VHPB MULTI-COUNTRY MEETING

Elimination of viral hepatitis in the
Balkan countries

Lessons learnt and the way forward

Background document

27-28 October 2022

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VHPB Secretariat
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MEETING OBJECTIVES

• provide an overview of the current viral hepatitis situation in the countries: surveillance systems, epidemiology, screening, burden, prevention, treatment and the cascade of care
• discuss achievements and challenges in the prevention and control of viral hepatitis, the possible implementation of new prevention strategies, control measures and monitoring system in the countries
• discuss the development and the implementation of a national hepatitis plans
• assess the needs to achieve the goal of eliminating viral hepatitis as a major public health threat by 2030 as set out in the renewed WHO Global Strategy and WHO Europe Action Plan, building on the UN Sustainable Development Goals’ (SDG) commitments
• discuss successes, issues and barriers to overcome and the way forward.

PARTICIPANTS (± 50)

• Viral Hepatitis representatives in first instance, opinion leaders, representatives of the ministers of health, policymakers, public health and health care professionals, responsible for national hepatitis plan, civil society of the different Balkan countries
• VHPB advisors
• Some selected observers

INTENDED IMPACT
Putting Prevention and control of viral hepatitis on the national public health agendas, list the most important challenges, opportunities, best practices and the way forward to eliminate viral hepatitis in the Balkan by 2030.

VENUE AND OUTLINE OF THE MEETING
Limak Hotel Skopje

Str. Jordan Mijalkov No.31 Skopje 1000

Republic of Macedonia
NOTE: This pre-meeting document contains general background information on the topic(s) of the VHPB meeting. It contains a list of selected abstracts/references from a Pubmed MEDLINE search of July-August 2022 on different search terms depending on the topics discussed in the session of the meeting.

The references are sorted by publication year (most recent first). This document should guide you in the preparation of the meeting, it should not be considered as complete literature review, but hopefully, it will give an overview of what has been published on the topics of the meeting.
LITERATURE REVIEW

General information

There is no universal agreement on what constitutes the Balkans. However, the following are usually included: Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Kosovo, Montenegro, North Macedonia, Romania, Serbia, and Slovenia. Portions of Greece and Turkey are also within the Balkan Peninsula. Balkans | Definition, Map, Countries, & Facts | Britannica

 Entirely within the Balkan Peninsula:

- **Albania**: 28,749 km² (100% of total land)
- **Bosnia and Herzegovina**: 51,180 km² (100%)
- **Bulgaria**: 110,993.6 km²⁴⁷⁴⁸ (100%); according to another source, 110,372 km²³⁹ (100%)
- **Kosovo**: 10,908 km² (100%)
- **Montenegro**: 13,810 km² (100%)
- **North Macedonia**: 25,713 km² (100%)

 Mostly within the Balkan Peninsula:

- **Greece (mainland)**: 110,496 km² (83.7%); according to another source, 106,247 km² (80.5%); including islands adjacent to the Balkan Peninsula, 126,023 km² (95.5%)
- **Serbia (Central Serbia)**: 51,000 km² (65.8%)

 Partly within the Balkan Peninsula:

- **Croatia (southern mainland)**: 24,013 km² (42.4%)
- **Slovenia (south-western part)**: 5,000 km² (24.7%)
- **Romania (Northern Dobruja)**: 11,000 km² (4.6%)
- **Turkey (East Thrace)**: 23,764 km² (3%)
- **Italy (Monfalcone and Trieste)**: 200 km² (0.1%)
In 2016, the WHO announced a plan to eliminate viral hepatitis as a public health threat by 2030. In this narrative review, experts from Bulgaria, Croatia, the Czech Republic, Hungary, Latvia, Lithuania, Poland and Slovakia assessed the feasibility of achieving the WHO 2030 target for HCV infections in Central Europe. They focused mainly on HCV micro-elimination in prisons, where the highest incidence of HCV infections is usually observed, and the impact of the COVID-19 pandemic on the detection and treatment of HCV infections. According to the presented estimates, almost 400,000 people remain infected with HCV in the analyzed countries. Interferon-free therapies are available ad libitum, but the number of patients treated annually in the last two years has halved compared to 2017-2019, mainly due to the COVID-19 pandemic. None of the countries analyzed had implemented a national HCV screening program or a prison screening program. The main reason is a lack of will at governmental and prison levels. None of the countries analyzed see any chance of meeting the WHO targets for removing viral hepatitis from the public threat list by 2030, unless barriers such as a lack of political will and a lack of screening programs are removed quickly.


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BACKGROUND: Harm reduction (HR) interventions are essential to reduce human immunodeficiency virus (HIV) and hepatitis C virus (HCV) transmission in people who inject drugs (PWID). Preliminary testing of the Individually Tailored Support and Education for Safer Injection (ITSESI) evidence-based educational intervention for PWID was performed in France in 2011. We created the Eurosider project to implement and evaluate ITSESI at a wider European level, with a view to its future pan-European diffusion. METHODS: We performed a mixed-methods study involving quantitative (a 6-month before-after study with PWID) and qualitative (focus groups with field workers) components. The study was conducted in 2018-2019 with 307 eligible PWID participating in four existing HR programmes in Bulgaria, Greece, Portugal, and Romania. ITSESI consists in trained field workers observing PWID injection practices and providing an educational exchange. For the present study, PWID participants were allocated to either the control group (i.e., they continued receiving only the current HR services) or the intervention group (i.e., current HR services plus ITSESI). We used the RE-AIM QuEST framework to assess the effectiveness of ITSESI and its acceptability by field workers. Effectiveness was defined as a reduction in both syringe sharing - the highest HIV/HCV transmission risk practice - and in cutaneous abscesses. We used a multivariable mixed logit model to analyse both effectiveness outcomes and to provide adjusted odds ratios (aOR) and 95% confidence intervals (CI). Field workers’ acceptability of the intervention was described using a thematic analysis of the qualitative data. RESULTS: Of the 307 PWID, 55% received ITSESI. Syringe sharing and cutaneous abscesses decreased during follow-up in the intervention group (from 25 to 16% and from 27 to 14%, respectively). Reductions were smaller in the control group (from 29 to 24% and from 23 to 18%, respectively). The multivariable analyses confirmed the effect of the intervention on both of these outcomes (aOR [95% CI]: 0.38 [0.17, 0.85]) and (aOR [95% CI]: 0.38 [0.16, 0.90], respectively). Our qualitative data on acceptability showed the feasibility of involving field workers as proactive research partners in making ITSESI more accessible and acceptable across Europe. CONCLUSIONS: We demonstrated both the effectiveness of ITSESI in reducing syringe sharing and cutaneous abscesses in four European countries, and a high level of intervention acceptability by field workers. Our findings provide important insights into how ITSESI can be adapted for pan-European implementation.


Background: A robust estimate of the number of people with chronic hepatitis C virus (HCV) infection is essential for an appropriate public health response and for monitoring progress toward the WHO goal of eliminating viral hepatitis. Existing HCV prevalence studies in the European Union (EU)/European Economic Area (EEA) countries are heterogeneous and often of poor quality due to non-probability based sampling methods, small sample sizes and lack of standardization, leading to poor national representativeness. This project aimed to develop and pilot standardized protocols for undertaking nationally representative HCV prevalence surveys in the general adult population. Methods: From 2016 to 2019 a team from the Robert Koch-Institute contracted by the European Centre for Disease Prevention and Control synthesized evidence on existing HCV prevalence surveys and survey methodology and drafted a protocol. The methodological elements of the protocol were piloted and evaluated in Bulgaria, Finland and Italy, and lessons learnt from the pilots were integrated in the final protocol. An international multidisciplinary expert group was consulted regularly. Results: The protocol includes three alternative study approaches: a stand-alone survey; a “nested” survey within an existing health survey; and a
retrospective testing survey approach. A decision algorithm advising which approach to use was developed. The protocol was piloted and finalized covering minimum and gold standards for all steps to be implemented from sampling, data protection and ethical issues, recruitment, specimen collection and laboratory testing options, staff training, data management and analysis and budget considerations. Through piloting, the survey approaches were effectively implemented to produce HCV prevalence estimates and the pilots highlighted the strengths and limitations of each approach and key lessons learnt were used to improve the protocol. Conclusions: An evidence-based protocol for undertaking HCV prevalence serosurveys in the general population reflecting the different needs, resources and epidemiological situations has been developed, effectively implemented and refined through piloting. This technical guidance supports EU/EEA countries in their efforts to estimate their national hepatitis C burden as part of monitoring progress toward the elimination targets.


AIM OF THE STUDY: To collect and analyse data obtained from HCV opinion leaders/experts from central European countries, on factors which can affect the WHO target of HCV elimination by 2030. MATERIAL AND METHODS: Data were collected from opinion leaders/experts involved in management of HCV infections in Central European countries which participated in 9th Conference of the Central European Hepatologic Collaboration (Warsaw, 10-11 October 2019). A dedicated questionnaire collected current information related to HCV elimination in Bulgaria, Croatia, the Czech Republic, Hungary, Latvia, Lithuania, Poland and Slovakia. RESULTS: The HCV prevalence rate in particular countries varied from 0.2% to 1.7%. In most central European countries all the HCV infected population is eligible for reimbursement of treatment. However, in some countries there are still some limitations related to the stage of the disease and people who inject drugs. All countries have access to at least one pangenotypic regimen. The most common barrier to HCV elimination in all countries is insufficient political will to establish priority for HCV. None of the reporting countries has established a national screening programme. CONCLUSIONS: Access to therapy for HCV is similar and the majority of patients in Central Europe can be treated according to the current guidelines. Unfortunately there are still some limitations and a lack of political will to implement national screening programmes. According to collected data HCV elimination will not be possible in the region by 2030.


BACKGROUND: New hepatitis C virus (HCV) treatments spurred the World Health Organization (WHO) in 2016 to adopt a strategy to eliminate HCV as a public health threat by 2030. To achieve this, key policies must be implemented. In the absence of monitoring mechanisms, this study aims to assess the extent of policy implementation from the perspective of liver patient groups. METHODS: Thirty liver patient organisations, each representing a country, were surveyed in October 2018 to assess implementation of HCV policies in practice. Respondents received two sets of questions based on: 1) WHO recommendations; and 2) validated data sources verifying an existing policy in their country. Academic experts selected key variables from each set for inclusion into policy scores. The similarity scores were calculated for each set with a multiple joint correspondence analysis. Proxy reference countries were included as the baseline to contextualize results. We extracted scores for each country and standardized them from 0 to 10 (best). RESULTS: Twenty-five countries responded. For the score based on WHO recommendations, Bulgaria had the lowest score whereas five countries (Cyprus, Netherlands, Portugal, Slovenia, and Sweden) had the highest scores. For the verified policy score, a two-dimensional solution was identified; first dimension scores pertained to whether verified policies were in place and second dimension scores pertained to the proportion of verified policies in-place that were implemented. Spain, UK, and Sweden had high scores for both dimensions. CONCLUSIONS: Patient groups reported that the European region is not on track to meet WHO 2030 HCV goals. More action should be taken to implement and monitor HCV policies.

AIM: This systematic review and meta-analysis characterizes the prevalence of hepatitis C virus (HCV) infection among intravenous drug users (IDUs) in upper middle-income countries. METHODS: Five databases were searched from 1990-2016 for studies that took place in countries with a GDP per capita of $7,000 to $13,000 USD. The data extraction was performed based on information regarding prevalence, sample size, age of participants, duration of intravenous drug use (IDU), recruitment location, dates of data collection, study design, sampling scheme, type of tests used in identifying antibody reactivity to HCV, and the use of confirmatory tests. The synthesis was performed with a random effects model. The Cochrane statistical Q-test was used to evaluate the statistical heterogeneity of the results. RESULTS: The 33 studies included in the analysis correspond to a sample of seven countries and 23,342 observations. The point prevalence value estimates and confidence intervals of the random effects model were 0.729 and 0.644-0.800, respectively for all seven countries, and were greatest for China (0.633; 0.522-0.732) as compared to Brazil (0.396; 0.249-0.564). Prevalence for Montenegro (0.416; 0.237-0.621) and Malaysia (0.475; 0.177-0.792) appear to be intermediate. Mexico (0.960) and Mauritania (0.973) had only one study with the largest prevalence. A clear association was not observed between age or duration of IDU and prevalence of HCV, but the data from some groups may indicate a possible relationship. The measures of heterogeneity (Q and I²) suggest a high level of heterogeneity in studies conducted at the country level and by groups of countries. CONCLUSIONS: In this systematic review and meta-analysis, we found that the pooled prevalence of HCV was high (0.729) among a group of seven upper middle income countries. However, there was significant variation in the prevalence of HCV observed in China (0.633) and Brazil (0.396).


