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Original Article

The prevalence and the risk factors for hepatitis C virus infection in Serbia

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Abstract

Introduction: The epidemiological characteristics of the hepatitis C virus (HCV) infection in Republic of Serbia have not been studied sufficiently so far. The aim of this study was to estimate the prevalence of anti-HCV positivity in the general population of Serbia and determine the risk factors for this infection.

Methodology: Estimation of the prevalence was done using the median ratio method with data from several regional countries to a previously determined prevalence of anti-HCV positivity among volunteer blood donors of 0.19%. In order to determine the risk factors a matched case-control study was conducted of 106 subjects with confirmed HCV infection from the Clinic for Infectious and Tropical Diseases, Clinical Center of Serbia and the same number of hospital controls matched by sex and age.

Results: The estimated prevalence of anti-HCV positivity in the general population of Serbia was 1.13% (95% CI: 1.0-1.26%). The most important predictive risk factors of HCV infection were: intravenous drug use (OR = 31.0; 95% CI: 3.7-259.6), blood transfusions (OR = 3.7; 95% CI: 1.6-8.7), invasive dental treatment (OR = 3.1; 95% CI: 1.4-6.8), and low level of education (OR = 2.2; 95% CI:1.1-4.7). A total of 91.5% of the persons with hepatitis C had at least one of the significant risk factors.

Conclusion: The prevalence of anti-HCV positivity ranks Serbia in the range of mid-endemic European countries. Preventive measures should be directed at preventing drug use, on education about getting the infection, creating safe conditions for blood transfusions, and strict adherence to adopted practices in dentistry.

Key words: hepatitis C virus; prevalence; case-control study; risk factors; Serbia.

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Introduction

Hepatitis C virus (HCV) infection is currently one of the most important health problem worldwide. It has been estimated that more than 150 million people throughout the world are positive to antibodies to HCV (anti-HCV), while 71million suffer from it as a chronic infection [1]. Furthermore, HCV is the most frequent cause of chronic hepatitis, with the frequency of 25-50% (depending on the world region), and it is one of the most significant risk factor of hepatocellular carcinoma, found among approximately some 60% of those afflicted by this malignancy [2]. HCV, as the cause of end stage of liver disease (ESLD), is the most frequent cause for liver transplants with approximately of 40% of liver transplant recipients infected by this virus [3].

Considering the spread of the infection and the significance of hepatitis C, for both the afflicted patient and for society on the whole, in 2006 the European Centre for Disease Prevention and Control (ECDC) introduced a system of active HCV infection monitoring. This system envisages the monitoring of the epidemiological characteristics of HCV infection (prevalence, incidence, routes of transmission, assets invested in controlling it, effectiveness of recommended measures, etc.) in the European Economic Community countries (the European Union member states with Norway, Iceland and Lichtenstein).

Unfortunately, Serbia is not included in this program. The main problem is the absence of adequate epidemiological data on the spread of the infection within the general population or on the means of virus transmission. The studies that have been conducted in Serbia so far were mainly focused on persons receiving antiviral treatment or were limited to certain risk groups, such as people who inject drugs (PWID) [4,5].

The aim of this study was to estimate the prevalence of anti-HCV positive persons in the general population of Serbia and to determine the risk factors for the transmission of this infection.

Methodology

A two-part study was conducted in order to find the answers to the aboveepidemiological facts. In the first part of the study the prevalence of anti-HCV positive persons was estimated by using the median ratio method. In the second part risk factors for HCV infection were determined by using the matched case-control study.

Estimation of the prevalence of anti-HCV positive persons in the general population

Estimating the frequency of anti-HCV positive persons among the general population of Serbia was done by using the median ratio method to the determined prevalence of anti-HCV positive persons among voluntary blood donors in the previous part of our research.This part of research was conducted at 10 major transfusion centers in Serbia, thus covering the whole country, during the year 2013. In total a cohort of 27,160 subjects (voluntary blood donors who gave blood for the first time) were included in this research's part. The prevalence rate of anti-HCV positivity was 0.19% (95% CI: 0.14–0.24%) [6].

