





THE INCIDENCE OF HEPATITIS B OVER A TEN-YEAR PERIOD IN THE HERZEGOVINA-NERETVA AND SPLIT-DALMATIA COUNTIES

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ABSTRACT

Introduction: Hepatitis B is a viral infection of the liver that can present as both an acute and chronic disease, caused by the hepatitis B virus (HBV). Despite the availability of an effective vaccine and antiviral therapies capable of suppressing viral replication, hepatitis B remains a significant public health concern. The aim of the study is to collect, statistically analyze, and compare data on age, gender, and the number of hepatitis B cases in the Herzegovina-Neretva (HNC) and Split-Dalmatia (SDC) Counties.

Participants and methods: In this retrospective study, data were collected on the number of inhabitants and the number of registered patients with hepatitis B in the areas of these two counties, as well as demographic data of patients (age, gender) for the period from January 1, 2014, to December 31, 2024.

Results: In HNC region, 11 individuals with hepatitis B were registered during the study period, with nearly equal numbers of women and men. The affected men were significantly younger than the women ($p < 0.05$). In the SDC, 55 individuals with hepatitis B infection were registered during the same period, with significantly more men than women ($p < 0.05$), while there was no statistically significant difference in the age of the patients ($p > 0.05$). The average annual rate of reported hepatitis B infections in the observed period in the HNC was 0.42 ‰, while in the SDC, it was 0.96 ‰. The overall notification rate of cases in the SDC was 12.21 ‰, significantly higher than in the HNC, where it was 4.66 ‰ ($p < 0.05$).

Conclusion: It was determined that both counties have a low incidence rate of hepatitis B. The epidemiological data on hepatitis B obtained in this study are important for guiding prevention and treatment of the disease in the areas studied and contribute to one of the World Health Organization (WHO) goals, which is the elimination of hepatitis worldwide by 2030.

Keywords: hepatitis B, incidence, elimination, Split-Dalmatia County, Herzegovina-Neretva County.

INTRODUCTION

Viral hepatitis B is an acute and chronic liver disease caused by the hepatitis B virus (HBV), which remains a public health concern despite the availability of an effective vaccine and antiviral drugs capable of suppressing viral replication. It is estimated that there are over 250 million people worldwide with chronic hepatitis B, and in 2022, 1.1 million people died from the disease, primarily due to decompensated cirrhosis or hepatocellular carcinoma (HCC) (1-12). It is estimated that 3.6 million people in the Europa Union (EU) are living with chronic infection, and the prevalence and incidence increase from north to south and from west to east across Europe (1-5).

Croatia is classified as a country with a low prevalence of HBV infection. The prevalence of chronic hepatitis B in adult population is 0.7%, which corresponds to approximately 25,000 HBV carriers, many of whom remain undiagnosed. Half of them typically have active disease and are candidates for treatment. The prevalence of HBV infection is lower than 0.1% among voluntary blood donors, 0.2% among pregnant women, and higher in at-risk groups, with 3% among drug users and 5 % among HIV-positive individuals. After the initiation of screening of pregnant women and vaccination against hepatitis B in 1999, the prevalence of this disease significantly decreased in the young population (6,7).

HBV is most commonly transmitted sexually, but it can also be transmitted parenterally/percutaneously (through blood or plasma transfusions, as well as

contaminated donated sperm and organs, insufficiently sterilized needles and instruments, and other items that have been in contact with the blood of an infected person or virus carrier). There is also vertical transmission, where HBV is transmitted from mother to child. The spread of HBV infection is also influenced by close contact with an infected person (saliva, blood, sweat, etc.), and adults are more likely to develop the disease than children (8-12).

Treatment of hepatitis B

The main goal of hepatitis B treatment is to stop the replication of the virus and reduce the inflammatory activity of the disease, which significantly reduces the risk of developing fibrosis, cirrhosis and HCC.

The therapy also improves the patients quality of life.

HBsAg negativity occurs very rarely, only in 1-2% of cases (in HBeAg negative patients) and up to 10% (in HBeAg positive patients) over 5 years of treatment. This usually represents a functional cure, and in such cases, therapy is discontinued. In all other cases, therapy is usually permanent (1,13).

Before deciding on treatment, it is necessary to assess the disease activity. We distinguish between chronic hepatitis B, which mostly includes patients with a clear indication for treatment, and chronic HBV infection, in which treatment is indicated only in certain cases, but monitoring is always necessary (14).