The significance of hepatitis E virus (HEV) as an important public health problem is rising. Until a decade ago, cases of HEV infection in Europe were mainly confined to returning travelers, but nowadays, hepatitis E represents an emerging zoonotic infection in many European countries. The aim of this manuscript is to perform a systematic review of the published literature on hepatitis E distribution in humans, animals and environmental samples ("One Health" concept) in the South-Eastern European countries. Comparison of the available data showed that the anti-HEV seroprevalence in the South-Eastern Europe varies greatly, depending on the population studied, geographical area and methods used. The IgG seroprevalence rates in different population groups were found to be 1.1%-24.5% in Croatia, up to 20.9% in Bulgaria, 5.9%-17.1% in Romania, 15% in Serbia, up to 9.7% in Greece and 2%-9.7% in Albania. Among possible risk factors, older age was the most significant predictor for HEV seropositivity in most studies. Higher seroprevalence rates were found in animals. HEV IgG antibodies in domestic pigs were detected in 20%-54.5%, 29.2%-50%, 38.94%-50% and 31.1%-91.7% in Serbia, Bulgaria, Romania and Croatia, respectively. In wild boars seroprevalence rates were up to 10.3%, 30.3% and 31.1% in Romania, Slovenia and Croatia, respectively. A high HEV RNA prevalence in wild boars in some countries (Croatia and Romania) indicated that wild boars may have a key role in the HEV epidemiology. There are very few data on HEV prevalence in environmental samples. HEV RNA was detected in 3.3% and 16.7% surface waters in Slovenia and Serbia, respectively. There is no evidence of HEV RNA in sewage systems in this region. The available data on genetic characterization show that human, animal and environmental HEV strains mainly belong to the genotype 3.


BACKGROUND: Hepatitis C virus (HCV) infection is a global health problem especially for its increasing level of mortality. Detailed knowledge of HCV genotypes prevalence has clinical relevance since the efficacy of therapies is impacted by genotypes and subtypes distribution. Moreover, HCV exhibits a great genetic variability regionally. To date, there are no published studies assessing HCV genotypes distribution in specific countries of the Mediterranean basin. The aim of this study was to review data published from 2000 to 2017 with the purpose to estimate genotypes distribution of HCV infection in nine European countries all located in the Mediterranean basin. METHODS: A systematic research of peer-reviewed journals indexed in PubMed, Scopus, and EMBASE databases selected if containing data regarding distribution of HCV genotypes in nine selected European countries (Albania, Bosnia, Croatia, France, Greece, Italy, Montenegro, Slovenia, and Spain) was performed. RESULTS: Genotype 1 is the most common (61.0%), ranging from 80.0% in Croatia to 46.0% in Greece, followed by genotype 3 (20.0%),
Factors influencing the morbidity and mortality associated with viremic hepatitis C virus (HCV) infection vary from 38.0% in Slovenia to 7.0% and 8.0%, respectively, in Italy and in Albania and by genotype 4 (10.0%) that shows an increase of 1.1% with respect to data obtained till 2014 probably due to the increasing migrants arrivals to Southern Europe. G2, the fourth most frequent genotype (8.5%), particularly common in Italy (27.0%) and Albania (18.0%) might be probably introduced in Southern Italy as a result of Albanian campaign during Second World War and more and more increased by the migration flows from Albania to Italy in the 90s. CONCLUSION: Epidemiology of HCV infection shows a high variability across the European countries that border the Mediterranean Sea. HCV genotyping is a relevant tool to monitor the dynamic process influenced by both evolving transmission trends and new migration flows on HCV scenario.


BACKGROUND: Treatment with direct acting antiviral agents (DAAs) has provided sustained virological response rates in >95% of patients with chronic hepatitis C virus (HCV) infection. However treatment is costly and market access, reimbursement and governmental restrictions differ among countries. We aimed to analyze these differences among European and Eurasian countries. METHODS: A survey including 20-item questionnaire was sent to experts in viral hepatitis. Countries were evaluated according to their income categories by the World Bank stratification. RESULTS: Experts from 26 countries responded to the survey. As of May 2016, HCV prevalence was reported as low (≤1%) in Croatia, Czech Republic, Denmark, France, Germany, Hungary, the Netherlands, Portugal, Slovenia, Spain, Sweden, UK; intermediate (1-4%) in Azerbaijan, Bosnia and Herzegovina, Italy, Kosovo, Greece, Kazakhstan, Romania, Russia, Serbia and high in Georgia (6.7%). All countries had national guidelines except Albania, Kosovo, Serbia, Tunisia, and UK. Transient elastography was available in all countries, but reimbursed in 61%. HCV-RNA was reimbursed in 81%. PegIFN/RBV was reimbursed in 54% of the countries. No DAAs were available in four countries: Kazakhstan, Kosovo, Serbia, and Tunisia. In others, at least one DAA combination with either PegIFN/RBV or another DAA was available. In Germany and the Netherlands all DAAs were reimbursed without restrictions: Sofosbuvir and sofosbuvir/ledipasvir were free of charge in Georgia. CONCLUSION: Prevalence of HCV is relatively higher in lower-middle and upper-middle income countries. DAAs are not available or reimbursed in many Eurasia and European countries. Effective screening and access to care are essential for reducing liver-related morbidity and mortality.


Factors influencing the morbidity and mortality associated with viremic hepatitis C virus (HCV) infection change over time and place, making it difficult to compare reported estimates. Models were developed for 17 countries (Bahrain, Bulgaria, Cameroon, Colombia, Croatia, Dominican Republic, Ethiopia, Ghana, Hong Kong, Jordan, Kazakhstan, Malaysia, Morocco, Nigeria, Qatar and Taiwan) to quantify and characterize the viremic population as well as forecast the changes in the infected population and the corresponding disease burden from 2015 to 2030. Model inputs were agreed upon through expert consensus, and a standardized methodology was followed to allow for comparison across countries. The virologic prevalence is expected to remain constant or decline in all but four countries (Ethiopia, Ghana, Jordan, and Oman); however, HCV-related morbidity and mortality will increase in all countries except Qatar and Taiwan. In Qatar, the high-treatment rate will contribute to a reduction in total cases and HCV-
related morbidity by 2030. In the remaining countries, however, the current treatment paradigm will be insufficient to achieve large reductions in HCV-related morbidity and mortality.


The prevalence and management of chronic hepatitis B virus (HBV) infection differ among European countries. The availability and reimbursement of diagnostics and drugs may also vary, determining distinct treatment outcomes. Herein, we analyse differences in medical facilities for the care of patients with chronic HBV infection across Europe. A survey was sent to the members of the ESCMID Study Group for Viral Hepatitis, all of whom are experts in chronic HBV infection management. The comprehensive survey asked questions regarding hepatitis B surface antigen (HBsAg) prevalence, the availability of diagnostics and drugs marketed, and distinct clinical practice behaviours in the management of chronic HBV infection. World Bank data were used to assess the economic status of the countries. With 16 expert physicians responding (69%), the HBsAg prevalence rates were <1% in France, Hungary, Italy, The Netherlands, Portugal, Spain, and the UK, intermediate (1-5%) in Turkey, Romania, and Serbia, and high (>5%) in Albania and Iran. Regarding the availability and reimbursement of HBV diagnostics (HBV DNA and liver stiffness measurement), HBV drugs (interferon, lamivudine, tenofovir, and entecavir), HBV prophylaxis, and duration of HBeAg-positive and HBeAg-negative HBV infection, the majority of high-income and middle-income countries had no restrictions; Albania, Iran and Serbia had several restrictions in diagnostics and HBV drugs. The countries in the high-income group were also the ones with no restrictions in medical facilities, whereas the upper-middle-income countries had some restrictions. The prevalence of chronic HBV infection is much higher in southern and eastern than in western European countries. Despite the availability of European guidelines, policies for diagnostics and treatment vary significantly across European countries.

The natural history of hepatitis B virus infection is not uniform and affected from several factors including, HBV genotype. Genotype D is a widely distributed genotype. Among genotype D, several subgenotypes differentiate epidemiologically and probably clinically. D1 is predominant in Middle East and North Africa, and characterized by early HBeAg seroconversion and low viral load. D2 is seen in Albania, Turkey, Brazil, western India, Lebanon, and Serbia. D3 was reported from Serbia, western India, and Indonesia. It is a predominant subgenotype in injection drug use-related acute HBV infections in Europe and Canada. D4 is relatively rare and reported from Haiti, Russia and Baltic region, Brazil, Kenya, Morocco and Rwanda. Subgenotype D5 seems to be common in Eastern India. D6 has been reported as a rare subgenotype from Indonesia, Kenya, Russia and Baltic region. D7 is the main genotype in Morocco and Tunisia. D8 and D9 are recently described subgenotypes and reported from Niger and India, respectively. Subgenotypes of genotype D may have clinical and/or viral differences. More subgenotype studies are required to conclude on subgenotype and its clinical/viral characteristics.

Knowledge of hepatitis B and C prevalence, and numbers infected, are important for planning responses. Published HBSAg and anti-HCV prevalences for the 20 WHO European Region countries outside the EU/EFTA were extracted, to complement published data for the EU/EFTA. The general population prevalence of HBSAg (median 3.8%, mean 5.0%, seven countries) ranged from 1.3% (Ukraine) to 13% (Uzbekistan), and anti-HCV (median 2.3%, mean 3.8%, 10 countries) from 0.5% (Serbia, Tajikistan) to 13% (Uzbekistan). People who inject drugs had the highest prevalence of both infections (HBSAg: median 6.8%, mean 8.2%, 13 countries; anti-HCV: median 46%, mean 46%, 17 countries), and prevalence was also elevated in men who have sex with men and sex workers. Simple estimates indicated 13.3 million (1.8%) adults have HBSAg and 15.0 million (2.0%) HCV RNA in the WHO European Region; prevalences were higher outside the EU/EFTA countries. Efforts to prevent, diagnose, and treat these infections need to be maintained and improved. This article may not be reprinted or reused in any way in order to promote any commercial products or services.
The burden of disease due to chronic viral hepatitis constitutes a global threat. In many Balkan and Mediterranean countries, the disease burden due to viral hepatitis remains largely unrecognized, including in high-risk groups and migrants, because of a lack of reliable epidemiological data, suggesting the need for better and targeted surveillance for public health gains. In many countries, the burden of chronic liver disease due to hepatitis B and C is increasing due to ageing of unvaccinated populations and migration, and a probable increase in drug injecting. Targeted vaccination strategies for hepatitis B virus (HBV) among risk groups and harm reduction interventions at adequate scale and coverage for injecting drug users are needed. Transmission of HBV and hepatitis C virus (HCV) in healthcare settings and a higher prevalence of HBV and HCV among recipients of blood and blood products in the Balkan and North African countries highlight the need to implement and monitor universal precautions in these settings and use voluntary, nonremunerated, repeat donors. Progress in drug discovery has improved outcomes of treatment for both HBV and HCV, although access is limited by the high costs of these drugs and resources available for health care. Egypt, with the highest burden of hepatitis C in the world, provides treatment through its National Control Strategy. Addressing the burden of viral hepatitis in the Balkan and Mediterranean regions will require national commitments in the form of strategic plans, financial and human resources, normative guidance and technical support from regional agencies and research.