The prevalence estimation was done using the median ratio method between the anti-HCV positive in the general population and among voluntary blood donors in tenregional countries with available data. The data from regional countries is shown in Table 1 [7-17]. The next step was to determine individually the value of the median of the anti-HCVpositive in the general population and among voluntary blood donors in these countries. Their rationswere applied to the previously determined prevalence of the anti-HCV positive among voluntary blood donors in Serbia, which gave an estimate for the general population.It isexpressed as a value corresponding to the 95% confidence interval (95% CI). This method was used in the investigation by Hope *et al.* for estimating the prevalence of hepatitis B and hepatitis C in the European region [7].

Determining risk factors for HCV infection

A matched case-control study was conducted in order to determine the risk factors for HCV infection. A total of 106 cases and the same number of matched controls were collected from the Clinic for Infectious and Tropical Disease, Clinical Centre of Serbia, during the year 2014. The cases represented persons with HCV infection confirmed in the last five years, who had not therapy initiated yet, nor did have co-infection with other inoculation viruses (HBV, HIV).For each case, hospital control from the same clinic was matched by sex and age (±5 years) from among patients hospitalized during the same period of time for various clinical conditionsexcluding liver disease and HCV infection. All the patients had been explained in detail the aims and purposes of the research, and they agreed to participate in the study as volunteers. All participants in the study provided written informed consent.

All participants confidentially filled in an identical questionnaire on their own. The questionnaires were then assigned sequence numbers at the time of inclusion in the study. A register matching sequence numbers and subjects was kept on a separate form. The questionnaire consists of two parts. The first part contained general demographic questions of the subject, while the second part contained questions about previous exposure and potential risk factors for HCV infection (copies of the questionnaire are available from the authors). The questionnaire was tested previously on 10 persons hospitalized at the Clinic for Infectious and Tropical Diseases, five persons with and five without HCV infection.Suggestions and critiques of these patients were taken into consideration and the questionnaire was modified.Tests of these subjects were not included in the study.

Statistical Analysis

The statistical analysis of the data was descriptive and analytical. An odds ratio (OR) with 95% CI was used to determine the significance of individual HCV

Table 1. Prevalence of anti-HCV antibodies in regional countries with Serbia.

Country	Prevalence among blood donors (%)	Prevalence in general population (%)
Bulgaria	0.9	1.3
Hungary	0.3	0.7
Albania	0.7	3.0
Greece	0.3	1.9
Italy	0.03	2.7
Croatia	0.03	0.9
Romania	0.9	3.2
Slovenia	0.02	1.0
Bosnia and Herzegovina	0.267	1.5
FYROM	0.2	2.0

FYROM: The Former Yugoslav Republic of Macedonia

infection risk factors. The statistical *t*-test, chi-squared test and the Mann-Whitney U test were used to test significantdifference between cases and controls. Multivariate analysis was used to determine the main risk factors for which univariate analysis determinedstatistical significance of p<0.1, by using multiple logistic regression analysis for potential confounding and a definite conclusion. The IBM SPSS software package version 15.0 (SPSS Inc, Chicago, IL, US) was used for statistical analyses of parametric and non-parametric variables. P value <0.05 was considered significant with 95% confidence interval (CI).

Ethical approval for this study was obtained from the Ethics Committee of theMedical Faculty University of Belgrade, number 2013/29/IX-7. All subjects gave written consent for participation in the study.

Results

The estimated prevalence of anti-HCV positive persons in Serbia using the median ratio method was 1.13% (95% CI: 1.0-1.26%).

The basic demographic characteristics of the subjects are shown in Table 2. The subjects were predominantly male (64.2%), with the ration of sexes of 1:1.79. The average age of the subjects with HCV infection was 41.3±11.6 years, with the highest frequency between 25-44 years (67.9%). Both groups of patients were mainly from urban areaswithout difference in frequency (p = 0.091). The control group subjects compared to patients group had higher level of education, there were more of them who graduated from post-secondary educational institutions and universities (p<0.001). A significantly smaller percentage of HCV sufferers were marriedin comparison with control group (45.3% vs. 59.4; p = 0.039).

