

The Epidemiological Characteristics of Hepatitis B in Croatia: The Results of the Prevention

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ABSTRACT

This study shows epidemiological characteristics and preventive measures implemented for the prevention and control of hepatitis B infections in Croatia. We analyzed the data from obligatory infectious disease reports and notifications of death due to infectious diseases, data on the hepatitis B infections in Croatia, and data collected by survey of the population. The average prevalence of the disease is 3.67 per 100,000 annually. All age groups are affected, but still a higher rate of the disease is found in the age groups from 15 – 19 and 20 – 29 years of age. Hepatitis B disease is 1.4 times more likely in men than in women. For the past 18 years, the average rate of mortality was 0.2%. The incidence of HbsAg-positive donors of blood is within the range of 0.65% in 1992 to 0.012% in 2011. The largest part of preventive measures implemented in Croatia against hepatitis B is predicted and required by legislation. The registrations of acute and chronic carriers of the virus are obligatory. High-risk groups have started being vaccinated since 1992. The obligatory vaccination of infants was introduced in the mandatory vaccination program in 2007. Routine testing of blood exclusively from voluntary donors for HbsAg presence is obligatory. The non-governmental organization »Help« created for intravenous drug users, along with the »Harm reduction« program implemented hepatitis B, C, and HIV/AIDS prevention program in 1995. In order to gain a better understanding of epidemiological characteristics of hepatitis B in Croatia, the specifics of its dynamics in small communities are required since the research of Croatian public health officials and researchers have shown that hepatitis B is spread in different ways.

Key words: hepatitis B, epidemiology, preventive measures, Croatia

Introduction

Hepatitis B is a global public health issue due to its worldwide presence, and the World Health Organization (WHO) estimates that two billion people in the world are infected with hepatitis B virus (HBV). Chronic carriers are estimated to be from 300 to 500 million persons. HBV can cause acute hepatitis leading to acute liver failure in some cases, while about 5% become chronic carriers and are at risk for developing liver cirrhosis and hepatocarcinogenesis¹. WHO estimates that between 500,000 and 700,000 people in the world die each year from HBV infection and the consequences of the condition²⁻⁵. Prevalence and modes of transmission vary from one country to another; HBV infection poses the greatest problem in developing and poor countries¹⁻⁶. Primary HBV infections occur at much higher frequencies and at much earlier ages in

high-prevalence geographic areas of the world such as parts of Asia and Africa⁷⁻¹¹. Transmission can be prevented by a 95% effective vaccine, which has been available since 1982⁸.

Natural History of Hepatitis B

The conversion of acute to chronic hepatitis depends on age and immune response at the onset of infection^{9,10}. Hepatitis B e antigen (HBeAg) status can be characterized on the basis of the course of HBV infection. Immunologic tolerance to HBV occurs during perinatal infection or in early childhood and lasts for a lifetime¹⁰. Although the mechanisms involved in immune-tolerance to HBV remain unclear, minor HBV-associated liver injury despite high-level HBV replication indicate immune tolerance to HBeAg¹².

After seroconversion, most patients remain negative for HBeAg and positive for anti-HBe antibody. This phase reflects relatively higher immunologic tolerance early and relatively lower tolerance later in the natural history of chronic HBV infection acquired early in life. This phase is usually referred to as the »inactive carrier state«^{10,12}. Hepatitis B's antigen (HBsAg) can still be found in the blood of patients of one part of infected patients even after recovery but with no other symptoms of the disease (the so-called healthy inactive HBsAg carriers). In some patients who have recovered, co-infection with the wild-type virus and mutations has been shown^{4,13-16}. The number of inactive carriers in certain countries and larger geographic areas is a good indicator of HBV infection prevalence^{4,13,16-19}.

HBeAg-reactive chronic HBV infection is followed by high-level HBV replication, and spontaneous sero-conversion from HBeAg-positive to antibody (anti-HBe)-positive infection coincides with a reduction in HBV replication and clinical improvement^{20,21}.

Routes of Transmission

The predominant transmission of HBV infection is through contact with infected blood and serous fluids⁸. Saliva can also be infectious, and epidemiological studies suggest human bite as possible route of transmission²². Risks for parenteral or mucosal transmission includes injection drug use, transfusion and dialysis, acupuncture, working in health care settings, tattooing, household contacts, and others who are likely to come into contact with potentially infected blood and blood products^{6,12,13,16,23}.

HBV can be transmitted through infected blood or body fluids that enter through mucous membranes, sexually, and perinatally^{8,9}. The highest concentrations of virus are in blood and serous fluids⁸.

Transmission of HBV from carrier mothers to their babies can occur during the perinatal period, and appears to be the most important factor in determining the prevalence of infection in high endemic areas, particularly in China and Southeast Asia^{6,7}. Transmission mostly occurs during delivery (perinatally), seldom intrauterinally (up to 10%) and in the early post-delivery period¹⁴. Infection of infants with HBV is efficient: 70% – 90% will become infected from perinatal exposure to a mother positive for both HBsAg and HBeAg, while 20% of infants will become infected from a mother if positive for only HBsAg. A high frequency (>90%) of these infected infants will become chronic carriers due to immaturity of the infant's immune system, although it seems that the final outcome does not depend only on the infant's immunocompetence and the level of the mother's viremia, but on the heterogenetic characteristics of the virus^{6,8,13-16,24}.

The sexual transmission of hepatitis B is a major source of infection in all areas of the world, and is the predominate mode of transmission in areas where the prevalence of HBV infection is low, such as North America and Western Europe^{4-7,11,13,16,24-27}. Sexual partners of injection drug users,

sex workers, and other people with high risk sexual behaviors are at particularly high risk for infection. In heterosexuals, factors associated with an increased risk of HBV infection include duration of sexual activity, number of sexual partners, history of sexually transmitted diseases, and a positive serology for syphilis²³.