The drugs used in HBV infection are nucleoside/nucleotide analogues (NAs)

with strong antiviral effects and a high barrier to resistance development. According to the guidelines of the Reference Center for Diagnostics and Treatment of Viral Hepatitis in the Republic of Croatia, the first-choice therapy includes tenofovir disoproxil (TDF) and entecavir (ETV), while tenofovir alafenamide (TAF) is recommended for certain indications.

These drugs inhibit the synthesis of HBV DNA outside the hepatocyte nucleus; therefore, therapy is usually permanent, as HBV replication resumes upon discontinuation (14,15).

TDF has the best barrier to the development of resistance, which practically never occurs during therapy. It can be used during pregnancy and in decompensated cirrhosis.

It is not suitable for patients with severe osteoporosis. ETV can be given to children older than two years and in cases of decompensated cirrhosis, but it is not recommended for pregnant women.

TAF has lower renal toxicity and is therefore reserved for patients with chronic HBV infection who have renal insufficiency or osteoporosis, and who cannot receive ETV due to prior resistance to ETV or lamivudine (LAM). Initiation of therapy with LAM is no longer recommended due to the rapid development of resistance. Only patients who have been on long-term LAM therapy with sustained viral suppression and no adverse effects may continue treatment until resistance emerges. After five years of treatment, the development of viral resistance to LAM reaches up to 50%. Adefovir and telbivudine are no longer

used frequently due to their lower efficacy compared to the previously mentioned drugs (1,3,13–15).

Prevention and control

In addition to drug therapy, prophylactic measures should be implemented in infected individuals (1,16,17).

For the purpose of prophylaxis and preventing the spread of hepatitis B, general and special protection measures should be implemented. General measures include the application of all available personal protective procedures to prevent contact with infectious materials (blood, saliva, semen), as well as the implementation and continuous monitoring of the quality of disinfection and sterilization of medical instruments, proper disposal of infectious waste, and blood testing of all blood, tissue, and organ donors (1,18,19).

Special protection measures include pre-exposure and post-exposure immunoprophylaxis.

Pre-exposure prophylaxis is carried out through vaccination. In the Republic of Croatia, vaccination of at-risk groups began in 1994; since 1999, children from 12 years of age have been vaccinated, and since 2007, all newborns have been vaccinated (1-3, 5-8, 16-19).

Post-exposure prophylaxis should be administered to newborns of HBsAg-positive mothers in the first few hours after delivery, after a single exposure to the HBV virus (stabbing incident) and in persons who had sexual contact with infected persons (1,5,20-23).

In the prevention of HBV infection and the care of patients with hepatitis B, nurses,

technicians, and other healthcare professionals can make a significant contribution by adopting a positive attitude toward hepatitis B immunization, promoting a healthy lifestyle, as well as in pointing out bad lifestyle habits and the potential risks associated with such behavior (24-27).

RESEARCH GOAL

The aim of the research is to collect, statistically analyze, and compare data on age, gender and the number of hepatitis B cases in HNC and SDC.

SUBJECTS AND METHODS

In this retrospective study, data were collected on the population size in the studied areas according to official census records, the number of registered hepatitis B cases in those areas, and the demographic data of the affected individuals (age, sex), over the period from January 1, 2014, to December 31, 2024.

For the purpose of this research, data were obtained from the database of the Public Health Institute of the Federation of Bosnia and Herzegovina, specifically the Health Statistical Yearbook, as well as from the database of the Croatian Institute of Public Health, namely the Croatian Health Statistical Yearbook. A review of the publications provided data on hepatitis B surveillance in HNC and SDC. (28, 29).

In this study, the diagnosis of hepatitis B includes both acute and chronic cases of infection.

Statistical analysis

All collected data were entered and stored in the computer program Microsoft Excel 2007 (Microsoft, USA) and were analyzed using the statistical software SPSS for

Windows (version 13.0, SPSS Inc., Chicago, Illinois, USA). Descriptive statistical methods were used for data analysis. Qualitative variables were presented as absolute numbers and percentages, while quantitative variables were expressed as mean values (M) and standard deviations (SD). The t-test was used to assess the statistical significance of differences between two arithmetic means, and the χ^2 test was used to examine associations between categorical variables. A p-value of < 0.05 was considered statistically significant (30,31).

RESULTS

According to the 2013 population census HNC had 236,278 inhabitants, with slightly more women (52%) than men (48%). According to the 2011 census SDC had 454,798 inhabitants, while the 2021 census recorded 423,407 inhabitants. In both censuses, women were more numerous (51.5%) than men (48.5%).