Results on factors for HCV infection using the univariate analysis are shown in Table3. The following risk factors were independent predictors for acquiring HCV infection: psychoactive substance usein general (OR = 12.2; 95% CI: 4.6-32.6; p < 0.001),receiving transfusion (OR = 4.4; 95% CI: 1.1-5.1; p = 0.019), invasive dental procedures (OR = 2.4; 95% CI: 1.2-4.8; p = 0.012), body piercing (OR = 8.6; 95% CI: 1.9-38.5; p = 0.001), tattooing (OR = 2.4; 95% CI: 1.2-4.8; p = 0.016), prison stay (OR = 4.2; 95% CI: 1.4-13.1; p = 0.008) and sexual relations with persons at risk of HCV infection (OR = 7.4; 95% CI: 3.3-16.9; p < 0.001). Persons who abused psychoactive substancemost often use drugs intravenously. Of these 27,22 (81.5%) stated that they had used drugs in this manner earlier in life, three (11.1%) only tried them, and one each (3.7%) responded that they still usedthem regularly or occasionally. Only one subject from the controls used

Table 2. Demographic characteristicsof the participants in the study.

Variables	Cases (n = 106)	Controls (n = 106)	P value
Gender			
Male	68 (64.2%)	68 (64.2%)	1.00
Female	38 (35.8%)	38 (38%)	
Age categories (years)			
18-24	1 (0.9%)	3 (2.8%)	
25-34	35 (33.0%)	35 (33.0%)	
35-44	37 (34.9%)	33 (31.1%)	0.81
45-54	14 (13.2%)	19 (17.9%)	
55-65	15 (14.2%)	13 (12.3%)	
>65	4 (3.8%)	3 (2.8%)	
Place of residence			
Urban environment	80 (75.7%)	92 (86.8%)	
Suburban areas	16 (15.1%)	10 (9.4%)	0.091
Countryside	10 (9.4%)	4 (3.8%)	
Educacion level			
Primary school (8yrs of education)	16 (15.1%)	6 (5.7%)	
Secondary school (12 yrs of education)	68 (64.2%)	59 (56.6%)	0.017*
High school (15 yrs of education)	8 (7.5%)	17 (16.0%)	
University (>15 yrs of education)	12 (11.3%)	26 (21.7%)	
Marital status			
Not married	38 (35.8%)	33 (31.1%)	
Married	48 (45.3%)	63 (59.4%)	0.029*
Divorced	18 (17%)	6 (5.7%)	
Widowed	2 (1.9%)	4 (3.8%)	

*p < 0.05

Table 3. Independent predictive risk factors for acquiring HCV infection.

Risk factor	Cases (n = 106)	Controls (n = 106)	mOR	95% CI	P value
Drug use (total)	40 (37.7%)	5 (4.7%)	12.24	4.59-32.62	< 0.001*
Intravenous drug use	27 (25.5%)	1 (0.9%)	35.88	4.77-269.7	< 0.001*
Nasal - drug use	13 (12.3%)	4 (3.8%)	3.57	1.12-11.32	< 0.001*
Transfusion	25 (23.6%)	12 (11.3%)	4.418	1.142-5.117	0.019*
Surgical procedures	69 (65.1%)	58 (54.7%)	1.543	0.888-2.683	0.123
Invasive dental procedures	30 (28.3%)	15 (14.2%)	2.395	1.20-4.777	0.012*
Tatooing	28 (26.4%)	14 (13.2%)	2.359	1.161-4.793	0.016*
Body piercing	15 (14.2%)	2 (1.9%)	8.571	1.909-38.49	0.001*
Previous imprisonment	15 (14.2%)	4 (3.8%)	4.203	1.346-13.12	0.008*
Sexual intercourse	105 (99.1%)	103 (97.2%)	3.1	0.3-29.9	0.313
Avoiding condom use	92 (88.5%)	83 (80.6%)	1.8	0.9-4.0	0.117
Sexual intercourse with high-risk partners	40 (37.7%)	8 (7.5%)	7.4	3.3-16.9	< 0.001*
Anal sexual intercourse	17 (16.3%)	12 (11.8%)	1.5	0.7-3.3	0.345

mOR: matched odds ratio (age and gender); CI: confidence interval; *p < 0.05.

drugs intravenously, and only tried it at that, while the remainder administered them nasally. Of the subjects with HCV infection with this risk, 10 (37%) stated that they shared needles.

Recipients of blood and blood derivatives had 4.4 more times for HCV infection. Considering the year when the transfusion was received, most of the persons with HCV infection (76%) received transfusions before 1994. The majority of both groups received only one transfusion, and regardless of their numbers significance was not found.