In areas where the prevalence of HBV infection is low, occupational blood exposure predominates^{2-5,13,16,24-27}.

The aim of this report is to describe epidemiological characteristics and preventive measures implemented for the prevention and suppression of HBV in Croatia.

Methods

Data from the National Institute of Public Health on infectious disease reports²⁸, and data from legal acts about preventive measures against hepatitis B infection were analyzed. The County of Split – Dalmatia has been used for comparison, because in this county hepatitis B infection was major public health problem.

The data used in this report are from the Croatian National Institute of Public Health and are regularly cited in publications like the Croatian Health Service Yearbook and Epidemiological News from 1996 to 2012. Incidence and prevalence have been calculated for the number of inhabitants according to the 2001 and 2011 Census data. According to the 2001 Census, 4,437,460 people live in the Republic of Croatia and 463,676 people live in the County of Split-Dalmatia. According to the 2011 Census, 4,284,889 people live in the Republic of Croatia and 454,798 people live in the County of Split-Dalmatia²⁸. Hepatitis B surveillance and reporting conducted in the County of Split-Dalmatia do not differ from the surveillance strategies at the national level.

Data on the number of the infected, the number of HBV carriers, and the age and sex structure of the infected were obtained from the Epidemiology Department of the Croatian National Institute of Public Health as reported by physicians' offices.

Acute hepatitis B is reported on the basis of several clinical outcomes (e.g. fatigue, with or without jaundice, increase in serum alanine aminotransferase (ALT) levels by more than 2.5 times) and serological test results which include HBsAg-positive or IgM anti-HBc positive and anti-Hepatitis A virus (anti-HAV) IgM negative findings^{2,3,16,25}.

Persons who have had HBsAg-positive results twice within a period of six months are reported as chronic virus carriers. The inactive carrier is an HBsAg-positive person with undetectable viremia (HBV DNA negative) and normal transaminases.

Results

Hepatitis B morbidity in Croatia

In the period from January 1, 1995 to December 31, 2012, 2,939 new cases of acute HBV infections were re-

TABLE 1
THE NUMBER OF REPORTED CASES OF ACUTE HBV INFECTION AND CHRONIC HBV CARRIERS IN CROATIA DURING THE 1996 – 2012 PERIOD

Godina	No of cases		No of carriers	
	Incidence N Mb 0/0000	Prevalence N 0/0000	Prevalence N 0/0000	
1995	214/1*	4.60	194	4.37
1996	198	4.46	169	3.81
1997	263/1*	5.81	250	5.63
1998	211/1*	4.73	200	4.51
1999	215/1*	4.75	228	5.14
2000	189	4.42	169	3.81
2001	200	4.60	310	6.99
2002	205	4.87	221	4.98
2003	180	3.85	159	3.58
2004	217	4.89	176	3.97
2005	164	3.70	164	3.70
2006	148	3.33	129	2.91
2007	127	2.86	114	2.56
2008	140	3.15	111	2.50
2009	116	2.61	98	2,20
2010	58/1*	1.30	122	2,74
2011	56/1*	1.30	118	2,75
2012	38	0.88	98	2,28
Total/average	2939	3.67	3030	3,69

*died; source: Croatian Health Service Yearbook 2012; Croatian National Institute for Public Health

ported in Croatia, six of whom died (case fatality rate 0.2%). During the same period, 3,030 chronic HBV infected carriers were reported. The number of reported cases of acute HBV infection and chronic HBV carriers in Croatia during the 1995 – 2012 period can be seen in Table 1. During this study period, we can see a significantly lower number of cases in the recent years, and the average number of 163 cases.

Comparison of hepatitis B morbidity in the County of Split-Dalmatia and Croatia

The morbidity dynamics of hepatitis B was analyzed in the County of Split-Dalmatia, an area with different socioeconomic characteristics as compared to the rest of Croatia. During the period of the Croatian War of Independence from 1991 to 1995, intravenous drug abuse was a significant problem in this county where 10% of the country’s population lives. The local community recognized the problem and in cooperation with non-governmental organizations (NGOs) started the »Help« program in 1995 for injection drug addicts

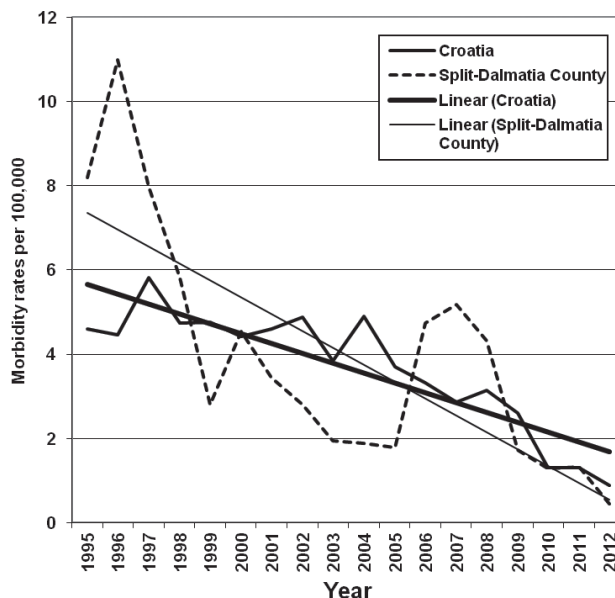


Fig. 1. Morbidity per 100,000 and linear trend of newly reported HBV cases* in Croatia and Split-Dalmatia County during the 1995-2012 period. Source: Croatian National Institute of Public Health.