In the HNC, 11 cases of hepatitis B infection were registered between 2014 and 2024, including 6 women and 5 men (M=44.27; SD=14.74; minimum age (min)=19; maximum age (max)=61), which does not represent a statistically significant difference in the incidence by sex ($\chi^2=0.09$, $p>0.05$). There is a statistically significant difference in age between female and male patients ($t=2.11$; $p=0.03$). Men diagnosed with hepatitis B in the HNC were, on average, younger (M=35.4; SD=16.1; min=19; max=61) compared to women (M=51.6; SD=9.1; min=35; max=60).

In SDC, 55 cases of hepatitis B infection were registered during the same period, including 16 women and 39 men (M=49.32 years; SD=13.84; min=16; max=73). In

this county, men were statistically significantly more likely to be diagnosed with hepatitis B than women ($\chi^2=9.61$, $p<0.05$), while there was no statistically

significant difference ($t=0.47$; $p=0.31$) in the age of female ($M=48$; $SD=15.9$; $\min=20$; $\max=72$) and male patients ($M=49.9$; $SD=12.9$; $\min=16$; $\max=73$).

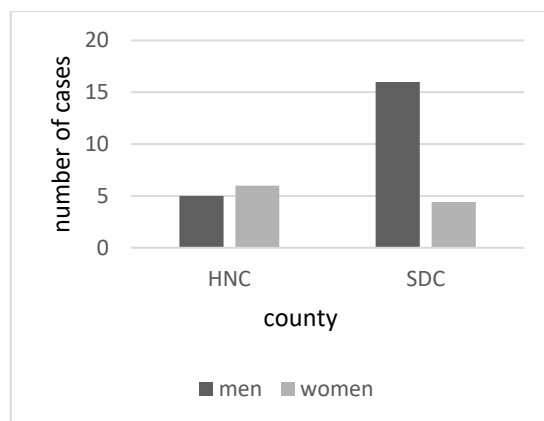


Figure 1. Distribution of reported hepatitis B infections from 2014 to 2024, by sex in HNC and SDC.

There is no statistically significant difference in the age at which hepatitis B was diagnosed in patients from both counties ($t=1.09$; $P=0.14$), but when comparing the age of patients by gender, it is found that men with hepatitis B infection in SDC are statistically significantly older than men from HNC ($t=2.29$; $P=0.01$),

while there is no age difference for women ($t=0.52$; $P=0.3$).

The number of registered cases of hepatitis B infection by year from 2014 to 2024 in HNC is shown in Table 1, and in SDC in Table 2. The rates are expressed per 100,000 inhabitants.

Table 1. Number of reported hepatitis B cases and rates per 100 000 population in the HNC by year, from 2014 to 2024.

years	2014.	2015.	2016.	2017.	2018.	2019.	2020.	2021.	2022.	2023.	2024.	test*	
	N°	N°	N°	N°	N°	N°	N°	N°	N°	N°	N°	χ^2	p
	%000	%000	%000	%000	%000	%000	%000	%000	%000	%000	%000		
	1 0,42	0 -	2 0,85	1 0,42	3 1,27	1 0,42	0	2 0,85	0	0	1 0,42	10	>0.05
							-		-	-			

*Fisher exact test

In the HNC, during the observed period, a total of 11 hepatitis B cases were registered, with the highest number (3 cases) reported in 2018. No cases were registered in 2015, 2020, 2022, and 2023.

The average annual notification rate was 0.42 %000, and there was no statistically significant difference in the number of reported cases across the years ($\chi^2=10$, $p>0.05$).

Table 2. Number of reported hepatitis B cases and rates per 100 000 population in the SDC by year, from 2014 to 2024.

years	2014.	2015.	2016.	2017.	2018.	2019.	2020.	2021.	2022.	2023.	2024.	test*	
	N°	N°	N°	N°	N°	N°	N°	N°	N°	N°	N°	χ^2	p
	%000	%000	%000	%000	%000	%000	%000	%000	%000	%000	%000		
	5	11 2,42	11 2,42	7	4	8	2	0	0	2	5	30,8	<0.05
	1,1			1,54	0,88	1,76	0,44	-	-	0,47	1,18		

*Fisher exact test

In the SDC, the highest number of hepatitis B cases (11) was registered in 2015 and 2016, while no cases were reported in 2021 and 2022. The average annual notification rate of hepatitis B infection was 0.96 ‰, with a statistically significant difference in the number of cases across the years ($\chi^2=30.800$, $p<0.05$).