Surgical treatmentwas not predictor for HCV infection, opposite to invasive dental procedures (apicoectomy, curettage, root canal work), regardless of their numbers.

Tattooing and body piercing also showed significance for HCV infection (p = 0.016 and p = 0.001, respectively).No significance was found in the frequency of these practice.

HCV infected persons had stayed in prison significantly more often than controls (p = 0.008). None of the subjects was incarcerated more than once. The length of prison stay was an average of 24 months for HCV infected persons and 2.25 months for the controls, which was statistically significant (p = 0.045).

Sexual relations were not significant as a predictive factor for HCV infection (p = 0.313). However, persons with HCV had a statistically higher number of sex partners than the controls (9 vs.4 partners; p = 0.024), and they had sexual encounters more frequently with persons at risk of HCV infection (p < 0.001). Only three subjects from both groups stated that they had engaged in same sex acts.

Similar to same sex acts, acupuncture, circumcision, living with persons having hepatitis C and professional exposure to blood could not be properly analyzed considering the small number of subjects who gave affirmative responses to these risks.

Significant factors brought into correlation with HCV infection at the p<0.1 levelusing univariate statistical tests were submitted to multivariate logistic regression analysis. Independent risk factors that remained statistically significant were: intravenousdruguse (OR = 31.0; 95% CI:3.7-259.6; p = 0.002), blood transfusions (OR = 3.7; 95% CI:1.6-8.7; p = 0.002), invasive dental treatment (OR = 3.1; 95%

Table 4. Multivariate analysis using logistic regression of risk factors for HCV infection.

Risk factor	Mutivariate analysis		
	OR	95% CI	P value
Marital status	1.06	0.53-2.13	0.854
Education level**	2.23	1.07-4.67	0.033*
Injection-drug use	31.0	3.71-259.6	0.002*
Nasal-drug use	3.92	0.94-16.38	0.061
Transfusion	3.75	1.62-8.69	0.002*
Invasive dental procedures	3.06	1.38-6.79	0.006*
Tatooing	1.18	0.42-3.30	0.752
Body piercing	5.70	0.98-32.9	0.052
Sexual activity with high-risk partners	1.23	0.85-1.78	0.267
Previous imprisonment	2.11	0.50-8.87	0.306

OR: odds ratio; CI: confidence interval; *p < 0.05; **Primary and secondary schools *vs.* high school and university.

CI:1.4-6.8; p = 0.006) and a low level of education, either elementary or secondary versus post-secondary and university education (OR = 2.2; 95% CI:1.1-4.7; p = 0.033) (Table 4).

Finally, out of 106 subjects with HCV infection, 97 of them (91.5%) replied affirmatively to at least one statistically significant risk factor of HCV infection. Additional investigationsestablished that 42 subjects (39.6%) knew exactly the time when they were infected.

Discussion

The prevalence of anti-HCV positive persons in the general population of Serbia is estimated on average 1.13% (from 1.0% - 1.26%). This places Serbia in the group of mid-endemic European countries with a rate of HCV infection of around 1.5%, together with Ireland, Poland, Slovakia, Belarus, and Belgium. Lower prevalence (around 0.5%) is found in the developed countries of northern and central Europe (The Netherlands, Denmark, Great Britain, Czech Republic, France, Germany). A higher prevalence about 2% is found in the southern and eastern countries in Europe (Italy, Spain, Portugal, Lithuania and Latvia). According to data, the highest prevalence of anti-HCV positive persons in Europe was reported from Ukraine, Russia and Moldova (around 4%) [12].

Among regional countries with Serbia, the estimated prevalence of anti- HCV positive persons in the general population is similar to that in Croatia, Slovenia and Bulgaria (around 1%), while ishigher than in Hungary (0,7%) [9,10,14,16]. However, a higher prevalence in the general population has been registered in Bosnia and Herzegovina, Macedonia and Greece (from 1.5% to 2%), as well as in Albania and Romania (around 3%) [11,12,15-17].