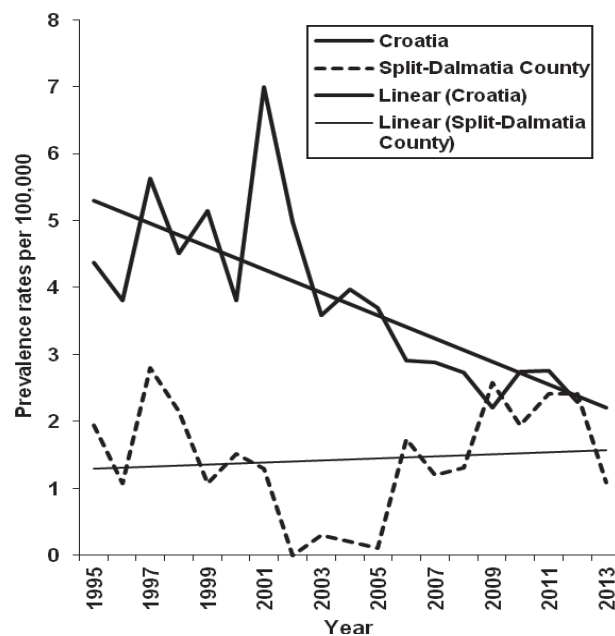


Fig. 2. Rate of reported cases of HBV carriers (chronic cases) and linear trend (calculated by Excel (Microsoft, 2005)) in Croatia and Split-Dalmatia County, 1995-2008. Source: Croatian National Institute of Public Health.

which, among other intervention activities, provided free needles and syringes. The interventions implemented through »Help« resulted in an evident decrease in the number people infected with hepatitis B, as illustrated in Figure 1.

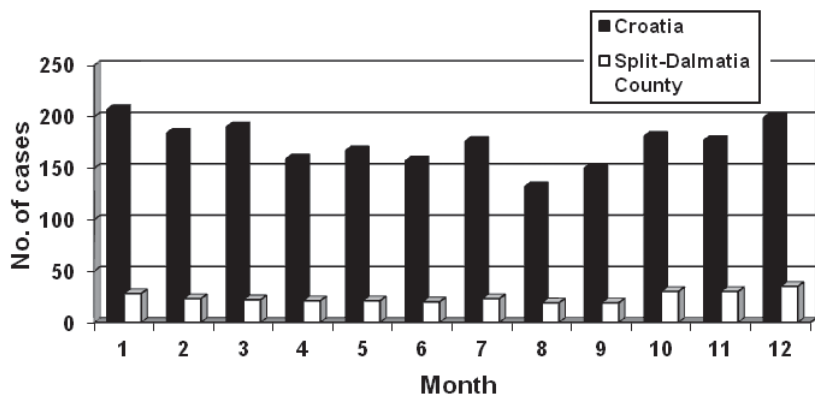


Fig. 3. Number of HBV cases by month in Croatia and Split-Dalmatia County, 1995-2012. Source: Croatian National Institute of Public Health.

HBV chronic carriers

The annual number of reported HBV carriers, which on average is 168 persons in Croatia, varied significantly during the period studied when compared to the average. For example, 310 cases were reported in 2001 and 98 in 2012. The reason why a greater number of HBV carriers was reported in 2001 is because HBV (and HCV) testing was performed on all persons who received hemodialysis that year. In the period studied, there is a significant decline trend in the number of chronic virus carriers in Croatia, while in the County of Split-Dalmatia the trend shows a slight increase during recent years, Figure 2.

Number of hepatitis B infected by month

No significant differences exist in the number of those diseased by month, except for a slightly smaller number of diseased persons in August and other summer months

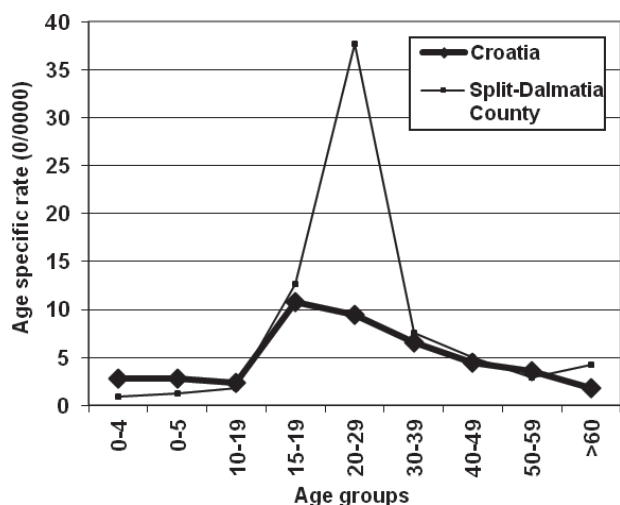


Fig. 4. Incidence of HBV cases (age specific rate) in Croatia and Split-Dalmatia County, 1995-2008. Sources: Croatian National Institute of Public Health and Institute of Public Health in Split-Dalmatia County.

in general, which can be attributed to the summer holiday season when hepatitis B reporting is less frequent. With regard to transmission, seasonal occurrence is not to be expected with hepatitis B. The number of HBV cases by month in Croatia and Split-Dalmatia County, from 1995 to 2012 is shown in Figure 3.

Age and sex structure of hepatitis B diseased patients

Hepatitis B infection in Croatia is recorded in all age groups. The greatest number of cases is recorded in the 20 – 29 years of age group. In the county of Split-Dalmatia morbidity is somewhat greater in that age group – 51.8 per 100,000. In Croatia, the same age group accounts for 26.8 per 100,000 of the diseased. The incidence of HBV cases among different age groups (age specific rate) in Croatia and Split-Dalmatia County from 1995 to 2008 period can be seen in Figure 4.