More than 20 million hepatitis C virus (HCV) carriers live in the countries of the Eastern Mediterranean. We determined HCV genotype distribution among chronically infected patients in Montenegro and investigated the phylodynamics and phylogeography of the most represented HCV subtypes. The HCV-NS5b sequences of the Montenegrin patients were compared with sequences isolated in different known localities of the Mediterranean area, Europe and Asia. A Bayesian approach was used in order to allow the simultaneous estimation of the evolutionary rate, time-scaled phylogeny, demography and ancestral spatial status. The most frequent HCV subtypes among the Montenegrin patients, were 1b (34.7%) and 3a (24.7%), but there was also a significant prevalence of 1a and 4d (19.5%). Subtype 3a was significantly more frequent among younger patients and intravenous drug users (IDUs), whereas subtype 1b was more frequently associated with iatrogenic exposure and older ages. The spatio-temporal analysis of the epidemic suggested that HCV-1b penetrated Europe at the beginning of the XX century, probably through Greece and Cyprus and in the 1920s reached Montenegro, where there was an exponential increase in the effective number of infections between the 1950s and 1970s. The phylogeographic and phylodynamic analysis of HCV 3a showed that its most probable origin was in the Indian sub-continent (Pakistan in our reconstruction) about 300 years ago. The evolutionary dynamics analysis showed that HCV-3a reached Montenegro more recently in the late 1970s and underwent multi-phasic growth still persisting. Our data suggest multiple introduction of HCV subtypes in the area, supported by different causes of dispersion: adverse social conditions and unsafe medical practices for HCV-1b and i.v. drug use for HCV-3a.

Hepatitis B virus genotype D can be found in many parts of the world and is the most prevalent strain in south-eastern Europe, the Mediterranean Basin, the Middle East, and the Indian sub-continent. The epidemiological history of the D genotype and its subgenotypes is still obscure because of the scarcity of appropriate studies. We retrieved from public databases a total of 312 gene P sequences of HBV genotype D isolated in various countries throughout the world, and reconstructed the spatio-temporal evolutionary dynamics of the HBV-D epidemic using a bayesian framework. The phylogeographical
analysis showed that India had the highest posterior probability of being the location of the tree root, whereas central Asia was the most probable location of the common ancestor of subgenotypes D1-D3. HBV-D5 (identified in native Indian populations) diverged from the tree root earlier than D1-D3. The time of the most recent common ancestor (tMRCA) of the tree root was 128 years ago, which suggests that the common ancestor of the currently circulating subgenotypes existed in the second half of the XIX century. The mean tMRCA of subgenotypes D1-D3 was between the 1940s and the 1950-60s. On the basis of our phylogeographic reconstruction, it seems that HBV-D reached the Mediterranean area in the middle of the XX century by means of at least two routes: the first pathway (mainly due to the spread of subgenotype D1) crossing the Middle East and reaching north Africa and the eastern Mediterranean, and the second pathway (closely associated with D2) that crossed the former Soviet Union and reached eastern Europe and the Mediterranean through Albania. We hypothesise that the main route of dispersion of genotype D was the unsafe use of injections and drug addiction.

Albania

Hepatitis C virus (HCV) genotype 2 causes about 10% of global infections and has the most variable circulation profile in Europe. The history of “endemic” HCV-2 subtypes has been satisfactorily reconstructed, instead there is little information about the recent spread of the "epidemic" subtypes, including HCV-2c. To investigate the origin and dispersion pathways of HCV-2c, 245 newly characterized Italian and Albanian HCV-2 NS5B sequences were aligned with 247 publicly available sequences and included in phylogeographic and phylodynamic analyses using the Bayesian framework. Our findings show that HCV-2c was the most prevalent subtype in Italy and Albania. The phylogeographic analysis suggested an African origin of HCV-2c before it reached Italy about in the 1940s. Phylodynamic analysis revealed an exponential increase in the effective number of infections and Re in Italy between the 1940s and 1960s, and in Albania between the 1990s and the early 2000s. It seems very likely that HCV-2c reached Italy from Africa at the time of the second Italian colonization but did not reach Albania until the period of dramatic migration to Italy in the 1990s. This study contributes to reconstructing the history of the spread of epidemic HCV-2 subtypes to Europe.


We aimed to evaluate a screening programme for infection in unaccompanied asylum seeking children and young people against national guidance and to described the rates of identified infection in the cohort. The audit was conducted by retrospective case note review of routinely collected, anonymised patient data from all UASC referred between January 2016 and December 2018 in two paediatric infectious diseases clinics. There were 252 individuals from 19 countries included in the study, of these 88% were male, and the median age was 17 years (range 11-18). Individuals from Afghanistan, Eritrea and Albania constituted the majority of those seen. Median time between arriving in the UK and infection screening was 6 months (IQR 4-10 months, data available on 197 UASC). There were 94% (238/252) of cases tested for tuberculosis (TB), of whom 23% (55/238) were positive, including three young people with TB disease. Of those tested for hepatitis B, 4.8% (10/210) were positive, 0.5% (1/121) were positive for hepatitis C and of 252 tested, none were positive for HIV. Of the 163 individuals who were tested for schistosomiasis, 27 were positive (16%).The majority of patients were appropriately tested for infections with a high rate of identification of treatable asymptomatic infection. Infections were of both individual and public health significance. Our findings of clinically significant rates of treatable infections in UASC highlight the importance of infection screening for all in this vulnerable patient group.


BACKGROUND: To create a representative picture of the prevalence and the total number of drug users in Albania from 2012 to 2016, and compare those numbers to previous years with other available data. METHODS: The required data for the conductance of this study was collected from three different fronts, namely The Institute of Forensic Medicine (IFM), Clinical Toxicology and Addictions Service, University Hospital "Mother Theresa" Tirana (CTS) and Methadone Maintenance Treatment Centers. The study targets all individuals who have consumed at least once abusive drugs and psychotropic substances
during the period 2012-2016 in the Republic of Albania. A total of 7050 reported cases over the given period were reviewed. RESULTS: Overall, Cannabis Sativa was the highest consumed drug, present in 62.58% of the cases. Other substances with a noticeable prevalence of use were heroin (15.02%) and cocaine (5.1%). It was found out that there were 36 drug-related deaths from 2012 to 2016. During this period of time, only 9 individuals resulted positive for Sexually Transmitted Infections (STI), of which, one positive for Hepatitis C and the remaining 8 positives for HIV. About 25% of drug users in Albania belong to the young subgroup of the population (13-32 years old). CONCLUSION: Overall, taking into consideration all three databases, the number of drug users has significantly increased. There are more officially reported drug users today compared to 2012, however, different trends are observed during different periods. Youngsters are more eager and tempted to use and experiment more with safer and less harmful drugs like cannabis, meanwhile, as age increases, there is a tendency to shift towards more potent and dangerous drugs. Prevention and reducing the prevalence of use of psychoactive drugs is one of the main goals of public health.


BACKGROUND: Preventive health care measures among immigrants and minority groups are generally underutilized. While there is data available regarding healthcare utilization among several ethnic minorities in the USA, little is known regarding health behavior among Albania American communities.

OBJECTIVES: To assess the rate of preventive health screening measures among Albanian American immigrants.

METHODS: Cross sectional analysis of data obtained through anonymous surveys offered to Albanian-American adults over eighteen years of age. RESULTS: Of the 175 participants, 52% were females in the age range of 18-80 years. Body Mass Index (BMI) measured as Kg/m2 was 29.0 ± 0.62 (± SEM) versus 26.3±0.73 for men and women respectively, P < 0.01. Of the above participants of 50 years of age and older, 62% had screening colonoscopy and 49% had hepatitis C screening test irrespective of their gender. Out of the eligible female participants, 68% had a pap smear and 71% had a mammogram.

CONCLUSION: Preventive health measures such as colonoscopy, mammography and hepatitis C screening, were somewhat comparable to USA population including minority groups. There was a higher rate of marriage among our Albanian cohort (67.5%), compared to that reported in the US A (50.0% reported in 2013). Interestingly, colonoscopy screening rate was higher among USA born and married Albanians.


Hepatitis B virus (HBV) is the infectious agent of both acute and chronic hepatitis. HBV exists in multiple genotypic variants that differ in their capacity to become persistent chronic infections and in their clinical manifestations, including hepatocellular carcinoma. The 8 genotypes (A-H) of HBV show a specific worldwide geographic distribution and are correlated with different disease course, severity, and response to therapy. We isolated DNA from 75 HBV-positive blood donors, chosen randomly from the database of the National Blood Bank in Tirana, to specifically analyze the UGT1A1 polymorphism to determine its correlations with bilirubin levels and liver function. The large number of subjects who were HBV-positive carriers of heterozygosis or homozygosis for the UGT1A1*28 (TA)7 polymorphism suggests that these individuals may be more susceptible to cancer and should follow a strict regime of prevention.


Hepatitis C virus (HCV) infection is a worldwide concern. Knowledge of the HCV genotype is clinically important because it predicts the rate of response to therapy and guides the treatment duration. Moreover, it allows molecular epidemiology to be performed. To our knowledge, the prevalence of HCV genotypes has been assessed only once in Albania, using a line probe genotyping assay. We determined HCV genotypes by population sequencing of HCV-infected patients in Tirana, Albania. HCV genotype and sequence analyses were performed for serum samples collected from January 2011 through May 2012 from 61 HCV-seropositive patients using population sequencing of the NS3 protease gene and alternatively the NS5b gene and the 5′ untranslated region (UTR). HCV RNA was retrieved from the blood samples of 50 patients. The HCV NS3 protease gene was sequenced for 28 patients and NS5b and/or 5′UTR fragments were sequenced for an additional 22 patients. The predominant genotype was 1b in 25
patients (50%), followed by genotypes 2c, 4a, 3a, and 1a in 18%, 14%, 8%, and 6% of cases, respectively. Best matches for these HCV RNAs in GenBank were obtained in different countries worldwide. One NS3 protease naturally harbored an amino acid conferring minor drug resistance to newly available HCV protease inhibitors. In conclusion, HCV-1b was predominant in the present Albanian population, as in southeastern Europe.


BACKGROUND: Treatment of Hepatitis C in children has a better outcome than in adults, and for this reason the treatment had different views. However, in pediatric age hepatitis C is seen to have an evolution towards chronicity. Today is a normal option to treat chronic hepatitis C as early as possible according to certain criteria. The aim of this study is to show the results of treatment with interferon and ribavirin and the follow-up of children diagnosed with chronic hepatitis C in our service. PATIENTS AND METHODS: This is a prospective study which has included children 3 up to 15 years old (13 boys and 4 girls) diagnosed with chronic hepatitis C. All patients underwent a certain protocol, including liver biopsy prior to treatment. Treatment consisted in use for 48 weeks of INF α-2b, 3 MIU/m2 three times a week s/c and ribavirin 15 mg/kg orally divided bid. Two patients were treated with PEGINF α-2b with dose 1.5 mcg/kg once a week s/c and ribavirin 15 mg/kg. After the treatment all patients have stayed under our control for an average period of 24 weeks. RESULTS: At the end of the treatment we detected a patient with HCV-RNA positive. End Treatment Viral Response was 94%. Six months later we found three patients who showed relapse of disease. Sustained Viral Response was approximately 83% CONCLUSION: The combination therapy of interferon with Ribavirin in treatment of children with chronic hepatitis C provides a higher SVR when treatment is initiated at the earliest stages of hepatic changes. Side effects of therapy are insignificant in comparison with results obtained.


Despite a recent decrease in the prevalence of HBsAg in the general population, Albania is still highly endemic for HBV infection. Genotype D is the most prevalent HBV strain in the Mediterranean area. We studied the prevalence and distribution of HBV genotypes and subgenotypes in a total of 73 HBsAg-positive patients living in Albania, and reconstructed the epidemiological history of the most prevalent HBV D subgenotype using a "phylogenetic" framework. A time-scaled genealogy of the Albanian patients' and reference P gene sequences with known sampling dates was reconstructed using an MCMC Bayesian approach that allows population growth to be estimated on the basis of coalescent theory. All of the Albanian subjects were infected with the HBV D genotype, and a percentage varying from 44.4% to 100% (depending on the ethnic or risk group) were infected with subgenotype D2, the most prevalent in the study population (72.4%). The other subgenotypes present in a minority of subjects were D1 (13.8%) and D3 (13.8%). The Bayesian skyline plot population dynamics analysis showed that genotype D2 entered the Albanian population in the late 1960s, and that the effective number of infections grew gradually until the second half of the 1980s and more rapidly until the mid-1990s, when it reached a plateau that still persists today. Our data suggest that political and socio-economic factors played an important role in determining the rapid spread of HBV infection in Albania.

