting factors, transplantation, drug users, intimate relationship with HBV or HCV positive partner, sexual transmissible diseases, more than 2 sexual partners in last 12 months, sexual intercourse with a person of the same sex, a family member with viral hepatitis).

For all HBsAg-positive respondents, HBV-quantitative molecular testing was performed.

Serological testing (HBsAg, HBeAg, anti-HBs, anti-HBc IgG, anti-HBc IgM, anti-HBe) was performed using the Architect system (Abbott) and LIAISON® XL (DiaSorin), based on chemiluminescent immunoassay technology. HBV DNA testing was performed using the Abbott RealTime HBV assay which is an in vitro reverse transcription polymerase chain reaction (RT-PCR) quantitative assay. Molecular assay was used following the manufacturer's instructions using the Abbott m24 sample preparation and Abbott m 2000 rt modules.

Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp). The Chi-square test (χ^2) and Fisher's exact test for categorical variables were used to establish the difference between HBV-positive and control groups according to various respondent categories. The odds ratio (OR) and 95%

confidence interval (CI) for the risk factors were calculated. A P value of 0.05 was considered to be statistically significant. A binary logistic regression calculation was used to assess the dominant risk factor. Study was approved by the Ethics Committee No. 1898/16 and No. 01-1-234/16.

Results

SOCIODEMOGRAPHIC CHARACTERISTICS OF HBV-POSITIVE INDIVIDUALS

The study included 63 respondents who were serologically diagnosed with HBV infection, and 62 control respondents. Out of a total of 63 respondents in the research group, 39 (61.9%) were men, and 24 (38.1%) were women. The average age was 56.90 ± 15.576 years, with the youngest respondent being 19 and the oldest 91. The average age of men was 56.33 ± 4.592 years, with the youngest being 19 and the oldest 91. The average age of women was 57.83 ± 17.342 years, with the youngest woman being 26 and the oldest 86.

There was no statistically significant difference between HBV and control respondents regarding employment status ($p=0.071$), educational level ($p=0.336$) and marital or intimate status ($p=0.573$) (Tab. I).

RISK FACTORS FOR HBV INFECTION

Risk factors for HBV infection were calculated by comparing the group of subjects who were in contact with HBV with the control group using the χ^2 test, the Odds Ratio (OR) and the 95% confidence interval (Tab. II). p -value 0.05 was considered to be statistically significant.

Of all the risk factors we observed, contact with other people's blood showed a statistically significant difference compared to the control group.

Answering the question of how they came into contact with other people's blood, the majority of respondents, eight of them (42.10%), indicated transfusion, seven (36.84%) providing help for various injuries, in the war and traffic accidents. Two healthcare professionals and one police officer reported contact with other people's blood at the workplace (15.79%).

Binary logistic regression of risk factors for HBV infection also singled out contact with other people's blood as a risk factor for HBV infection (Tab. III). In the binary logistic regression, only the variables where there was an incidence in both groups were included. Variables that were more frequent in the control group and variables with zero in one of the groups were not included in the model due to the impossibility of estimating the odds ratio (problem of complete separation).

Discussion

An analysis of the socio-demographic characteristics of the respondents who were in contact with HBV revealed that out of a total of 63 HBV subjects, 39 (61.9%) were

Tab. I. Socio-demographic characteristics of HBV infected respondents.

Socio-demographic characteristics		HBV group N=63 N (%)	Control group N=62 N (%)	<i>p</i>
Gender	Male	39 (61.9)	38 (61.3)	1.000*
	Female	24 (38.1)	24 (38.7)	
Age	0–40	7 (11.1)	7 (11.3)	0.991
	41–65	36 (57.2)	36 (58.1)	
	>65	20 (31.7)	19 (30.6)	
Employment	Employed	21 (33.3)	34 (54.8)	0.071
	Unemployed	13 (20.6)	6 (9.7)	
	Retired	29 (46.1)	22 (25.5)	
Educational level	Uncompleted elementary school	6 (9.5)	2 (3.2)	0.336
	Elementary school	8 (12.7)	7 (11.3)	
	Secondary school	42 (66.6)	41 (66.1)	
	High school/academy	7 (11.1)	12 (19.4)	
Marital/intimate status	Married	46 (73.0)	41 (66.1)	0.573
	Single	5 (7.9)	10 (16.1)	
	Widow	10 (15.9)	9 (14.5)	
	Divorced	2 (3.2)	2 (3.3)	

Tab. II. Risk factors for HBV infection.