In terms of sex structure, the number of male patients is greater in both Croatia and the County of Split-Dalmatia. In Croatia, 40.7 per 100,000 women are infected, while in the County of Split-Dalmatia women account for one-third of the infected at 33.2 per 100,000. Men are mostly infected between the ages of 20 and 29. The greatest number of infected women is in the 15-19 years of age group (Figure 5).

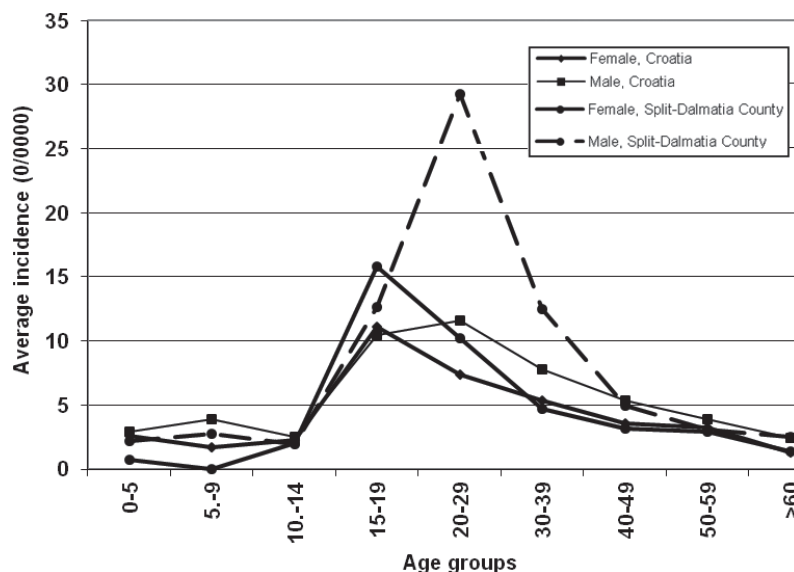
Case fatality rate

In the period observed the average case fatality rate for hepatitis B in Croatia was 0.2% : 6 out of the 2,939 diseased patients died. One death was recorded in 1995, 1997, 1998, 1999, 2010 and 2011 respectively. In the past ten years there have been no deaths due to HBV infection in the County of Split-Dalmatia.

Incidence of HBsAg-positive markers in volunteer blood donors

The incidence of HBsAg-positive blood donors is a good but indirect indicator of the prevalence of inactive HBV

Fig. 5. Average incidence of HBV by age and sex, Croatia and Split-Dalmatia County, 1995-2008. Sources: Croatian National Institute of Public Health and Institute of Public Health in Split-Dalmatia County.



carriers in a population. The prevalence of HBsAg-positive blood donors in Croatia has been constantly decreasing during recent years. The prevalence (%) of HbsAg-positive markers in volunteer blood donors in Croatia from 1993 to 2011 and the County of Split-Dalmatia from 1999 to 2013 is illustrated in Figure 6.

Data on the prevalence of HbsAg-positive blood donors in the County of Split-Dalmatia from 1999 to 2013 show higher values than the average found in the Republic of Croatia, which is probably a consequence of a greater number of infected patients in the past.

Compulsory hepatitis B vaccination for adults and children in Croatia

Table 2 shows the number of infants and school children vaccinated against HBV infection during 2007-2012

TABLE 2
THE PERCENT OF INFANTS AND SCHOOL CHILDREN VACCINATED AGAINST HBV INFECTION, CROATIA, PERIOD 2007-2012

Year	Infants School children	
	%	
2007	94.4	94.4
2008	96.8	98.4
2009	97.0	98.1
2010	97.0	98.6
2011	96.4	98.2
2012	96.2	97.9

Source: Croatian Health Service Yearbook 2012; Croatian National Institute for Public Health

period. Starting in 2000, all children aged 11 – 12 years were required to receive the hepatitis B vaccine. A routine infant vaccination schedule was added in 2007, resulting in an increase in the number of scheduled and vaccinated persons. Vaccination coverage remained over 90% from 2007 to 2012.

Discussion

In Croatia, high-risk groups for HBV infection include injection drug users, household contacts, sexual partners of HBV carriers, health care workers, patients receiving chronic hemodialysis, and organ transplant recipients. In addition, medical and dental interventions, tattoos and acupuncture are not to be excluded^{16,24-26}.

It is interesting to note that females are younger than males when infected with HBV in Croatia – between the

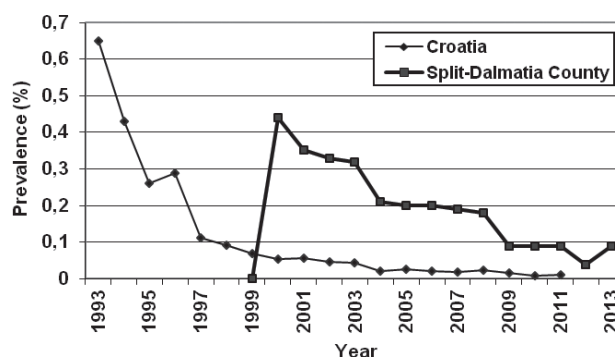


Fig. 6. Prevalence (%) of HbsAg-positive markers in volunteer blood donors in Croatia 1993-2007 and Split-Dalmatia County 1999-2011. Sources: Croatian Health Service Yearbook 2012 and Department of Blood Transfusion, Clinical Hospital Split.

ages of 15 and 19. At this period in life they probably get infected through sexual transmission as the average age of girls' first sexual intercourse is 15 and usually with a partner several years older than themselves²⁹.