Bosnia-Herzegovina

Drlje IT and Arapović J (2022). "Prevalence of hepatitis B surface antigen (HBsAg) in blood donor population in Bosnia and Herzegovina: Impact of the pre-donation questionnaire implementation and mandatory hepatitis B virus (HBV) vaccination schedule - 20 years’ experience of the University Clinical Hospital Mostar." Transfus Clin Biol.

OBJECTIVES: Currently, there are limited data on the prevalence of HBsAg in Bosnia and Herzegovina. This study aimed to evaluate the trend of HBsAg prevalence during a period of 20 years in relation to the implementation of pre-donation questionnaires based on parenteral and sexual risk factors and mandatory HBV vaccination. MATERIAL AND METHODS: This is a retrospective analysis performed on 67,336 blood donors at the University Clinical Hospital Mostar during three distinct periods: before introducing of mandatory HBV vaccination and pre-donation blood donor questionnaires (1998-2002);
after introducing of pre-donation blood donor questionnaires, but without mandatory immunized blood donors (2004-2008); and after introducing of mandatory pre-donation blood donor questionnaires and mandatory vaccination (2015-2019). RESULTS: According to implementation of mandatory pre-donation blood donor questionnaires and mandatory HBV vaccination the prevalence of HBsAg significantly decreased among blood donors in all three studied periods of time (0.303% in 1998-2002, 0.236% in 2004-2008, and 0.021% in 2015-2019; P<0.001). Out of 67,336 tested donors, there were 98 (0.145%) HBsAg-positive donors during analysed periods, with a mean age of 34.76±11.37 years. The mean age of HBsAg-positive donors was 30.72±10.40, 37.56±10.13, and 47.28±12.14 in the 1998-2002, 2004-2008, and 2015-2019 periods, respectively (P<0.001). CONCLUSION: This study clearly shows a decreased rate of HBV infections among blood donors with respect to implementation of the HBV vaccination schedule and mandatory pre-donation blood donor questionnaires based on parenteral and sexual risk factors.


BACKGROUND: Chronic hepatitis C was until recently treated with a combined therapy of interferon and ribavirin. More recently, direct antiviral agents (DAA), are being introduced. They are more tolerable and have fewer side effects, with better treatment results. In the Federation of Bosnia and Herzegovina we have started using this new therapy, with a limited financial opportunity. Large numbers of patients with chronic hepatitis C are former or current addicts, some of them treat their addiction with methadone or buprenorphine. These patients often formerly have a depression disorder and during treatment of chronic hepatitis need supervision of a psychiatrist, due to one of the side effects of interferon being deterioration of depression. Using this research we wanted to valorize the depression disorder of our patients, to indicate the effects of interferon on depression deterioration and the need for a new therapy protocol. SUBJECTS AND METHODS: Examinees were patients with chronic hepatitis C on interferon therapy, which we divided into three groups: those who were never addicts, then the group of patients who were earlier addicts and have a long abstinence and patients who treat their addiction with a replacement therapy of methadone or buprenorphine. All patients completed Beck’s test, which determines the level of depression, before and after interferon therapy. RESULTS: Patients who used to be addicts or were on replacement therapy had mild or moderate depression before interferon treatment in a large number. After interferon therapy, there was a statistically substantial increase of patients with serious depression, which was not noted before the therapy. CONCLUSION: Interferon therapy deteriorates depression in patients with chronic hepatitis C and there should be a strive for new therapies with less side effects in treatment. No patients stopped therapy. That is a result of community work and supervision over patients from both hepatologists and psychiatrists.


INTRODUCTION: Prior to the 1990s, the most common sources of HCV infections were blood transfusions, unsafe injections and I.V. drug use. Screening of blood products for HCV has eradicated transfusion-transmitted hepatitis C in most countries since 1992-in Bosnia and Herzegovina, however, since 1995, due to the war. AIM: To investigate the impact of the source of HCV infection on the therapeutic response in patients treated for chronic HCV infection with dual combined therapy. METHODS: We diagnosed chronic HCV infections amongst 246 patients over a period of five years and selected them according to the reported source of infection. Pegylated interferon alfa 2a or alfa 2b with ribavirin was administered during the time that was genotype-dependent. HCV RNA levels in sera were measured by real time PCR. Liver histology was evaluated in accordance with the level of necroinflammation activity and the stadium of fibrosis. RESULTS: Regardless of the genotype of the virus and the source of infection, SVR was achieved in 67% of the patients. Therapeutic response (ETR) was not achieved in 25% of the patients who were infected with an untested blood transfusion and 6% of the patients who had had wartime surgery. Amongst the different sources of infections, patients with a war-surgery source of infection responded better to therapy than those with a blood transfusion source of infection (p = 0.023). A blood transfusion source of infection implies a larger fibrosis stage than in blood donors; (g = 1.177; s(2) = 0.577). A blood transfusion source of infection implies a significantly larger necroinflammatory activity than in blood donors; (g = 1.456; s(2) = 0.618). CONCLUSIONS: An untested blood transfusion was a significant risk factor for more advanced liver diseases in regards to necroinflammatory activity and the fibrosis stage. This source of infection was also a risk factor for low responses to antiviral therapy. At the same time, I.V. drug users had more progressive necroinflammatory activity, but a high therapeutic response to antiviral therapy.
The prospective study, which was made from Jan 1st 2009 till Dec 31st 2010, in the Clinic for Infectious Diseases within Clinical Hospital Mostar has been implemented in the areas of three southwestern cantons of the Federation of Bosnia and Herzegovina. We wanted to define the seroprevalence of the researched area using seroepidemiological testing of different groups of the population, based on the distribution by sex, age, education, residence and watersupply. The aim of this research was to prove the hypothesis that the decrease of seroprevalency of Hepatitis A has been directly related to the improvement of socio-economic conditions of life that at the end brought the decrease of the total prevalence in patients in younger age groups. The total of 420 examinees from the reasserted sample were analysed and they were classify into age groups. The first group was for the children up to 10 years. Then the group 11-20 follows and etc up to the last group, that complies examinees older than 60. In this way we have got seven groups of 60 examinees, from which the half of them was urban, and the other half was rural inhabitants. In every group analysed the half of examinees were females and the other half were males. The results we acquired with this research did not show any statistically relevant differences of seroprevalence of Hepatitis A between the urban and rural areas, between the sexes, nor between the populations which used different wattersupply objects. A statistically relevant difference was found between populations of different levels of education, but the most important difference was found between seroprevalency in different age groups. Seroprevalence in younger age groups was substantially low and increased in groups rising with age. Comparing this data to results from other similiar researches from developed and undeveloped countries we concluded that the researched area, by the level of seroprevalency of Hepatitis A belongs to the category of developed countries.

Aim To determine the prevalence of hepatitis C virus infection (HCV) among prisoners in Zenica prison, and to investigate the relation between HCV and risky behaviors: intravenous drugs use (IDU), tattooing, promiscuity. Methods This cross-sectional study conducted at the High Security Penitentiary in Zenica involved 200 convicted persons who gave their consents for the research. Their blood was tested by AraGen Hepatitis C Test. Risky behaviors (IDU, tattooing, promiscuity) were tested by an anonymous self-administered questionnaire. Results The prevalence of HCV was 13% (26/200). There was a statistically significant correlation of HCV infection and drug abuse before imprisonment (p=0.00), injection drug abuse before imprisonment (p=0.00), tattooing in prison (p=0.03) and having sex with homosexual partners (p=0.00). Conclusion The prevalence of HCV in prisoners at Zenica prison was significantly higher than in the general Bosnia and Herzegovina population. Intravenous drugs use had highest risk for HCV infection among prisoners.

BACKGROUND: The current standard treatment of chronic hepatitis C in Bosnia and Herzegovina consists of pegylated interferon alpha in combination with ribavirin. Interferon therapy has many psychiatric side effects, with depressive symptomatology being most prominent. The aim of the study was to establish the frequency and severity of depression in patients with chronic hepatitis C during two months of the aforementioned therapy. SUBJECTS AND METHODS: The overall sample consisted of 46 subjects, divided into three subgroups, aged 18 to 65. The study population consisted of subjects treated for chronic hepatitis C (n = 15), subjects infected but not treated for chronic hepatitis C (n = 15), and healthy controls (n = 16). The assessment and level of depression were based on the Structural clinical interview (SCID), Montgomery-Asberg Depression Rating Scale and Zung Self-Rating Depression Scale. The assessments were conducted before interferon therapy (on the day 0), after 4 and 8 weeks of therapy. RESULTS: Regarding its frequency, MADRS scoring showed that the number of depressed subjects receiving therapy increased after 8 weeks (46.7%). There was statistical significance between the subgroups after 4 and 8 weeks. Likewise, the ZUNG scale showed that the number of depressed subjects receiving therapy increased after 8 weeks (73.3%). There was statistical significance between the subgroups on the day 0, after 4 and 8 weeks. CONCLUSIONS: Depression was significantly more frequent
in chronic hepatitis C subjects treated with interferon alpha in combination with ribavirin than in subjects in the group without therapy. Mild depression was most prevalent.


INTRODUCTION: Use of intravenous heroin carries a risk of serious medical conditions, including acquiring blood-borne infections. Therefore, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection represent a threat for people who inject drugs (PWID). The objectives of this study were to determine the extent and characteristics of risk factors for acquiring HBV and HCV infection in PWID included in opiate substitution treatment in the southern part of Bosnia and Herzegovina (B&H). METHODOLOGY: The study included 120 adult PWID of both sexes who participated in opiate substitution treatment. All participants were interviewed, and their blood samples were tested for the presence of the surface hepatitis B virus antigen (HBsAg) and hepatitis C virus antibodies (anti-HCV). Prevalence data were obtained and compared to the serological status. RESULTS: HBsAg prevalence among PWID was 0.8% (1/120), whereas seroprevalence of anti-HCV was 52.5% (63/120). PWID exposed to risk-behavior factors (such as unsafe sexual activity, serving prison sentence, and tattooing) were more frequently anti-HCV positive. Sharing drug paraphernalia was found to be the most significant risk factor. The highest predictive values for acquiring HCV-infection were attributed to PWID who used heroin for more than three years and who were unmarried. CONCLUSIONS: HBsAg prevalence among PWID is rare (0.8%), while HCV-infection (52.5%) presents an important health and social issue among PWID in B&H. Sharing drug paraphernalia and intravenous heroin use longer than three years were the most prominent risk-behavior factors among the patients we investigated.


BACKGROUND: Health Professional exposures of health care workers (HCW) to potentially infective blood and body fluids presents a serious health threat, including hepatitis B, hepatitis C and HIV transmission. This study was conducted to assess the risk for and reporting of needle stick injuries, sharp injuries and other occupational exposures of health care workers in a large healthcare center in Sarajevo. METHODS: This cross-sectional survey was conducted in May 2013. The study target population included all hospital health care workers who had a high potential for exposure. The estimated sample size was 48 physicians, 132 nurses/technicians and 30 auxiliary personnel. RESULT: During their career, 124 (63.3%) HCW reported exposures to blood and body fluids. In total, needle stick injuries (66.1%) were the most common source of exposure, followed by contact with intact skin (12.1%) and cut with sharp object (11.3%). Only 43 (35.5%) reported any of these exposures to health authorities during their career. The odds of exposure to needle stick injuries and other occupational exposures to blood and bodily fluids were significantly higher among medical nurses/technicians (AOR=4.98, 95%CI=1.52-16.1) and auxiliary (AOR=4.30, 95% CI=1.07-17.34) personnel when compared to physicians. HCW in the operation room, intervention ambulance and laboratory (AOR=3.73, 95%CI=1.43-9.72) had higher odds of exposure than workers in the ambulatory departments. CONCLUSIONS: Needle stick Injuries, Sharp Injuries and other Occupational Exposures to Blood and Body Fluids among health care workers are underestimated hazard. Especially, for HCW who work in operation room/interventional ambulance. There is a need for preventive programs for HCW and further work on the establishment of an effective surveillance system.