Table 3 presents a comparison of the number of cases and infection rates of hepatitis B in the HNC and SDC for the

observed period from 2014 to 2024. The overall notification rate of hepatitis B in SDC was 12.21‰, compared to 4.66 ‰, in HNC, representing a statistically significant difference ($\chi^2=29.333$, $p<0.05$). The infection rate in SDC was significantly higher than in HNC in 2015 and 2016 ($\chi^2=6.231$, $p<0.05$), in 2017 ($\chi^2=4.5$, $p<0.05$), and in 2019 ($\chi^2=5.444$, $p<0.05$), while no statistically significant differences were observed in the remaining years.

Table 3. Comparison of the number of hepatitis B cases and infection rates by year between the HNC and SDC from 2014 to 2024.

Number of cases and infection rates per 100 000 population						
Year	HNC		SDC		χ^2	p
	Number	%000	Number	%000		
2014.	1	0.42	5	1.10	2.667	>0.05
2015.	0	-	11	2,42	6,231	<0.05
2016.	2	0.85	11	2,42	6,231	<0.05
2017.	1	0.42	7	1,54	4,5	<0.05
2018.	3	1.27	4	0.88	0,143	>0.05
2019.	1	0.42	8	1.76	5.444	<0.05
2020.	0	-	2	0.44	2	>0.05
2021.	2	0.85	0	-	2	>0.05
2022.	0	-	0	-	-	-
2023.	0	-	2	0.47	2	>0.05
2024.	1	0.42	5	1,18	2,667	>0.05
OVERALL	11	4.66	55	12,21	29,333	<0.05

DISCUSSION

In the conducted research, it was determined that the average annual rate of reported infections in both counties is below 1 per 100,000 inhabitants, while the rate of reported hepatitis B infections in the

HNC and SDC during the observed period was also low 4.66 per 100,000 and 12.21 per 100,000, as demonstrated in previous studies (1-3, 6-12). The overall rate of hepatitis B infection in the SDC is significantly higher than in the HNC

($p < 0.05$). This difference reflects a significantly higher number of reported hepatitis B cases in four years: 2015, 2016, 2017, and 2019, while no such difference was observed in other years ($p > 0.05$). During the COVID-19 pandemic (2020–2023), there was a very small number of reported hepatitis B infections in both counties. This could be justified by the fact that, during the pandemic years, there was a noticeable underreporting of other infectious diseases. A similar effect, particularly in 2020, was observed in EU countries, where there was a sharp decline in infection reports due to the disruption of services responsible for disease prevention. Furthermore, COVID-19 restrictions limited the movement of the population and reduced potential risky sexual activities. The increased reporting after 2021 can be explained by the end of pandemic restrictions, the recovery of the healthcare system, the revival of testing initiatives, changes in disease surveillance, increased migration, and a rise in infection transmission (4,5).

The significantly higher rates of hepatitis B in SDC compared to HNC are also attributed to the geographical location of SDC. Due to higher traffic of people, goods, and drugs, as well as more developed tourism, maritime traffic, and the presence of world-renowned destinations for youth entertainment, there are greater opportunities for risky behavior (unprotected sexual intercourse, drug use) (1-3, 6-12, 16-18, 20-22).

In SDC, during the observed period, significantly more men than women were reported ($p < 0.05$), which could likely be explained by the fact that men tend to engage in riskier behaviors. Such gender differences were not observed in HNC, but

overall, the number of registered cases is small, making it difficult to draw definitive conclusions. There is a significant difference in the age structure of reported hepatitis B infections in HNC, where women are, on average, older than men ($p < 0.05$), while the results from SDC indicate no such difference ($p > 0.05$). The registered age difference in hepatitis B cases in HNC can be explained by the small number of reported patients rather than any age-related risk factor.

In EU countries, between 2014 and 2019, the highest number of reported hepatitis B infections, around 30%, was in the age group of 25-34 years. From 2020 to 2022, the number of reported cases became almost equal in the age groups of 25-34 years and 35-44 years, which together account for 50% of the total number of reported cases (4,5).

In SDC, the highest number of reported hepatitis B infections is in the age group of 55-64 years (31%), followed by the age group of 45-54 years (16%). In HNC, the most common age for detection and reporting of infection is also 55-64 years (36%). This indicates that the detection of hepatitis B infections in younger age groups is very rare in both HNC and SDC, which is likely due to the mandatory hepatitis B vaccination program. A similar effect is observed in EU countries, where less than 20% of all reported hepatitis B infections are detected in individuals under 25 years of age. The shift in hepatitis B incidence to older age groups is understandable due to the introduction of the mandatory vaccination program in Croatia in 1999 for children at the age of 12, and in 2007 for infants, which has protected younger age groups at a time

when they are otherwise most exposed to infection risks (1,2,4-8).