Numerous HBV prevention measures are employed in Croatia, but most public health research experts and authorities agree that vaccination is the most efficient form of prevention^{6,13,27}. Vaccination against hepatitis B has been mandatory since 1992 for all persons exposed to infection in Croatia³⁰. The hepatitis B vaccine available in Croatia is a highly effective and safe vaccine produced through the genetic engineering of yeast fungi³¹. HBV has a stable, long-enduring covalently closed circular DNA structure which means that the virus has low mutagenicity levels, assuring vaccine effectiveness^{2-3,32}. However, the emergence of naturally occurring mutations may be a potential problem for the current HBV vaccine, as the mutations change the characteristics of HBsAg enabling the mutated virus to «escape» from the immunological response. It seems that such mutations are rare at the moment, but if they occur frequently, then necessary changes in the HBV vaccine and diagnostic protocols will be needed^{2,16,24}.

A Rulebook on the methods of implementing immunization, seroprophylaxis, and chemoprophylaxis against contagious diseases stipulates that vaccination is mandatory for all healthcare workers, newborns of HBsAg-positive mothers, patients on hemodialysis, family contacts of HBsAg-positive persons, mental institution staff, intravenous drug users and patients suffering from hemophilia and leukemia^{33,34}.

Universal vaccination of school children (11 – 12 years of age) not previously vaccinated with the hepatitis B vaccine started in 2000²⁸. In 2007, following a recommendation from the World Health Assembly for global HBV vaccination, the Croatian National Institute of Public Health approved universal vaccination of newborns and introduced a routine infant schedule. In addition, the implementation of selective vaccination against hepatitis B started in 1992 did not yield a reduction in prevalence, creating a stimulus for universal vaccination of all newborns in Croatia. In 2007 94.4% of infants/school children were vaccinated against hepatitis B²⁸. For infants with normal immune status, hepatitis B vaccine is given in three doses at month 0, 1, and after 6 months. Children with normal immune status also receive three doses of the vaccine with the second and third doses given 1 to 3 and 2 to 17 months respectively after the first. Newborns born to HbsAg-positive mothers are protected after one dose of HBIG (human hyperimmune gamma globulin) and by fast (several hours after birth) scheme vaccination recommended at 0, 1, 2, and 12 months. Fast vaccine application and high doses of HBIG ensure protection of 94% of newborns from HBsAg whose mothers are HBsAg-positive. In half of these, 6% of newborns will become chronic carriers despite vaccination due to intrauterine infection before birth. For these infants, any postnatal attempt at vaccine protection would be ineffectual^{6,13,33,34}.

According to the WHO recommendations, a booster dose of hepatitis B vaccine can be given 15 years after the first dose because completely immunized persons are protected until that time, even if the titer of antibodies cannot be measured because the immunological memory secures a protective recall response after HBV exposure^{3,5,35}. On the other hand, the European Consensus Group on hepatitis B immunity recommends that booster doses are unnecessary in immunocompetent persons following a complete course of vaccination³⁶. The latest Croatian Rulebook on the methods of implementing immunization, seroprophylaxis, and chemoprophylaxis against contagious diseases does not include the possibility of booster vaccination after a fully implemented immunization³⁴.

We assume that in certain counties of Croatia intravenous drug abuse plays a significant role in spreading hepatitis B, but no studies to date have explored intravenous drug abuse as a major mode of transmission on a county level³⁷. From epidemiological data, people aged 20 – 29 are a high-risk group for HBV infection through injection drug use. Based on these findings, additional educational and prevention programs should be created to target this high-risk group with the realization that this group lacks awareness of the risk and consequences of hepatitis and are predicted to have low vaccine completion rates^{8,37}. In order to achieve complete protection against hepatitis B, vaccination efforts for infants, adolescents, and high-risk groups will continue³⁸. The effect of any vaccination efforts will be evident from a decrease in the incidence and prevalence of HBV infection after a number of years, therefore a final evaluation of intervention success can only occur in the future. Decline of incidence and prevalence of hepatitis B in Croatia is already visible. In countries such as Italy and the U.S. the incidence of acute hepatitis B has declined dramatically during the past decade after the implementation of hepatitis B vaccination programs, particularly among persons in younger age groups^{39,40}. To assess the immune status of vaccinees, an evaluation of vaccination impact could be performed by measuring HBsAg prevalence in cohorts of vaccinated children. Currently, there are no data available on the impact of infant or childhood hepatitis B vaccination programs in Croatia. In Croatia comprehensive, legally stipulated measures (Public Protection from the Infectious Diseases Act and various rulebooks) are being implemented with the aim of combating and preventing hepatitis B infection – the screening of blood donations, mandatory testing for all pregnant women, vaccination and seroprophylaxis in infants born to HBsAg-positive mothers, vaccination according to the immunization schedule and according to epidemiological indications, as well as all other preventive measures in medicine and dentistry. Although vaccination is mandatory for all healthcare workers^{33,34} in Croatia, the percentage of coverage is unsatisfactory. Some authors have tried to look into the possible reasons why hepatitis B vaccination is avoided by healthcare workers and have come to the conclusion that fear is a factor present among health workers due to a lack of information about the vaccine^{41,42}.

Research has shown that until 1990, 20% of all patients hospitalized for acute hepatitis B in the Zagreb area were healthcare workers from high-risk groups, mostly nurses, and there has been a significant decrease in this percentage since the introduction of vaccination against hepatitis B in 1987⁴¹. Still, vaccination does not seem to extend to all healthcare workers. One study of a larger group of research subjects has shown that 58.1% of all healthcare workers are not vaccinated for different reasons⁴³.