In our studythe majority of HCV infected persons are men aged 24-45 years. Domination of maleswas also registered in most other countries, although there are countries where the ratio of the sexes is similar, such as in Mexico and Mongolia. It has been assumed that the greater ratio of infected males can be attributed to their more frequent exposure to infection risk factors of blood borne diseases in generally. Additionally, the study conducted in Serbia in 2009, it was also shown that drug use was more frequent in males, as the most important mode of HCV transmission [18]. The majority infected with HCV live in urban areas (75%), which is in accordance with other reports. It is assumed that the reason for the greater incidence of infected persons in urban areas is related to better testing capabilities than in other environments [19]. Furthermore, it is possible that urban populations are more exposed to behavior of greater risk than those in rural areas. Considering family relationship status as risk factor, HCV infected persons tend to be married less often than controls. We assumed that this difference most probably can be attributed to greater levels of promiscuous behavior among persons living the single lifestyle, engaging in same sex encounters or experiencing other forms of risky behavior.

In addition, HCV infected persons have in general lower level of education than the controls, so we can accept that education level is an independent risk factor of HCV infection. Other researchers obtained similar results. This may be explained by the fact that lower socio-economic status correlates to more frequent abuse of drugs and failure to follow advice on the use of disposable sterile syringes and needles [20]. It may be possible that persons with low education are less informed about viruses, blood borne diseases and how they are transmitted.

Multivariate analysis in our study shows that the greatest risk of HCV is intravenous drug abuse (IVDU). These persons have 30-fold greater chance of HCV infection. Nowadays, in other countries as well, this is the most significant route of HCV transmission. In European countries the percentage of infected persons among IVDU-s varies from 50% (in Cyprus) to around 80% as registered in Germany, Netherlands, Sweden, Portugal and Eastern European countries [21,22]. The study of this population in Serbia conducted in 2005 in Belgrade, the main and largest city in Serbia, showed that the percentage of anti-HCV positive among PWID was 63% [4]. Unfortunately, there is no information for other parts of the country. In our study among total number PWID, only 37% stated that they had shared needles. Such a low percentage was unexpected. For example, the study conducted in Scotland showed that 79.4% of HCV infected persons shared syringes and needles or other implements (containers, filters, water) during the preceding six months [23]. The lower percentage we found was perhaps the result of the insincerity of the subjects and their desire to hide that they belong to such a part of society.

Transfusions of blood and blood derivatives are also predictors for HCV infection, particularly for recipients before 1994. This is the year when Serbia introduced systematic testing for HCV of all voluntary blood donors. Furthermore, before the 1990s transfusions were the main route route of HCV transmission and this was a very easy route for transmission of the disease. Interestingly, one study from 1995 showed that 81% of blood recipients

acquired HCV after receiving blood from a person who was anti-HCV positive [24]. Nowadays some developed countries are using tests that directly detect viral RNA in the blood of donors, whereby this risk is reduced to a minimum (approximately 1 per 1,000,000 units of blood) [25]. Unfortunately, due to the high costs of these tests, only third generation serological ELISA test is still in use in transfusion centers in Serbia. We must remind that these tests detect the immune response, the production of HCV antibodies, considering the impossibility of recognition the window period from the moment of infection to appearance of detectable levels of antibodies.

Furthermore, we have found that an invasive dental treatment is a risk factor for HCV infection in Serbia. Also persons who have had any of these interventions have a three times higher risk for it. The presence of HCV in oral fluids may be of importance for virus transmission. As a result, dentists are in professional risk group for HCV infection [26]. They can also transmit HCV to their patients if they do not adhere to infection control measures and practices. Previous studies showed that the risk of HCV infection was increased with invasive dental treatment, such as apicoectomy, oral surgery and root canal treatment [27]. Contrary to this, studies on pediatric population failed to identify dental treatment as a risk factor of hepatitis C. Regardless of these different findings, it is generally accepted that HBV and HCV transmission during dental treatment is possible, from patient to patient, from dentist to patient and from patient to dentist, and great attention must be directed at its prevention. Prevention measures include the use of disposable instruments wherever possible, proper sterilization and strict adherence to the principles of asepsis, wearing gloves and other protective gear during all dental interventions [28].

Finally, of the 106 persons with HCV infection who took part in the study, 91.5% replied affirmatively to at least one of the identified risk factors of HCV infection. This result confirms the assumption of Alter that careful questioning of patients with hepatitis C could reduce the percentage of those for whom the route of transmission cannot be determined down to only 10% [29].