Association of Gastroenterologists and Hepatologists of Bosnia and Herzegovina based on the experiences of domestic and foreign centers operating in the field of hepatology and accepted guidelines of the European and the U.S. Association for Liver Diseases adopted the consensus for the diagnosis and treatment of chronic viral hepatitis B and C. The guidelines are intended for specialists in gastroenterology and hepatology, and infectious diseases physicians working in primary health care and
family medicine, but also other physicians who are confronted with this disease in their practice, with the aim of facilitating and shortening the diagnostic and treatment protocols of patients with chronic viral hepatitis B and C. This ensures faster, more efficient, more rational and cost-effective care of patients with hepatitis, with an emphasis on stopping the deterioration of liver disease to liver cirrhosis and eventually hepatocellular carcinoma. Key words: Chronic hepatitis B and

Bulgaria


It is debatable whether HIV-infected patients are at greater risk for hepatitis E virus (HEV) infection compared with healthy subjects. The reported anti-HEV seroprevalence among different groups in Bulgaria varied from 9.04% to 25.9%, but the information regarding the HIV population is still missing. The aim of the present study was to evaluate hepatitis E seroprevalence among HIV-infected patients in Bulgaria and to analyze demographic and immunological factors associated with HEV infection. Serum samples of 312 HIV-infected patients were analyzed retrospectively. Age, sex, residence and laboratory markers for HEV, HBV, HCV and HIV infection, and lymphocytes subpopulations were collected for all patients. None of the tested samples were positive for HEV RNA. HEV seroprevalence among HIV-infected patients was 10.9%. Males were more affected with the highest prevalence of positivity in the age group > 30 to ≤ 40 years. The documented HIV transmission routes in HIV/HEV co-infected group were heterosexual, homosexual, intravenous drug use (IDU), and vertical with predominance of the heterosexual route (z = 0.2; p = 0.804). There was a statistically significant trend of HIV mixed infection with routes of HIV transmission other than homosexual - heterosexual in HIV/HEV group and injection drug use in HIV/HBV/HCV co-infected group. The route of HIV transmission, in contexts of patients’ behavior, was associated with HEV prevalence among HIV-infected patients.


Hepatitis E virus (HEV) infection is widespread among domestic pigs, industrial swine, and wild boars in Bulgaria. The aim of the current research was to present the HEV seroprevalence among blood donors in Bulgaria. In the present study, 555 blood donors (479 males and 76 females) were enrolled from five districts in the country (Shumen, Pleven, Stara Zagora, Plovdiv, and Sofia districts). All blood samples were tested for anti-HEV IgG using the recomWell HEV IgG ELISA test (Mikrogen GmbH, Neuried, Germany). Each participating donor completed a short, structured, and specific questionnaire to document data on the current study. Anti-HEV IgG positive results were detected in 144 (25.9%) blood donors, including 129 (26.9%) males and 15 (19.7%) females. The established HEV seropositivity was 28.8% (23/80) in Shumen district, 23.2% (22/95) in Pleven district, 27.1% (38/140) in Stara Zagora district, 27.5% (44/160) in Plovdiv district, and 21.3% (17/80) in Sofia district. A high HEV seroprevalence was found for persons who declared that they were general hunters (48.7%; 19/39; p = 0.001) and hunters of wild boars (51.6%; 16/31; p = 0.001). We present the first seroprevalence rates of HEV infection in blood donors from Bulgaria. The results of our research showed high HEV seropositivity among blood donors.


A goal of the WHO strategy on the elimination of hepatitis as a public threat is a 65% reduction in the attributable mortality. Deaths related to hepatitis B and C infections are mostly due to decompensated cirrhosis and hepatocellular carcinoma (HCC) but accurately measuring mortality is challenging as death certificates often do not capture the underlying disease. The aim of this collaborative study between European Centre for Disease Prevention and Control (ECDC) and the European Association for the Study of the Liver (EASL) was to assess a WHO-developed protocol to support countries in implementing studies to collect data on the fraction of cirrhosis and hepatocellular carcinoma attributable to hepatitis B and C. Three sentinel sites (in Bulgaria, Norway and Portugal) collected data for patients first admitted or seen in their centres during 2016. Patients with cirrhosis or HCC were identified through patient files or healthcare databases using ICD-10 codes. The proportion of patients with cirrhosis and HCC who tested positive for HBV and HCV were calculated to estimate the aetiological fractions. After the pilot study was completed, each site was asked about the feasibility and acceptability of the protocol. A total of 1249
patients presenting with cirrhosis and/or HCC were evaluated across the three sites. The prevalence of HBV and HCV among cases of cirrhosis showed that in Norway and Portugal, HCV was responsible for about one-quarter of the cases, whereas in Bulgaria, HBV was more common. For HCC, HCV was responsible for more than one-third of cases in Norway and Portugal, while in Bulgaria HBV was more frequent as the underlying cause. Results obtained during the pilot study were comparable to published estimates obtained through statistical modelling or meta-analyses. Several challenges were reported from the sites involved in the pilot including the considerable time needed for reviewing the hospital records and extracting patient data. The pilot demonstrated the feasibility of collecting data on the prevalence of HBV and HCV infection among patients with cirrhosis and HCC in sentinel sites. This method can be used to estimate mortality attributable to HBV and HCV for elimination monitoring. Where easily implementable, sentinel studies are the best way to empower countries, get up-to-date data and closely monitor the changes in the attributable fraction at a country level.


OBJECTIVE: This study piloted a European technical protocol for conducting chronic hepatitis C prevalence surveys in the general population. The pilot study took place in the Bulgarian city of Stara Zagora in 2018, and results of setting up, conducting and evaluating the survey are presented. RESULTS: A probability-based sample of the general adult population was drawn from the local population registry, stratified by age and sex. A sample size of 999 was calculated, and accounting for 50% non-response, 1998 registered invitation letters were sent. Venous blood samples and questionnaire data were collected by the Regional Health Inspectorate in Stara Zagora. Blood samples were tested for anti-HCV, and if reactive for RNA, 252 (21.6%) of the participants were included in the study. Mean age and sex distribution differed between the participants (55.9 years, 60.3% females) and the total sample (48.9 years, 53.4%). The weighted chronic HCV prevalence among participants was 0.9% [95% CI 0.2-4.2%]. The approach of only sending registered letters contributed to a low response rate, and more efforts are needed to reduce non-response, especially among men and younger age groups. Results of the evaluation were integrated in the final technical protocol.


BACKGROUND: Over the past two decades, more thorough investigations for hepatitis E virus (HEV) infection have been done in the world. Reports from Southeast European countries have increased. AIM: The current article presents a critical analysis of all studies for HEV in Bulgaria. MATERIAL AND METHODS: A literature search was done using available medical databases. We analysed the literature in PubMed databases and Bulgarian medical databases for English and Bulgarian languages sources. Preference was given to the sources published within the past 24 years (January 1995 - September 2018). RESULTS: Two thousand two hundred and fifty-seven blood serums were tested for the analysed period (1995 - 2018), and 13.1% of them were positive for acute HEV (Mean ± SD: 20.38 ± 25.77%; 95% CI: 1.29
The following subtypes were established in the country - HEV Subtype 3e, HEV Subtype 3f, HEV Subtype 3c, HEV Subtype 3i, HEV Subtype 3hi and HEV Subtype 1. CONCLUSION: We hope that the National Health Organizations will take adequate and timely measures to increase the knowledge and research for HEV among Bulgarian citizens.


INTRODUCTION: Bulgaria joined European Union (EU) on 1 January 2007. Since the accession all regulations, directives, decisions, recommendations, and opinions of the European Parliament, the Council of the European Union, and the European Commission are being implemented. AIM: The purpose of this study was to present the morbidity of acute hepatitis B virus (HBV) and acute hepatitis C virus (HCV) in Bulgaria before and after accession to the EU. MATERIALS AND METHODS: A retrospective study was performed. The morbidity of acute HBV and acute HCV infections in Bulgaria was analyzed over a period of sixteen years (2000-2016). The collected data were based on the National Center of Infectious and Parasitic Diseases (NCIPD) and the National Center of Public Health and Analyses (NCPHA). RESULTS: Between 2000 and 2016, 11038 cases of acute HBV infection and 1681 cases of acute HCV infection were reported in Bulgaria. Before the accession to EU, the morbidity rates of acute HBV and acute HCV infections were 12.77 cases per 100 000 population (95% CI: 11.45-13.97) and 1.52 cases per 100 000 population (95% CI: 1.17-1.96), respectively. After the accession to the EU, the morbidity rates of acute HBV and acute HCV infections were 5.29 cases per 100 000 population (95% CI: 3.86-6.73) and 1.14 cases per 100 000 population, respectively. CONCLUSION: Analysis of the data suggests that there is a tendency for lower morbidity rates of acute HBV. The situation with acute HCV is relatively stable over the years regardless of EU membership.


Background: The main objective of this study was to analyse the spread of hepatitis C virus (HCV) genotype in patients with chronic liver disease; commenting on the molecular characterization of HCV and gender and age in Varna, Bulgaria. Across Europe and the world, HCV is a significant economic concern and public health crisis. Defined by genotype variations, HCV is the leading cause of chronic liver disease, liver related morbidity, and mortality worldwide. Active examination for asymptomatic patients is essential, initiating early treatment aimed at the specific HCV genotype, effective outcomes, and reducing transmission and mortality in Bulgaria. Methods and materials: Nucleic acid extraction and amplification were performed with commercially available test kits on 115 patients blood samples collected from March 2018 to October 2018. Male (n = 58) (50.43%, 95% CI = 41.29%-59.57%) and female (n = 57) (49.57%, 95% CI = 41.29%-59.57%) samples were equally distributed (mean age = 51.4 years; SD = ±16.5 years; range = 17-87 years old). Results: Genotype 1b predominated (73%, 95% CI = 64.89%-81.11%), followed by high prevalence of 1a (13.9%, 95% CI = 7.58%-20.22%) and 3 genotypes (11.3%, 95% CI = 5.51%-17.09%). Genotypes 2 and 4 were equally the least prevalent (0.9%, 95% CI = -0.83%-2.63%). In genotype 1b, 60.7% were women and 39.3% were men; in genotype 1a, 25% were women and 75% were men; and in genotype 3, only 7.7% were women and 92.3% were men. Males were most prevalent in genotypes 1a (75%) and 3 (92.3%), while women were most prevalent in genotype 1b (60.7%). Conclusions: HCV genotype 1b is the predominant variant within the epidemiological pattern of HCV genotypes in patients with chronic liver diseases in North Eastern Bulgaria.


Hepatitis E virus (HEV) infection in Bulgaria is endemic, as demonstrated by the seroprevalence of antibody against the virus in the general population and by the high prevalence of clinical cases registered. In this study, a deep Bayesian phylogenetic analysis has been performed to provide information on the genetic diversity and the spread of HEV genotypes in Bulgaria. Three different data sets of HEV virus was built for genotyping by the maximum likelihood method, for evolutionary rate estimated by Bayesian Markov Chain Monte Carlo approach, for demographic history investigation and for selective pressure analysis. The evolutionary rate for genotype 3e, was 351 × 10(-3) substitution/site/year (95% highest posterior density [95% HPD]: 145 × 10 (-3) -575 × 10 (-3) ). The root of the time to the most recent common ancestor of the Bayesian maximum clade credibility tree of HEV 3e genotype corresponded to 1965 (HPD 95% 1949-1994). The Bulgarian sequences mainly clustered in
the main clade (clade A). The monophyletic clade included all Bulgarian genotype 3e sequences. The demographic history showed a slight growth from 1995 to 2000, followed by a sort of bottleneck in 2010s, a peak in 2011 and a new growth to 2015. Selection pressure analysis did not show sites under positive pressure but 64 statistically significant sites under negative selection. Molecular epidemiological surveillance by Bayesian phylogeny of HEV virus can contribute to trace the way of human infection after contact with swine source directly or heating meat improving public health control.


Hepatitis C virus (HCV) is a positive-stranded RNA virus which belongs to the family of Flaviviridae, predominantly infecting liver hepatocytes. HCV infection is a major cause for morbidity worldwide. Aim: The primary objective was to evaluate the comparative effectiveness of pan-genotypic therapies for the treatment of patients with HCV infection in Bulgaria. Materials & methods: The databases MEDLINE, EMBASE, Cochrane Library, PubMed and clinicaltrials.gov were searched to identify studies evaluating the therapeutic efficacy of sofosbuvir/velpatasvir/voxilaprevir, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir for the treatment of HCV patients. Results: The range of sustained virologic response rates among all genotypes achieved after therapy with sofosbuvir/velpatasvir/voxilaprevir was 92-100% (8-week therapy) in treatment-naive patients and 99-100% (12-week therapy) in experienced patients. The range of sustained virologic response rates with glecaprevir/pibrentasvir was 91-100% (12-week therapy) and 97-100% (12-week therapy) with sofosbuvir/velpatasvir. Conclusion: Sofosbuvir/velpatasvir/voxilaprevir is a noninferior therapy offering a simple and short-term treatment regimen with high efficacy, favorable safety profile and good tolerability.