The Act on blood and blood products established by the Ministry of Health and Social Welfare stipulates that the Croatian Institute of Transfusion Medicine should keep a record of blood donors. In the Blood Donors Registry, data on persons who temporarily or permanently cannot donate blood are recorded separately. Medical information on blood donors, including test results are confidential and must be protected from unauthorized use. The Blood Donors Registry is a part of the national system for transfusion and must be available to all healthcare institutions that collect blood⁴⁴. In Croatia disease screening of donated blood is mandatory, and monitoring has shown a decrease in the risk of transmissible infections through transfusion^{44,45}.

It was relatively early that a needle exchange program began in Split-Dalmatia County for intravenous drug users³⁷. A non-governmental organization called 'Help' started operating in the Split area in 1995 to 1996. The main activity of this organization is to educate and counsel intravenous drug users, most of all through free exchange of needles and syringes, resolve their socio-legal problems, provide free and anonymous testing, refer them to treatment, and provide psychological support. As far as the rest of Croatia is concerned, »Help« implements the needle exchange and counseling program in the area of twenty cities in Croatia³⁷.

No published data exist on the number of intravenous drug users in Croatia who had or still have chronic HBV infection. However, according to unpublished data from the Epidemiology Department of the Croatian National Institute of Public Health, in the County of Split-Dalmatia 40% of all intravenous drug users tested through 'Help' have markers of recovery from an HBV infection and 3.9% have chronic HBV infection. Estimated prevalence of HBsAg in injecting drug users in Croatia in the years 2007-2008 is average 0.4% (from 0.0 to 0.8%). Estimated prevalence of anti HBe in injecting drug users in Croatia in the years 2007-2008 is average 36.6% (from 27.1 to 46%). WHO argues that injecting drug users (IDUs) are a key group that needs to be specifically targeted for prevention and treatment of viral hepatitis³⁸.

Data from Slovenia show that 17.5% of intravenous drug users have suffered from HBV infection, and only 2.5% are chronic virus carriers⁴⁷. Research conducted on intravenous drug users in the U.S. shows that 4.7% have chronic HBV infection, while 32.3% have markers of having recovered from an HBV infection⁴⁸. Other research also conducted in the U.S. shows a high incidence of occult HBV infection (no circulating HbsAg present in the se-

rum) in intravenous drug addicts with hepatitis C virus (HCV) infection⁴⁹.

Having considered the data found in the literature that up to 5% of intravenous drug users are HBsAg-positive, more than 3,000 are registered in the area of the County of Split-Dalmatia, and that in the Croatian register of patients treated for psychoactive substance abuse and/or addiction a total of about 35,000 persons⁵⁰ were registered from 1976 to the end of 2012, we believe that in addition to extensive implementation of all preventive medical and dental measures, the »Help« program has probably contributed to the decline in morbidity rates in the area of the County of Split-Dalmatia.

It is interesting that in Asian countries with a high prevalence of HBV chronic infection vertical transmission predominates, whereas in African countries acquired infections are mainly from horizontal transmission¹³⁻¹⁶.

Universal testing of pregnant women for HBsAg was introduced in Croatia in 1999^{34,37}. However, research conducted on a sample of 400 pregnant women in Split, the second largest city in Croatia, shows a low incidence of viral infection (0.75%)⁴⁶.

Studies conducted by authors in the County of Osijek-Baranja have shown that multiple household members living with one hepatitis B infectious person are more likely to be infected²⁵. Therefore, to prevent this type of transmission other HBsAg-positive family members need to be reported, while members negative for HBsAg should undergo vaccination.

In men who have sex with men (MSM), a high seroprevalence of HBsAg along with risky sexual behavior contribute to a higher incidence of acute hepatitis B compared with the general population^{27,52}. Data are not available regarding heterosexuals or MSM as high-risk groups for HBV in Croatia.

Conclusion

Thanks to the extensively implemented preventive measures and vaccination of adolescents and high-risk groups, the expected decrease in the prevalence of hepatitis B morbidity rates in Croatia did occur. Comprehensive vaccination (infants, adolescents, and high-risk groups) began in the year 2007. Studies from several immunization programs initiated in other countries 15 years ago show a significant reduction in hepatitis B morbidity rates, but not the elimination of HBV infection. Therefore, in order to better understand the epidemiology of hepatitis B in Croatia, specific research of its characteristics in high-risk settings is needed, in line with WHO recommendations. This would enable us to visualize certain peculiarities which would guide the development of counter-epidemic approaches aimed particularly at endangered target groups. Thus, along with the implementation of numerous unique counter-epidemic measures at the national level, it would be possible to implement such measures that would decrease the incidence of new hepatitis B cases in high-risk settings.

Limitations

The limitations of this report include the lack of surveillance data on high-risk groups, such as MSM and health care workers. Therefore, interpretation of the find-

ings may not be extended to these groups. This report was funded by the Croatian Ministry of Science, Education, and Sport, project N° 216-1080315-0289.