We accept the potential limitations of our study, and we have tried to minimize them. It is possible that estimated prevalence could differ from its actual value. However, in conditions in which it is not easy to conduct a population-based study that requires major funding, which have been conducted in only a handful of the most affluent countries, the ratio estimation method can be used cautiously to estimate the prevalence. This method was successfully used to determine the prevalence of HCV in the general population by researchers from England and WHO [7]. Other limitations pertain to potential recall bias. It may be expected that no one forgets using drugs or receiving a transfusion, but it is possible to mistake the correct time frame. To try to overcome this we included in the study those persons who learned of their HCV infection in the past five years. It is also impossible to overlook the fact that some respondents did not sincerely answer sensitive and delicate questions from the questionnaire that pertain to possible routes of transmission. We attempted to avoid this by guaranteeing anonymity -the respondents filled out the questionnaires on their own and in confidentiality and questionnaires were only marked with a number without any particulars of the respondent. Also, it is possible to take into consideration information bias since the respondents knew their HCV status. To reduce this bias authors provided detailed explanations to the respondents on the importance of the study and their answers, there were no deadlines for filling out the questionnaires, and standard questions and answers were used. Regardless of these limitations, we tried to reduce them as much as possible, and we believethat none of them jeopardize the validity of the study.

Conclusion

This is the first study that thoroughly deals with the epidemiological characteristics of the HCV infection in Serbia. It is established that Serbia belongs to the group of mid-endemic European countries on the prevalence of HCV infection, with intravenous drug use carrying the highest risk for this infection. Also transfusions of blood and blood derivatives continue to pose a real risks of this infection in Serbia. More attention should be paid to adhering to recommended practices for preventing blood borne diseases in dentistry, and in education on improving attitudes about HCV risk reduction. Determining these data is important step for the inclusion of Serbia in the system of monitoring HCV infection in Europe, for planning the costs of the health service and preventive measures. Considering limitations that cannot be overcome regardless of the invested effort, this reportcould serve as the initial premise for future targeted studies of the epidemiological characteristics of this important infection.