Risk factors	HBV group N (%) N=63	Control group N (%) N=62	OR	95 % CI	<i>p</i>
Tattoo	9 (14.3)	11 (17.7)	0.773	0.296-2.019	0.863*
"Piercing"	5 (7.9)	0	–	–	0.058*
Transfusion	15 (24.2)	8 (12.9)	2.154	0.839-5.531	0.165
Contact with other people's blood	19 (30.2)	7 (11.3)	3.393	1.308-8.799	0.014*
Receiving clotting factors	0	0	–	–	1.000
Transplantation	0	0	–	–	1.000
Drug usage	3 (4.8)	1 (1.6)	3.050	0.309-30.150	0.619
Intimate relationship with HBV or HCV positive partner	3 (4.8)	0	–	–	0.244
Sexual transmissible diseases	0	0	–	–	1.000
More than 2 sexual partners in the last 12 months	1 (1.6)	2 (3.2)	0.484	0.423-5.477	0.619*

*Fisher exact test

Tab. III. Binary logistic regression analysis of risk factors for HBV infection.

Variable	Adjusted OR	95% CI	<i>p-value</i>
Contact with other people's blood	2.92	1.03-8.27	0.044
Blood transfusion	1.46	0.51-4.19	0.478
Drug use	4.12	0.41-41.14	0.228

men and 24 (38.1%) were women, with the average age of the subjects 56.90 ± 15.576 years.

Contact with other people's blood showed a statistically significant difference compared to the control group ($p=0.014$; $OR=3.393$). Binary logistic regression analysis also singled out contact with others people blood as risk factor for acquiring hepatitis B virus infection.

By comparing with the control group, no statistically

significant difference was obtained according to gender and age, because the control group was chosen to be comparable in terms of gender and age to the research group. A higher frequency of HBV chronic carriage in men is already known in the literature, as well as a faster progression of liver damage. This data is linked to greater exposure to HBV in men, but also to a better immune response in eliminating the virus in women [9]. The average age of the subjects which were in contact with HBV of 56.90 ± 15.576 years in Bosnia and Herzegovina, could be explained with the implementation of HBV vaccination. Namely, vaccination against HBV in Bosnia and Herzegovina was introduced in 1999 for first-graders, and in 2004, vaccination of newborns after birth was introduced according to the scheme 0, 1, 6 months. The effect of HBV vaccination on HBsAg seroprevalence was presented in a paper from 2022,

which showed a statistically significant decline in HBsAg seroprevalence from 0.345% in 1998 to 0.028% in 2019 among voluntary blood donors in Herzegovina. In the same paper, an increase in the average age of HBsAg-positive donors was also determined through three periods, namely 30.52 ± 10.26 ; 37.56 ± 10.13 and 47.28 ± 12.14 during the periods from 1998 to 2002, from 2004 to 2008 and from 2015 to 2019 [5].

By analyzing potential risk factors for hepatitis B virus infection, comparing HBV group with the control group, only contact with other people's blood was singled out as statistically significantly more frequent among persons who were in contact with HBV.

The most common way in which the respondents came into contact with other people's blood was transfusion, however 15 (24.2%) of the respondents received blood. Other reported ways of coming into contact with other people's blood were providing help for injuries, in war and traffic accidents in seven (36.84%) respondents and contact with other people's blood at the workplace in two healthcare professionals and one police officer (15.79%). It is known that the risk of HBV transmission through transfusion is very low, but it is still higher compared to other potential causes of blood-borne diseases for which mandatory testing is prescribed [10]. This could be explained by the variability of the clinical presentation of hepatitis B virus infection and the immune response of the host, but also by the replication of the virus and the dynamics of serological markers of HBV infection, all of which complicates donor selection and screening [11].