REFERENCES

1. CARDELL K, AKERLIND B, SÄLLBERG M, FRYDEN A, *J Infect Dis*, 198 (2008) 304. — 2. HEPATITIS B VACCINES, Weekly epidemiological record, 79 (2004) 255. — 3. HEPATITIS B VACCINES. Immunization, vaccines and biologicals. WHO. Available from: URL: www.who.int/vaccines.documents. Accessed: February 15, 2009. — 4. LIU CJ, KAO JH, *J Chin Med Assoc*, 70 (2007) 145. — 5. LEHMAN EM, WILSON ML, *Int J Cancer*, 124 (2009) 697. — 6. SZMUNESS W, HARLEY EJ, IKRAN H, ET AL. Sociodemographic aspects of the epidemiology of hepatitis B. (Philadelphia, Franklin Institute Press, 1978). — 7. WORLD HEALTH ORGANIZATION (WHO), Hepatitis B, 2008. Available from: URL: www.who.int/mediacentre/factsheets/fs204/en/print.html. Accessed: February 5, 2009. — 8. CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC). Hepatitis B. In: Epidemiology and prevention of vaccine-preventable diseases. Rev.ed. Atlanta (GA): National Center for Immunization and Respiratory Diseases; 2009. p. 99-122. Available from: URL: www.cdc.gov. Accessed: December 5, 2009. — 9. SORRELL MF, BELONGIA EA, COSTA J, GAREEN IF, GREM JL, INADOMI JM, KERN ER, MCHUGH JA, PETERSEN GM, REIN MF, STRADER DB, TROTTER HT, *Ann Intern Med*, 150 (2009) 110. — 10. PUNGAPONG S, KIM R, POTERUCHA JJ, *Mayo Clin Proc*, 82 (2007) 975. — 11. HOU J, LIU Z, GU F, *Int J Med Sci*, 2 (2005) 57. — 12. LOK AS, HEATHCOTE EJ, HOFFNAGLE JH, *Gastroenterol*, 120 (2001) 1853. — 13. ROBINSON WS. HEPATITIS B VIRUS AND HEPATITIS D VIRUS. Philadelphia: Churchill Livingstone. 2000 (Principles and practice of infectious diseases, 5th ed). — 14. MCMAHON BJ, ALWARD WL, HALL DB, HEYWARD WL, BENDER TR, FRANCIS DP, MAYNARD JE, *J Infect Dis*, 151 (1985) 603. — 15. BEASLEY RP, STEVENS CE, SHIAO IS, MENG HC, *Lancet*, 2 (1975) 741. — 16. CURRY MP, CHOPRA S. ACUTE VIRAL HEPATITIS. In: Mandell GL, Bennet JE, Dolin R, eds. (Elsevier, Churchill Livingstone. 2005). — 17. FUNK ML, ROSENBERG DM, LOK AS, *J Viral Hepat*, 9 (2002) 61. — 18. DIENSTAG JL, ISSELBACHER KJ, (Split, Placebo, 1997). — 19. GROSHEIDE P, VAN DAMME P ON BEHALF OF THE VIRAL HEPATITIS PREVENTION BOARD. Prevention and control of hepatitis B in the community. In: Hallauer J, Kane M, McCloy E, Meheus A, Roure C, eds., Communicable diseases. Series 1 3rd edn. (Viral Hepatitis Prevention Board, University of Antwerp, Wilrijk, Belgium, 1996). — 20. HOFFNAGLE JH, DUSHEIKO GM, SEEFF LB, JONES EA, WAGGONER JG, BALES ZB, *Ann Intern Med*, 84 (1981) 748. — 21. FATTOVICH G, RUGGE M, BROLLO L, PONTISSO P, NOVENTA F, GUIDO M, ALBERTI A, REALDI G, *Hepatol*, 6 (1986) 172. — 22. HUIAY, HUNG LC, TSE PC, LEUNG WK, CHAN PK, CHAN HL, *J Clin Virol*, 33 (2005) 254. — 23. SHAW-STIFFEL TA, Chronic Hepatitis. (Philadelphia, Churchill Livingstone, 2000). — 24. VRHOVAC B, Ed. Acute viral hepatitis (In Croatian). (Zagreb, Naprijed, 1997). — 25. MILAS J, ROPAC D, MULIĆ R, MILAS V, VALEK I, ZORIC I, KOZUL K, *Eur J Epidemiol*, 16 (2000) 208. — 26. WORLD HEALTH ORGANIZATION. HEPATITIS B, 2002. Available from: URL: www.who.int/csr/disease/hepatitis. Accessed: February 17, 2007. — 27. KOZIEL MJ, SIDDIQUI A, Hepatitis B Virus and Delta Virus. (Elsevier, Churchill Livingstone, 2005). — 28. CROATIAN HEALTH SERVICE YEARBOOK.