BACKGROUND: The rate of HIV infection in Bulgaria is low. However, the rate of HCV-HIV-coinfection and HCV infection is high, especially among high-risk communities. The molecular epidemiology of those infections has not been studied before. METHODS: Consensus Sanger sequences of HVR1 and NS5B from 125 cases of HIV/HCV coinfections, collected during 2010-2014 in 15 different Bulgarian cities, were used for preliminary phylogenetic evaluation. Next-generation sequencing (NGS) data of the hypervariable region 1 (HVR1) analyzed via the Global Hepatitis Outbreak and Surveillance Technology (GHOST) were used to evaluate genetic heterogeneity and possible transmission linkages. Links between pairs that were below and above the established genetic distance threshold, indicative of transmission, were further examined by generating k-step networks. RESULTS: Preliminary genetic analyses showed predominance of HCV genotype 1a (54%), followed by 1b (20.8%), 2a (1.4%), 3a (22.3%) and 4a (1.4%), indicating ongoing transmission of many HCV strains of different genotypes. NGS of HVR1 from 72 cases showed significant genetic heterogeneity of intra-host HCV populations, with 5 cases being infected with 2 different genotypes or subtypes and 6 cases being infected with 2 strains of same subtype. GHOST revealed 8 transmission clusters involving 30 cases (41.7%), indicating a high rate of transmission. Four transmission clusters were found in Sofia, three in Plovdiv, and one in Peshtera. The main risk factor for the clusters was injection drug use. Close genetic proximity among HCV strains from the 3 Sofia clusters, and between HCV strains from Peshtera and one of the two Plovdiv clusters confirms a long and extensive transmission history of these strains in Bulgaria. CONCLUSIONS: Identification of several HCV genotypes and many HCV strains suggests a frequent introduction of HCV to the studied high-risk communities. GHOST detected a broad transmission network, which sustains circulation of several HCV strains since their early introduction in the 3 cities. This is the first report on the molecular epidemiology of HIV/HCV coinfections in Bulgaria.


INTRODUCTION: Hepatitis B virus (HBV) is one of the most significant human pathogens responsible for a huge number of acute and chronic liver infectious diseases worldwide. AIM: To find the duration of
post-vaccination immune response in individuals allocated to five age groups from 6 months to 20 years.

MATERIALS AND METHODS: All tested subjects were born between 1999 and 2018 and therefore covered by the compulsory vaccination program against hepatitis B. For the serological marker anti-HBs Ab we investigated 449 serum samples taken from ambulatory people and patients of St Marina University Hospital in Varna. RESULTS: A positive antibody response (anti-HBs Ab > 10 mIU/ml) was reported in 79.7% (n = 51) of the group of subjects up to one year old, in 70.0% (n = 196) of the subjects in the age range 1 year/1 month to 15 years, and in 39.3% (n = 33) of the subjects 15 years/1 month to 20 years old. Female sex had a better post-vaccination response than male sex with statistically significant relationship between sex and anti-HBs Ab titer (χ² = 24.76, p <0.01). CONCLUSIONS: Regardless of the mass immunization against HBV in Bulgaria, the relative share of chronic HBV infections does not show a downward trend. Therefore, it is very important to study the duration of the post-vaccination immune response by demonstrating the anti-HBs antibodies and to apply a booster dose from the vaccine if needed.


BACKGROUND: In industrialized areas of the world, including Europe, Hepatitis E Virus (HEV) is considered an emerging pathogen. In fact, autochthonous cases caused by HEV genotype 3 (HEV-3) are increasingly reported. Several studies described the human HEV-3 subtypes and strains circulating in West Europe countries; in contrast, very little is known about the HEV strains responsible for acute hepatitis E in countries of East Europe/Balkans, such as Bulgaria. METHODS AND FINDINGS: Anti-HEV IgM positive serum samples (n = 103) from acute hepatitis cases (2013-2015) from all over Bulgaria were analysed for HEV RNA by Real-Time PCR. Viremia was detected in 90/103 samples. A fragment of the viral genome (ORF-2 region) was amplified by nested PCR from 76/90 viremic samples, leading to a sequence in 64 of them. Genotyping by phylogenetic analysis with standard reference sequences showed HEV-1 in 1/64 cases, HEV-3 in 63/64. Subtyping of HEV-3 sequences showed 3e (39/63, 62%), 3f (n = 15/63, 24%) and 3c (n = 8/63, 13%) subtypes; in one case the sequence subtype was uncertain and classified as 3hi. In the phylogenetic tree, most 3e sequences grouped in two well distinct clusters (A and B), each one with very low intragroup genetic distances. In contrast, 3f and 3c were interspersed with reference sequences and showed lower tendency to cluster and/or higher intragroup distances. Geographically, while 3f and 3c were scattered throughout the country, 3e was restricted to the South-West area, with most cases in two towns about 40 kilometres apart from each other. CONCLUSIONS: Most acute hepatitis E cases in Bulgaria are caused by HEV-3, subtypes 3e, 3f and 3c. Circulation of 3e appears quite different from 3f and 3c, with 3e restricted to the South-West area while 3f and 3c diffused over the country. The factors underlying the observed molecular and geographical differences remain to be investigated.


The purpose of this study was to analyze sequences of hepatitis A virus (HAV) Ia and Ib genotypes from Bulgarian patients to investigate the molecular epidemiology of HAV genotype I during the years 2012 to 2014. Around 105 serum samples were collected by the Department of Virology of the National Center of Infectious and Parasitic Diseases in Bulgaria. The sequenced region encompassed the VP1/2A region of HAV genome. The sequences obtained from the samples were 103. For the phylogenetic analyses, 5 datasets were built to investigate the viral gene in/out flow among distinct HAV subpopulations in different geographic areas and to build a Bayesian dated tree, Bayesian phylogenetic and migration pattern analyses were performed. HAV Ib Bulgarian sequences mostly grouped into a single clade. This indicates that the Bulgarian epidemic is partially compartmentalized. It originated from a limited number of viruses and then spread through fecal-oral local transmission. HAV Ia Bulgarian sequences were intermixed with European sequences, suggesting that an Ia epidemic is not restricted to Bulgaria but can affect other European countries. The time-scaled phylogeny reconstruction showed the root of the tree dating in 2008 for genotype Ib and in 1999 for genotype Ia with a second epidemic entrance in 2003. The Bayesian skyline plot for genotype Ib showed a slow but continuous growth, sustained by fecal-oral route transmission. For genotype Ia, there was an exponential growth followed by a plateau, which suggests better infection control. Bidirectional viral flow for Ib genotype, involving different Bulgarian areas, was
observed, whereas a unidirectional flow from Sofia to Ihtiman for genotype Ia was highlighted, suggesting the fecal-oral transmission route for Ia.


OBJECTIVES: Data on high frequency of hepatitis A virus (HAV) antibodies for wastewater treatment staff is contradictory. Literature lacks data on the seroprevalence of antibodies to HAV (anti-HAV) among workers in wastewater treatment plants (WWTPs) in Bulgaria. The aim of this study is to establish a specific humoral immune response to hepatitis A virus - anti-HAV total antibodies among staff in WWTPs.

MATERIAL AND METHODS: A complex study of health and working conditions included 110 subjects working in 3 WWTPs in Bulgaria (74% of all workers in the 3 studied WWTPs and 20% of all employees in Bulgaria registered in 2014 under the wastewater collection, discharge and treatment code of economic activity). Workers had been differentiated in 3 groups on the basis of their occupational work: operators, support staff and other workers exposed to biological agents. Venous blood from all 110 subjects was tested once for carriers of HAV antibodies. RESULTS: Anti-HAV total antibodies were found for 52.7% of workers in WWTPs. There is a positive association between activity performed in WWTPs (operators, maintenance personnel and others exposed) and a positive one for the presence of anti-HAV (Chi<sup>2</sup> = 6.882, df = 2, p = 0.032). Odds ratio (OR) for hepatitis A increases 2.9 times in the group of operators vs. others exposed to biological agents in WWTPs (OR = 2.914, 95% confidence interval (CI): 1.149-7.393, Fisher’s p = 0.039). Odds ratio for hepatitis A increases 4.3 times in the group of support staff from WWTPs vs. others exposed to biological agents in WWTP (OR = 4.295, 95% CI: 1.075-17.167, Fisher’s p = 0.049). CONCLUSIONS: Higher frequency of anti-HAV antibodies among operators and maintenance personnel at WWTPs has been established as compared to other workers exposed to biological agents in WWTPs. There is a positive association between increasing age of the workers and the presence of anti-HAV. Int J Occup Med Environ Health 2018;31(3):307-315.


In a representative nationwide study, we have determined the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfections among HIV-positive patients diagnosed during the period 2010-2014 in Bulgaria. Despite a relatively low rate of new HIV diagnoses, the rates of hepatitis B and C coinfections among these patients fell within the upper range reported in Europe. HBsAg and HCV antibodies (Ab) were found in 10.4% and 25.6% of the tested individuals, respectively. Importantly, high rates of active hepatitis infections were confirmed by detection of HBV DNA in 51.1% and HCV RNA in 78.1% of the tested individuals. Hepatitis coinfections affected mostly high risk groups and persons with multiple risk behavior, including people who inject drugs, men who have sex with men, prisoners, and Roma people.


BACKGROUND: Hepatitis A virus (HAV) infection is endemic in Eastern European and Balkan region countries. In 2012, Bulgaria showed the highest rate (67.13 cases per 100,000) in Europe. Nevertheless, HAV genotypes and strains circulating in this country have never been described. The present study reports the molecular characterization of HAV from 105 patients from Bulgaria. METHODS: Anti-HAV IgM positive serum samples collected in 2012-2014 from different towns and villages in Bulgaria were analysed by nested RT-PCR, sequencing of the VP1/2A region and phylogenetic analysis; the results were analysed together with patient and geographical data. RESULTS: Phylogenetic analysis revealed two main sequence groups corresponding to the IA (78/105, 74%) and IB (27/105, 26%) sub-genotypes. In the IA group, a major and a minor cluster were observed (62 and 16 sequences, respectively). Most sequences from the major cluster (44/62, 71%) belonged to either of two strains, termed “strain 1” and “strain 2”, differing only for a single specific nucleotide; the remaining sequences (18/62, 29%) showed few (1 to 4) nucleotide variations respect to strain 1 and 2. Strain 2 is identical to the strain previously responsible for an outbreak in the Czech Republic in 2008 and a large multi-country European outbreak caused by contaminated mixed frozen berries in 2013. Most sequences of the IA minor cluster and the IB group were detected in large/medium centers (LMCs). Overall, sequences from the IA major cluster were more frequent in small centers (SCs), but strain 1 and strain 2 showed an opposite relative frequency in SCs and LMCs (strain 1 more frequent in SCs, strain 2 in LMCs). CONCLUSIONS: Genotype IA predominated in
Bulgaria in 2012-2014 and phylogenetic analysis identified a major cluster of highly related or identical IA sequences, representing 59% of the analysed cases; these isolates were mostly detected in SCs, in which HAV shows higher endemicity than in LMCs. The distribution of viral sequences suggests the existence of some differences between the transmission routes in SCs and LMCs. Molecular characterization of an increased number of isolates from Bulgaria, regularly collected over time, will be useful to explore specific transmission routes and plan appropriate preventing measures.