"Piercing" is highlighted in the available literature as a risk factor for hepatitis B virus infection. Thus, a systematic review of 14 studies confirmed a statistically significant association between "body piercing" and hepatitis B virus infection. Although the same study showed a stronger risk effect of "piercing" for acquiring HCV compared to HBV, this data can be explained by the influence of vaccination [12]. Piercing was statistically more frequent among the anti-HCV-positive respondents compared to the control group in the study from 2024, but in the same study, binary logistic regression singled out drug usage as a dominant risk factor for acquiring HCV infection in Bosnia and Herzegovina [13].

Here, it is certainly important to mention the problem that population migration could bring with it. With the migration increase, there is also an increase in HBV prevalence in countries that were among low-prevalence countries. This is confirmed by the fact that the dominant risk factor for HBV infection in North America and Europe (including the UK) is actually the place of birth; an endemic area for HBV, intravenous drug use and male-to-male sex [14].

Contact with other people's blood and transfusion, as the most frequently mentioned way of coming into contact with other people's blood, still remains a threat in the transmission of HBV. Despite the introduction of molecular testing for viral DNA in transfusion activities, the residual risk still exists even in the most developed countries. The residual risk for HBV infection in

transfusion practice is not limited to preseroconversion window period but it extends to donors with occult HBV infection (OBI) characterized by the presence of HBV DNA in liver and the absence of HBsAg [15]. However, among the potential recipients of blood products there are certainly people who have not passed the mandatory HBV vaccination program.

The average age of persons who were in contact with HBV speaks in favor of the positive impact of the introduction of vaccination against HBV, meaning that persons who were in contact with HBV were not included in the program of compulsory vaccination against HBV. In this research we were unable to assess the risk of vertical transmission of HBV from mother to child due to the lack of information regarding the respondent's mothers HBV status at the delivery time. This survey also did not include testing of household members. The above mentioned and the number of participants included in the research represents the limitations of the research itself. Also, case-control design does not allow estimation of population-level prevalence of HBV infection. Future studies using population-based cross-sectional designs, potentially with nested case-control analyses, may provide more comprehensive insights into both prevalence and risk factors. Nevertheless, the present design is appropriate for identifying associations and generating hypotheses regarding HBV risk factors.

Conclusion

Twenty years after the implementation of mandatory HBV vaccination, people who have been in contact with HBV are more likely to be male and older, with no specific sociodemographic characteristics (employment status, educational level and marital or intimate status). Factor recognized as risk factor for acquiring HBV infection is contact with others people blood. The most common way of coming into the contact with other people's blood in this research was transfusion.

Although the higher average age of people who have been in contact with HBV confirms the positive impact of the introduction of vaccination, we should certainly be aware of the risk that comes with the migration of the unvaccinated population.

Acknowledgements

None.

Conflict of interest statement

None.

Authors' contributions

ITD: Conceptualization, data curation, formal analysis,

investigation, methodology, project administration, supervision, validation, visualization, writing - original draft and writing - review & editing.

BS: Conceptualization, data curation, formal analysis, investigation, methodology, validation, writing - original draft and Writing - review & editing.

JA: Conceptualization, methodology, project administration, supervision, validation, writing - original draft and writing - review & editing.

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Received on Marc 31, 2026. Accepted on April 30, 2026.

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How to cite this article: Talić Drlje I, Šušak B, Arapović J. Twenty years after the implementation of HBV vaccination: Epidemiology and risk factors for hepatitis B infection in the south of Bosnia and Herzegovina. *J Prev Med Hyg* 2026;67:E163-E167. <https://doi.org/10.82082/2421-4248/jpmh2026.67.2.3911>

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