This study identified differences in the rates of reported hepatitis B infections between the observed counties, which geographically border each other but belong to separate countries. Similarly, there are differences in infection reporting rates among EU countries. The highest rates of reported infections are found in the northern and western countries of Europe. Geographical variations are primarily a reflection of testing policies, reporting practices, and epidemiological differences. The highest rates of reported hepatitis B infections have been observed in countries of Southern and Eastern Europe. The detection of chronic hepatitis B infections is a result of the intensity of either local or national screening and testing strategies. It has been proven that the highest rates of detected hepatitis B infections are found in countries with comprehensive testing programs, such as Finland, Norway, Sweden, Latvia, Ireland, Iceland, Luxembourg, the Netherlands, Germany, Poland, and Austria (5). Therefore, the differences observed in this study may not necessarily reflect the actual prevalence of hepatitis B. The epidemiological data on hepatitis B obtained in this study are important for guiding the prevention and treatment of this disease and contribute to the progress toward the global goal of hepatitis elimination. In fact, the WHO adopted the Global Hepatitis Strategy in 2017 with the aim of eliminating the disease by 2030. To achieve this, it is necessary to reduce the incidence of chronic hepatitis by 90% and related mortality by 65% compared to 2015 levels. Comprehensive vaccination programs, testing in high-risk groups, treatment of

patients, prevention of mother-to-child transmission, and programs targeting drug users are key to accelerating the elimination of hepatitis worldwide (4,5).

CONCLUSION

It has been determined that both counties have a low incidence rate of hepatitis B. Further research is needed to be conducted in both counties, covering a larger number of participants over a longer period of time, which would make the results more relevant. All the data on hepatitis established in this study, as well as the data that will be discovered in future research, contribute to the WHO's goal of hepatitis elimination worldwide by 2030.

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UČESTALOST OBOLJEVANJA OD HEPATITISA B U DESETOGODIŠNJEM RAZDOBLJU U HERCEGOVAČKO-NERETVANSKOJ I SPLITSKO-DALMATINSKOJ ŽUPANIJU

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SAŽETAK

Uvod: Virusni hepatitis B je akutna, ali i kronična bolest jetre prouzročena virusom hepatitisa B (HBV), koja je i dalje javnozdravstveni problem, unatoč učinkovitom cjepivu i antivirusnim lijekovima koji mogu zaustaviti replikaciju virusa. Cilj istraživanja je prikupiti, statistički obraditi i usporediti podatke o dobi, spolu i broju oboljelih od hepatitisa B u Hercegovačko-neretvanskoj (HNŽ) i Splitsko-dalmatinskoj županiji (SDŽ). **Ispitanici i postupci:** U retrospektivnoj studiji prikupljeni su podaci o broju stanovnika kao i broju registriranih bolesnika s hepatitisom B na područjima ovih dvaju županija, te demografski podatci oboljelih (dob, spol) kroz vremensko razdoblje od 01.01.2014. do 31.12.2024. godine. **Rezultati:** U HNŽ u ispitivanom razdoblju registrirano je 11 osoba s hepatitisom B, gotovo podjednak broj žena i muškaraca, a oboljeli muškarci su u prosjeku bili značajno mlađi od žena ($p < 0.05$). U SDŽ u istom razdoblju registrirano je 55 osoba s hepatitis B infekcijom, od čega značajno više muškaraca nego žena ($p < 0.05$), dok nije bilo statistički značajne razlike u dobi oboljelih ($p > 0.05$). Prosječna godišnja stopa prijavljenih infekcija hepatitisom B u promatranom razdoblju u HNŽ iznosila je 0.42 ‰, a u SDŽ 0.96 ‰. Ukupna stopa infekcije hepatitisom B u SDŽ iznosila je 12,21 ‰, i bila je značajno viša nego u HNŽ gdje je iznosila 4,66 ‰ ($p < 0.05$). **Zaključak:** Utvrđeno da područja obaju županija imaju nisku stopu obolijevanja od hepatitisa B. Epidemiološki podatci o hepatitisu B dobiveni u ovom istraživanju važni su za usmjeravanje prevencije i liječenja ove bolesti na ispitivanim područjima i doprinose jednom od ciljeva Svjetske zdravstvene organizacije (SZO), a to je eliminacija hepatitisa u svijetu do 2030. godine.

Ključne riječi: hepatitis B, incidencija, eliminacija, Splitsko-dalmatinska županija, Hercegovačko-neretvanska županija.

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