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References

1. World Health Organization (2017) Hepatitis C. Fact sheet. Available: http://www.who.int/mediacentre/factsheets/fs164/en/. Accessed 20 December2017.
2. Castello G, Scala S, Palmieri G, Curley SA, Izzo F (2010) HCV-related hepatocellular carcinoma: from chronic inflammation to cancer. Clin Immunol 134:237-250.
3. Verna EC, Brown RS Jr (2006) Hepatitis C virus and liver transplantation. Clin Liver Dis 10:919-940.
4. Judd A, Rhodes T, Johnston LG, Platt L, Andjelkovic V, Simic D, Mugosa B, Simic M, Zerjav S, Parry RP, Parry JV (2009) Improving survey methods in sero-epidemiological studies of injecting drug users: a case example of two cross sectional surveys in Serbia and Montenegro. BMC Infect Dis9:14.
5. Delic D, Mitrovic N, Popovic N, Urosevic A, Pesic I, Simonovic J (2012) Antiviral/immunomodulatory combination therapy: pegylated interferon alpha 2a and ribavirin in patients with chronic hepatitis C virus infection. Srp Arh Celok Lek 140:612-618.
6. Mitrovic N, Delic D, Markovic-Denic LJ, Jovicic M, Popovic N, Bojovic K, Simonovic Babic J, Svirtlih N (2015) Seroprevalence and risk factors for hepatitis C virus infection among blood donors in Serbia: A multicentre study. Dig Liver Dis 47:572–576.
7. Hope VD, Eramova I, Capurro D, Donoghoe MC (2014) Prevalence and estimation of hepatitis B and C infections in the WHO European Region: a review of data focusing on the countries outside the European Union and the European Free Trade Association. Epidemiol Infect142:270-286.
8. van der Poel CL, Janssen MP, Borkent-Raven B (2011) The collection, testing and use of blood and blood products in Europe. Nancy: Bialec 57 p.
9. Atanasova MV, Haydouchka IA, Zlatev SP, Stoilova YD, Iliev YT, Mateva NG (2004) Prevalence of antibodies against hepatitis C virus and hepatitis B coinfection in healthy population in Bulgaria. A seroepidemiological study. Minerva Gastroenterol Dietol 50:89-96.
10. European Centre for Disease Prevention and Control (2010) Surveillance and prevention of hepatitis B and C in Europe. Stockholm: ECDC. 145 p.
11. Schinaia N, Kodra Y, Sarmati L, Andreoni M, Bino S, Qyra S, Rezza G (2004) Prevalence of HHV-8 infection in Albanian adults and association with HBV and HCV. Eur J Epidemiol 19:467-469.
12. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H (2014) Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 61 Suppl 1:45-57.
13. Ansaldi F, Bruzzone B, Salmaso S, Rota MC, Durando P, Gasparini R, Icardi G (2005) Different seroprevalence and molecular epidemiology patterns of hepatitis C virus infection in Italy. J Med Virol 76:327-332.
14. Vilibic-Cavlek T, Kucinar J, Kaic B, Vilibic M, Pandak N, Barbic L,Stevanovic V, Vranes J (2015) Epidemiology of hepatitis C in Croatia in the European context. World J Gastroenterol 21:9476-9493.
15. Gheorghe L, Csiki IE, Iacob S, Gheorghe C, Smira G, Regep L (2010) The prevalence and risk factors of hepatitis C virus infection in adult population in Romania: a nationwide survey 2006-2008. J Gastrointestin Liver Dis19:373-379.
16. Esteban JI, Sauleda S, Quer J (2008) The changing epidemiology of hepatitis C virus infection in Europe. J Hepatol 48:148-162.
17. Petrovic J, Salkic NN, Ahmetagic S, Stojic V, Mott-Divkovic S (2011) Prevalence of chronic hepatitis B and hepatitis C among first time blood donors in Northeast Bosnia and Herzegovina: an estimate of prevalence in general population. Hepat Mon 11:629-633.
18. European Monitoring Centre for Drugs and Drug Addiction-EMCDDA (2009) Serbia Country Overview 2009. Luxembourg: Publications Office of the European Union. Available http://www.emcdda.europa.eu/attachements.cfm/att_100294_EN_CO_Serbia.pdf.Accessed 15 July 2017.
19. Monnet E, Collin-Naudet E, Bresson-Hadni S,Minello A, Di Martino V, Carel D, Jooste V, Gagnaire A, Evrard P, Obert-Clerc B, Miguet JP, Hillon P (2006) Place of residence and distance to medical care influence the diagnosis of hepatitis C: a population-based study. J Hepatol 44:499-506.
20. Brandão AB, Fuchs SC (2002) Risk factors for hepatitis C virus infection among blood donors in southern Brazil: a case-control study. BMC Gastroenterol2:18.
21. Demetriou VL, van de Vijver DA, Hezka J, Kostrikis LG (2010) Hepatitis C infection among intra-venous drug users attending therapy programs in Cyprus. J Med Virol 82:263–270.
22. Nelson P, Mathers B, Cowie B, Hagan H, Des Jarlais D, Horyniak D, Degenhardt L (2011) The epidemiology of viral hepatitis among people who inject drugs: results of global systematic reviews. Lancet 378:571–583.
23. Palmateer N, Hutchinson S, McAllister G, Munro A, Cameron S, Goldberg D,Taylor A (2014) Risk of transmission associated with sharing drug injecting paraphernalia: analysis of recent hepatitis C virus (HCV) infection using cross-sectional survey data. J Viral Hepat 21:25-32.
24. Vrielink H, van der Poel CL, Reesink HW, Zaaijer HL, Scholten E, Kremer LC,Cuypers HT, Lelie PN, van Oers MH (1995) Look-back study of infectivity of anti-HCV ELISA-positive blood components. Lancet 345:95-96.
25. Marwaha N, Sachdev S (2014) Current testing strategies for hepatitis C virus infection in blood donors and the way forward. World J Gastroenterol 20:2948–2954.
26. Mahboobi N, Porter SR, Karayiannis P, Alavian SM (2012) Oral fluid and hepatitis A, B and C: a literature review. J Oral Pathol Med 41:505-516.
27. Trasancos CC, Kainer MA, Desmond PV, Kelly H (2001) Investigation of potential iatrogenic transmission of hepatitis C in Victoria, Australia. Aust N Z J Public Health 25:241-244.
28. Mahboobi N, Porter SR, Karayiannis P, Alavian SM (2013) Dental treatment as a risk factor for hepatitis B and C viral infection. A review of the recent literature. J Gastrointestin Liver Dis 22:79-86.
29. Alter MJ (2002) Prevention of spread of hepatitis C. Hepatology 36 Suppl 1:93–98.

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