OBJECTIVE: HCV infection is a leading cause of chronic liver disease with long-term complications—extensive fibrosis, cirrhosis, and hepatocellular carcinoma. The objective of this study is to perform cost analysis of therapy of patients with chronic HCV-related cirrhosis hospitalized in the University Hospital "Queen Joanna-ISUL" for 3-year period (2012-2014). METHODS: It is a prospective, real-life observational study of 297 patients with chronic HCV infection and cirrhosis monitored in the University Hospital "Queen Joanna-ISUL" for 3-year period. Data on demographic, clinical characteristics, and health-care resources utilization (hospitalizations, highly specialized interventions, and pharmacotherapy) were collected. Micro-costing approach was applied to evaluate the total direct medical costs. The points of view are that of the National Health Insurance Fund (NHIF), hospital and the patients. Collected cost data are from the NHIF and hospitals tariffs, patients, and from the positive drug list for medicines prices. Descriptive statistics, chi-squared test, Kruskal-Wallis, and Friedman tests were used for statistical processing. RESULTS: 76% of patients were male. 93% were diagnosed in grade Child-Pugh A and B. 97% reported complications, and almost all developed esophageal varices. During the 3 years observational period, patients did not change the critical clinical values for Child-Pugh status and therefore the group was considered as homogenous. 847 hospitalizations were recorded for 3 years period with average length of stay 17 days. The mortality rate of 6.90% was extremely high. The total direct medical costs for the observed cohort of patients for 3-year period accounted for 1,290,533 BGN (€659,839) with an average cost per patient 4,577 BGN (€2,340). Statistically significant correlation was observed between the total cost per patient from the different payers’ perspective and the Child-Pugh cirrhosis score. CONCLUSION: HCV-related cirrhosis is resource demanding and sets high direct medical costs as it is related with increased hospitalizations and complications acquiring additional treatment.


BACKGROUND: Hepatitis A virus (HAV) infection is an acute, self-limited liver disease transmitted usually through the faecal–oral route via person-to-person contact. Bulgaria has intermediate HAV endemicity with higher susceptibility among adults and recurrent outbreaks. AIM: As HAV infection is strongly related to human movements and represents a significant risk to travelers and migrants, as well as to local population receiving these groups, we set out to analyze the epidemiological data on hepatitis A in five of the largest tourist border regions of Bulgaria located in its eastern part: Varna, Shumen, Dobrich, Burgas and Yambol. MATERIALS AND METHODS: We reviewed retrospectively all reported cases of acute hepatitis A in the eastern regions of Bulgaria over a 7-year period between 2008 and 2014. RESULTS: A total of 2879 newly infected patients were registered during the study period, the number varying widely: from 190 cases in 2014 to 923 in 2012. The average incidence of HAV was higher in the south-eastern regions than in the northeastern regions (55.30% vs 15.04% respectively, p < 0.0001). The most affected age group in all regions was the 5-9-year olds (p < 0.0001) and males were significantly more susceptible to HAV (p = 0.02). CONCLUSION: Hepatitis A is still a major public health problem in Bulgaria; there is a significant difference in the incidence of the disease in the regions in the south-east and those in the north-east and between the different age groups and sexes.


INTRODUCTION: Hepatitis E is one of the leading clinical manifestations of acute viral hepatitis in developing countries. In industrialized countries, during the past several years, sporadic "autochthonous" cases of HEV infection have been increased. OBJECTIVE: The aim of this study was to analyze the epidemiological, clinical and laboratory features of HEV infection among patients hospitalized at the Department of Infectious Diseases in Military Medical Academy, Sofia, Bulgaria. METHODS: A retrospective study of 806 cases of acute viral hepatitis was performed at the Department of Infectious
Diseases in Military Medical Academy, Sofia, Bulgaria, between December 2004 and September 2012. The etiological diagnosis was established by ELISA. The statistical analysis was performed using Excel 2007 (Microsoft, Redmond, Washington, USA) and SPSS Statistics 19.0 (IBM Corp., Armonk, New York, USA).

RESULTS: Specific reaction to anti-HEV-IgM and anti-HEV-IgG antibodies were detected in 20 (2.48%) of 806 patients. The most observed clinical presentations were jaundice (85%), fatigue (85%), anorexia (65%), abdominal discomfort (55%) and fever (40%). The mean values of aspartate transaminase and alanine transaminase were 521 IU/l and 881 IU/l, respectively. The cholestasis was slight, marked with mean values of gamma-glutamyl transferase and alkaline phosphatase, respectively 418 IU/l and 486 IU/l.

CONCLUSION: We report twenty autochthonous sporadic cases of acute infection with HEV. The zoonotic etiology of the virus as well as the foodborne transmission of the infection is discussed. We found that aging and pre-existing underlying diseases are risk factors for a severe course of the HEV infection.


The aim of the present study was to assess the prevalence of hepatitis B surface antigen among pregnant women in Varna Region, Bulgaria. During the period 2009-2013, an average prevalence of 2.26% (95% CI 1.75, 2.91) was measured in a total number of 2,700 samples. Analysis demonstrated that rural residence and minority ethnic origin are important risk factors for hepatitis B infection among pregnant women with hazard ratios of 2.40 (95% CI 1.46, 3.94), and 2.43 (95% CI 1.46, 4.05) when compared with urban residence and ethnic majority origin, respectively. J. Med. Virol. 88:2012-2015, 2016. © 2016 Wiley Periodicals, Inc.


Viral hepatitis, particularly hepatitis B and C, are diseases with worldwide distribution that present a significant public health problem. Seroprevalence studies allow assessment of the extent of the disease burden, the identification of populations at risk and the monitoring trends over time. A multi-center seroprevalence study, carried out in Bulgaria (covering the five largest cities - Sofia, Plovdiv, Varna, Ploeven, and Stara Zagora) in 1999-2000 estimated a crude seroprevalence rate of 3.9% for HBsAg and 1.3% for anti-HCV. A decade later, comparable rates were observed in a study including 865 outpatients consulting a clinical laboratory in Plovdiv, the second largest administrative region in Bulgaria. The crude seroprevalence rate measured for hepatitis B (HBsAg) was 3.9%. The HBsAg prevalence rate in individuals ≤19 years of age (targeted by vaccination) was significantly lower compared to the rate in adults ≥20 years of age - 1% versus 4.8%. The lack of dynamics in the overall level of HBsAg carriers is likely related to the excessively low hepatitis B vaccine coverage in individuals, born before the introduction of the universal vaccination of newborns in August 1991. Anti-HCV antibodies were detected in 0.7% of the subjects.


Hepatitis B virus infection is a global health problem. Based on the sequence divergence of the entire genome, hepatitis B virus has been classified into eight genotypes which have a characteristic geographic distribution. To date, no data are available on the molecular epidemiology of hepatitis B virus in Bulgaria. The aim of the present study was to reconstruct the epidemiological history of HBV genotypes/subgenotypes circulating in Bulgaria using a phylogenetic approach and a Bayesian statistical inference framework. Sequence analysis of the HBsAg/Reverse Transcriptase overlapping genomic regions revealed that D1 and A2 were the subgenotypes detected most frequently in the patients examined. The tMRCA estimations of the few HBV D1 Bulgarian significant clades dated back to 23-27 years ago, corresponding to the early 1980s. The HBV A2 Bulgarian sequences fell into two closely related supported clusters dated to 2003 and 1996 years, respectively, suggesting a more recent introduction of subgenotype A2 into Bulgaria. The study provides new information about the HBV subgenotypes in Bulgaria.


Registration of viral hepatitis cases by type started in 1982 in Bulgaria, and in August 1991 Bulgaria launched a mass immunisation programme to vaccinate infants against hepatitis B. The objective of this
dissertation thesis is to study the epidemiological status of hepatitis B virus (HBV) infection in Plovdiv region (the second largest administrative region in Bulgaria with a population of 683,027 people in 2011), and assess the epidemiological process dynamics as a result of the administration of a recombinant vaccine that has been used over the past two decades.


BACKGROUND: Bulgaria adopted the World Health Organization recommendation of routine universal infant vaccination against hepatitis B in 1991. Nevertheless, only a few studies evaluated the protection after the vaccination against hepatitis B, especially in children. The objective of this study was to investigate the duration of protection against hepatitis B in children aged 5-15 years after primary immunization, by measuring the immune and anamnestic immune response and possible breakthrough infections. METHODS: A total of 141 children (aged 5-17 years) were recruited randomly and divided into 3 groups, approximately 5 years (group 1), 10 years (group 2) and 15 years (group 3) after primary immunization with a recombinant hepatitis B vaccine; they were tested for hepatitis B markers: hepatitis B surface antigen anti-hepatitis core antibody and antibodies to hepatitis B surface antigen (anti-HB). A booster dose of vaccine was administered to 23 children with titers of anti-HBs antibodies below the threshold considered to be protective (<10 mIU/mL). Anti-HBs concentrations and geometric mean concentration (GMC) were determined before and 21-28 days after the booster vaccination. RESULTS: Protective anti-HBs antibodies were detected in 95 of 141 (67.4%) tested children, with a GMC of 63.57 mIU/mL. The seroprotection rate and GMC by groups was respectively: 84.6% and GMC of 76.05 mIU/mL in group 1; 55.8% and GMC of 58.1 mIU/mL in group 2; and 61.1% and GMC of 50.33 mIU/mL in group 3. Hepatitis B surface antigen and anti-hepatitis core antibody were found in 1 of the 141 subjects (0.7%). Of the remaining 140 children, 95 had anti-HBs ≥10 mIU/mL, and anti-hepatitis core antibodies were not detected. A booster dose of hepatitis B vaccine was administered to 23 of 45 (51%) children with anti-HBs <10 mIU/mL. Anamnestic immune response was shown in 100% of the children: the GMC was 337.38 mIU/mL and protective antibodies ranged between 15 and 955 mIU/mL. CONCLUSION: The study demonstrates the presence of immune memory and protection 5-15 years after the initial course of newborn immunization with recombinant vaccines against hepatitis B.

Kosovo


INTRODUCTION: Infections with hepatitis C are on the rise. The statistics on the general population of Kosovo infected with hepatitis C is lacking. The study tends to detect sero-prevalence in the following risk groups: haemodialysis patients; patients of surgical units, internal medicine units, and mental health units; HIV-diagnosed patients, health professionals, and women in the prenatal period. A number of institutions, providers of medical care to these groups’ patients, have been targeted. METHODOLOGY: A total of 378 samples were collected from various institutions, with 347 of them being tested for anti-HCV and 31 being tested for RT-PCR assays. RESULTS: From the total of 387 samples, 72 samples (19.05%) resulted positive. The highest number was recorded in haemodialysis centres. In other groups, a low prevalence was recorded. CONCLUSIONS: The study can conclude that high prevalence of HCV infection still remains a major health problem, especially in haemodialysis centres. In the future, it is planned to expand the study in the future to include other risk categories or the entire population.


BACKGROUND In the Republic of Kosovo, full vaccination status in children under age 2 years includes: 1 dose of Bacillus Calmette-Guerin (BCG) hepatitis B virus (HBV) vaccine; 3 doses of diphtheria, tetanus, pertussis, hepatitis B, polio, and Haemophilus influenzae type b (DTaP-HB-IPV-Hib) vaccine; 3 doses of inactivated polio vaccine (IPV); and 1 dose of measles, mumps, and rubella (MMR) vaccine. Lot quality assurance sampling (LQAS) is a method used to assess the performance of health quality indicators. MATERIAL AND METHODS A national cross-sectional study with children aged between 12 and 24 months from Kosovo was performed between 2018 and 2020. The vaccination status of children was
assessed with lot quality assurance sampling (LQAS) using randomized samples. RESULTS Among 430 children, more than 90% had completed the full immunization schedule. Delays in children’s immunizations were observed. Most vaccinations showed short delays of less than 1 month, followed by delays of up to 3 months. The main reason for vaccination delay was the COVID-19 pandemic, following by child’s illness at the scheduled time of vaccination or the parents were too busy to take the child to the vaccination site. Meanwhile, child age was the only parameter that showed difference among non-vaccinated and fully vaccinated (P<0.001). CONCLUSIONS LQAS analysis showed that between 2018 and 2020 lack of full immunization was due to delay caused by the parent not taking the child to the vaccination site, which may be prevented by improving information given to parents and the use of vaccination reminders.