Diseases, Immunization and Microbiological Diagnosis. (In Croatian). (Zagreb, Croatian National Institute of Public Health, 2012). — 29. BIJELIĆ N, HODŽIĆ A, Research of adolescent sexuality in Croatia (In Croatian), Available from: URL: www.plivazdravlje.hr/?section=sex&cat=y&show=1&id=4535. Accessed: April 14, 2009. — 30. LAW ABOUT CONTROL OF COMMUNICABLE DISEASE. (In Croatian) Official gazette Republic of Croatia, 60/92. Available from: URL: www.nn.hr. Accessed: May 30, 2009. — 31. STEPHENNE J, *Vaccine*, 8 (1990) 56. — 32. DEINSTAG JL, *N Eng J Med*, 359 (2008) 1500. — 33. THE RULEBOOK ON THE METHODS OF IMPLEMENTING IMMUNIZATION, SEROPROPHYLAXIS, CHEMOPROPHYLAXIS AGAINST CONTAGIOUS DISEASES. (In Croatian) Official gazette Republic of Croatia, 23/94. Available from: URL: www.nn.hr. Accessed: May 30, 2009. — 34. THE RULEBOOK ON THE METHODS OF IMPLEMENTING IMMUNIZATION, SEROPROPHYLAXIS, AND CHEMOPROPHYLAXIS AGAINST CONTAGIOUS DISEASES. (In Croatian) Official gazette Republic of Croatia, 103 (2013) 2322. — 35. WHO. IMMUNIZATION AGAINST DISEASES OF PUBLIC HEALTH IMPORTANCE. Available from: URL: www.who.int/mediacentre/factsheets/fs288/en/index.html. Accessed: May 30, 2009. — 36. EUROPEAN CONSENSUS GROUP ON HEPATITIS B IMMUNITY, *Lancet*, 355 (2000) 561. — 37. MULIĆ R, UGLEŠIĆ L, KLIŠMANIĆ Z, ROPAC D, SMOLJANOVIĆ M, MRATINOVIĆ MIKULANDRA J, ALERAJ B, LUČEV O, *Liječ Vjesn*, 128 (2006) 71. — 38. NELSON PK, MATHERS BM, COWIE B, HAGAN H, DES JARLAIS D, HORYNIAK D, DEGENHARDT L, *Lancet*, 378 (2011) 571. — 39. MANDATORY IMMUNIZATION PROGRAMME. (In Croatian) (Republic of Croatia, Ministry of Health, Zagreb, 2007). — 40. MELE A, STROFOLINI T, ZANETTI A, *J Med Virol*, 67 (2002) 443. — 41. LAVANCHY D, *J Viral Hepat*, 11 (2004) 107. — 42. PALMOVIĆ D, PALMOVIĆ CRNJAKOVIĆ J, *Eur J Epidemiol*, 15 (1999) 547. — 43. MULIĆ R, ROPAC D, *Med Jad*, 31 (2001) 70. — 44. ROPAC D, ZORIĆ I, PALMOVIĆ D, MULIĆ R, STAŠEVIĆ I, *Periodicum biologorum*, 103 (2001) 48. — 45. ACT ON BLOOD AND BLOOD PRODUCTS. (In Croatian) Official gazette Republic of Croatia. 79 (2006) 1916. — 46. GRGICEVIĆ D, BALIJA M, PIRC-TILJAK D, MIHALJEVIĆ I, GJENERO-MARGAN I, ZUPANCIĆ-SALEK S, MACEK P, *Croat Med J*, 41 (2000) 196. — 47. BAKLAN Z, GORISEK JR, POLJAK M, PIŠEC A, *Wien Klin Wochenschr*, 116 (2004) 7. — 48. ALTICE FL, BRUCE RD, WALTON MR, BUITRAGO MI, *J Urban Health*, 82 (2005) 161. — 49. TORBENSON M, KANNANGAI R, ASTEMBORSKI J, STRATHDEE SA, VLAHOV D, THOMAS DL, *Hepatology*, 39 (2004) 57. — 50. CROATIAN HEALTH SERVICE YEARBOOK. Croatian Registry of Treated Psychoactive Drug Addicts. (Zagreb, Croatian National Institute of Public Health, 2012). — 51. THE RULEBOOK ON THE METHODS OF IMPLEMENTING IMMUNIZATION, SEROPROPHYLAXIS, CHEMOPROPHYLAXIS AGAINST CONTAGIOUS DISEASES. (In Croatian). Official gazette Republic of Croatia, 62 (1999) 62. Available from: URL: www.nn.hr. Accessed: May 30, 2009. — 52. VAN RIJCKEVORSEL GGC, SONDER GJB, BOVEE LPMJ, THIESBRUMMEL HFJ, GESKUS RB, VAN DEN HOEK A, *Sex Transm Dis*, 35 (2008) 934.

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EPIDEMIOLOŠKE KARAKTERISTIKE HEPATITISA B U HRVATSKOJ: REZULTATI PREVENCIJE

SAŽETAK

Ova studija pokazuje epidemiološke karakteristike te preventivne mjere uključene u prevenciju i kontrolu hepatitis B infekcije u Hrvatskoj. Analizirani su podaci obveznih prijava zaraznih bolesti kao i prijava smrti zbog zaraznih bolesti, trenutno stanje hepatitis B infekcije u Hrvatskoj te anketni podaci prikupljeni iz opće populacije. Prosječna prevalencija ove bolesti kod nas iznosi 3,67 na 100,000 godišnje. Pogođene su sve dobne skupine, uz zamjetno veći broj zahvaćenih u dobnim skupinama od 15-19 te 20-29 godina. Hepatitis B infekcija je 1,4 puta učestalija kod muškaraca. Kroz zadnjih osamnaest godina zabilježena je prosječna smrtnost od 0,2%. Incidencija HbsAg-pozitivnih darovatelja krvi je unutar raspona od 0,65% 1992.godine do 0,012% u 2011. godini. Najveći broj preventivnih mjera protiv hepatitis B infekcije u Hrvatskoj je propisan zakonom. Prijava akutnih i kroničnih nositelja je obvezna. Vakcinacija visoko rizičnih skupina započeta je 1992.godine, dok je obvezna vakcinacija novorođenčadi uvedena u obveznom kalendaru cijepljenja 2007. godine. Obvezno je rutinsko testiranje krvi dobrovoljnih davaoca na prisustvo HbsAg antigena. Zahvaljujući nevladinoj organizaciji 'Pomoć' osnovanoj kao potpora intravenskim ovisnicima a zajedno s programom 'sanacije štete' 1995. godine dolazi do implementacije hepatitis B,C te HIV/AIDS preventijskog programa. Kako bismo bolje razumjeli epidemiološke karakteristike hepatitis B infekcije u Hrvatskoj, potrebna su dodatna istraživanja o specifičnosti i dinamici u malim sredinama, obzirom na različite načine širenja infekcije.