INTRODUCTION: It has recently been demonstrated that there is a very high prevalence of hepatitis C virus (HCV) infection among hemodialysis patients in Kosovo with HCV subtype 1 being the most prevalent subtype. In this study, we further detail the molecular epidemiology of HCV outbreaks occurring in seven dialysis centers in Kosovo. METHODOLOGY: In total, 273 samples obtained from HCV RNA positive patients undergoing hemodialysis at one of the seven centers in Kosovo were selected for this study: 171 subtype 1a samples, 91 subtype 4d samples, and 11 subtype 1b samples. A partial HCV NS5B region was amplified and sequenced. Subtype-specific phylogenetic analyses were performed with the inclusion of control sequences and transmission clusters were identified. RESULTS: NS5B sequences were successfully obtained in 257/273 (94.1%) of samples; 162 subtype 1a, 84 subtype 4d, and 11 subtype 1b sequences. Phylogenetic analyses showed a high degree of phylogenetic clustering of HCV sequences subtyped 1a (99.4%), 1b (63.6%), and 4d (76.2%). Distinct phylogenetic clusters of sequences obtained from hemodialysis patients were observed for all three subtypes studied. In addition, several smaller clusters within the large clusters were identified, mainly from a single dialysis center.

CONCLUSIONS: Phylogenetic analyses confirmed nosocomial transmission during dialysis as a major factor in the spread of HCV at the seven dialysis centers in Kosovo.


BACKGROUND: Patients on hemodialysis are at high risk for hepatitis C virus (HCV) infection if measures for effective control of HCV infection in the hemodialysis environment are not implemented. Whereas in developed countries isolated small-scale outbreaks of HCV in hemodialysis units are occasionally reported, HCV transmission in the hemodialysis environment still represents a substantial problem in low-resource countries. This study systematically assessed the prevalence of HCV infection among all patients at all hemodialysis centers in Kosovo, determined the HCV genotype distribution, and reviewed the main risk factors associated with HCV infection in this group of patients. METHODS: From January to March 2013, blood samples from all patients undergoing hemodialysis at all seven hemodialysis centers in Kosovo were collected. The samples were screened for the presence of anti-HCV antibodies, and seropositive samples were also tested for HCV RNA. Genotyping was performed by sequencing the core region of the HCV genome. Subsequently, face-to-face interviews were conducted with consented patients attending hemodialysis in December 2015 and with the management of all hemodialysis centers in Kosovo. RESULTS: The overall seroprevalence of HCV infection among hemodialysis patients in Kosovo was 53.0% (354/668), ranging from 22.3 to 91.1% at different centers. HCV RNA was detected in 323/354 (91.2%) seropositive patients. The most frequent HCV genotype was genotype 1a (62.2%), followed by genotypes 4d (33.1%), 1b (4.0%), and 2c (0.7%). The duration of hemodialysis and receiving dialysis at more than one center were identified as independent significant predictors of anti-HCV positivity. Shortage of staff, lack of resources, and inconsistent use of hygienic precautions and/or isolation strategies were observed. CONCLUSIONS: The prevalence of HCV infection among hemodialysis patients in Kosovo is extremely high. The relatively low prevalence of HCV infection in the general population, predominance of two otherwise rare HCV genotypes among hemodialysis patients, and longer history of hemodialysis as a predictor of HCV infection all indicate nosocomial transmission due to inappropriate infection control practices as the main transmission route.
Macedonia


BACKGROUND: Intergenotypic recombinant hepatitis C virus (HCV) strains emerge rarely during coinfection of the same individual with two HCV genotypes. Few recombinant HCV strains have been identified to date and only one, CRF01 2k/1b, has become a worldwide concern. This study reevaluated the genotyping of three HCV genotype 2 strains from a group of patients with an unusually low rate of sustained virological response after pegylated interferon/ribavirin treatment. In addition, genetic determinants of host interferon resistance were evaluated. METHODS: The HCV type 2 strains from the patients’ serum were subjected to partial sequencing of the core-E1, NS2, NS5A and NS5B regions by reverse transcription polymerase chain reaction. Furthermore, the IFNL3 rs12979860 and the IFNL4 rs368234815 single nucleotide polymorphisms were defined in two of the three patients. RESULTS: All three strains were phylogenetically related to the Russia-derived CRF01 2k/1b while they encompassed the exact same 2k/1b junction site within NS2. CONCLUSION: This is the first report of HCV 2k/1b recombinants in Greece and the greater area of the Balkans.


The aim of this study was to make a clinical characterisation of patients with hepatocellular carcinoma and to investigate the expression of a set of molecular markers in patients from the Republic of North Macedonia. We analysed 60 patients for clinicopathologic factors, and we investigated tumour tissue and surrounding liver tissue for immunoexpression of E-cadherin, β-catenin, cyclin D1, and p53. Infection with hepatitis virus B and C (p < 0.001), tumour dimension (p < 0.001), vascular invasion (p < 0.002), and tumour differentiation (p < 0.021) significantly influenced the survival of the patients. E-cadherin and β-catenin expression reduction and cyclin D1 and p53 overexpression were significantly higher in the tumour than in the non-tumour tissue (p < 0.001; p < 0.001; p = 0.001; p < 0.001, respectively). No significant correlation was found between clinicopathological characteristics and the analysed molecules nor between the molecules themselves. The immunoexpression of E-cadherin, β-catenin, cyclin D1, and p53 was not related to the tumour aggressiveness and prognosis. However, their significantly higher expression in HCC tissue compared to that in non-tumour tissue indicate their important role in hepatocarcinogenesis. The clinicopathological characteristics of the neoplasm remain highly predictive factors for the survival of the patients.


The prevalence of hepatitis C virus (HCV) genotypes depends on geographical location. HCV genotyping is important for epidemiological investigations and treatment management. The aim of this study was to determine the HCV genotype prevalence in the most prominent risk groups in the Republic of Macedonia in the last 5 years and to evaluate its association with patient’s age, gender, and mode of transmission. A total of 1,167 HCV positive patients, divided into three risk groups (intravenous drug use, chronic hemodialysis, and other risk factor), were genotyped using an in-house ASO hybridization method with genotype-specific oligonucleotide probes. The genotypes 1, 2, and 3 were present with 52.2%, 0.6%, and 47.0%, respectively. Genotype 1 was most prevalent in hemodialysis (89.0%) and other risk factor group (53.8%). It was found associated independently with hemodialysis, age >40 and female gender. Genotype 3 predominated in intravenous drug users (64.0%) and was associated significantly also with age ≤40 and male gender. Multivariable logistic regression analysis pointed out hemodialysis (P < 0.0001, Exp (B) = 12.0) as a positive predictor factor for genotype 1 and age ≤40 (P = 0.021, Exp (B) = 1.8) and intravenous drug use (P < 0.0001, Exp (B) = 8.4) as a positive predictor factors for genotype 3. In conclusion, the main transmission route of HCV infection in the Republic of Macedonia is intravenous drug use, followed by hemodialysis. HCV genotypes 1 and 3 dominate in these two most prominent risk groups in the Republic of Macedonia.

Hepatitis C virus (HCV) is a major public health problem. It is a leading cause of chronic liver disease and the most common indication for liver transplantation. The therapy for eradication of HCV infection is successful in only 50.0-80.0% of patients and is highly dependent on the HCV genotype. Molecular detection and characterization of HCV in the Republic of Macedonia started in 1990. Since then, more than 4000 samples have been analyzed at the Research Centre for Genetic Engineering and Biotechnology (RCGEB) "Georgi D. Efremov," Skopje, Republic of Macedonia. The prevalence of HCV infections in the healthy population of the Republic of Macedonia was found to be 0.4%, while it varies between 23.0 and 43.0% in different at-risk groups of patients. The prevalence of HCV genotypes, according to associated risk factors in HCV infected patients from the Republic of Macedonia, was analyzed. We found genotype 1 to be predominant in a group of hemodialysis patients, while genotype 3 was predominant in intravenous (IV) drug users. Association of six polymorphisms in the Oligoadenylate synthetase (OASL)-like interferon-stimulated gene with a sustained virological response was also analyzed. Our preliminary results suggest that non ancestral alleles in four of the six studies polymorphisms in OASL gene are associated with sustained virological response among HCV infected patients in R. Macedonia.

Montenegro


Few reports are available on HCV molecular epidemiology among IDUs in Eastern Europe, and none in Montenegro. The aim of this study was to investigate the HCV genotype distribution in Montenegro among IDUs and to perform Bayesian and evolutionary analysis of the most prevalent HCV genotype circulating in this population. Sixty-four HCV-positive IDUs in Montenegro were enrolled between 2013 and 2014, and the NS5B gene was sequenced. The Bayesian analysis showed that the most prevalent subtype was HCV-3a. Phylogenetic data showed that HCV-3a reached Montenegro in the late 1990s, causing an epidemic that exponentially grew between the 1995 and 2005. In the dated tree, four different entries, from 1990 (clade D), 1994 (clade A) to 1999 (clade B) and 2001 (clade C), were identified. In the NS5B protein model, the amino acids variations were located mainly in the palm domain, which contains most of the conserved structural elements of the active site. This study provides an analysis of the virus transmission pathway and the evolution of HCV genotype 3a among IDUs in Montenegro. These data could represent the basis for further strategies aimed to improve disease management and surveillance program development in high-risk populations.


BACKGROUND: People who inject drugs (PWID) have significantly higher rates of blood borne and sexually transmitted infections due to unsafe injecting practices and risky sexual behaviors. METHODS: We carried out an HIV bio-behavioral survey using respondent-driven sampling (RDS) in people who use drugs (PWID) in Podgorica, Montenegro in 2013 in order to determine the prevalence of HIV, hepatitis C (HCV), hepatitis B surface antigen (HBsAg) and risk behaviors. Data were analyzed using RDS Analyst and SPSS 12.0 to obtain prevalence estimates of key bio-behavioral indicators and assess correlates of needle and syringe sharing using multivariate logistic regression. RESULTS: A total of 402 PWID were recruited. HIV prevalence was 1.1%, while the prevalence of HCV and HBsAg was 53.0% and 1.4%, respectively. In the multivariate analysis, significant correlates of needle and syringe sharing in the past month were being older than 26 years, female, injecting drugs more than once per day, injecting in parks or on streets, not being able to obtaining free-of-charge sterile needles and syringes and reporting more than four partners in the past 12 months. CONCLUSIONS: The results indicate that the HIV epidemic in PWID in Montenegro might still be at a low level, though the HCV epidemic is well-established.


The Mediterranean area and the Balkans in particular show the highest level of genetic heterogeneity of HBV in Europe. Data about the circulation of HBV genotypes in Montenegro are lacking. It was studied
the prevalence and distribution of HBV genotypes/subgenotypes in a total of 150 HBV infected patients living in Montenegro. Phylogenetic analysis of 136 successfully amplified P sequences showed a high degree of genetic heterogeneity of HBV in Montenegro. Subgenotype D2 (36.8%) and D3 (32.3%) were the most prevalent, followed by genotype A (subgenotype A2 in all of the cases-19.8%). Eight patients were infected with recombinant strains. HBV-D1 which is the most spread HBV subgenotype in the southeastern Mediterranean countries, seems to be relatively rare in Montenegro, suggesting a penetration of HBV more probably from North-East or West than from Eastern Mediterranean countries. The relatively different prevalence of D3 and A2 among subjects infected through sexual route, seems to confirm the association of these subgenotypes with different route of transmissions (mainly parenteral for D3 and mainly sexual for A2) even in Montenegro. The low prevalence of D2 among children and its absence in perinatal transmission, suggests that this subgenotype circulated prevalently in the past. If this is due to changes in the most prevalent way of transmission and in the recent different contacts of Montenegro with other European countries, it remains to be established by other larger studies.


BACKGROUND: In Southeastern Europe, similar to other postsocialist regions on the continent, injection drug users (IDU) are exposed to a high risk of blood-borne infections. In this paper, we report the prevalence of HIV, hepatitis C (HCV) and hepatitis B (HBV) among IDUs in Montenegro. We also examine the risk factors associated with HCV diagnosis. METHODS: In 2008, 322 IDUs in Montenegro participated in a respondent-driven sampling survey. Blood specimens were collected and tested for HIV, HCV and HBV. Behavioral data were collected with self-administered questionnaires. RESULTS: In comparison to 2005, HCV prevalence had increased from an estimated 22 to 53.7%. Only one HIV and no HBV cases were detected. Anti–HCV positivity was associated with the region of origin, income, sharing injection equipment and frequency of injecting drugs. CONCLUSION: The increasing HCV prevalence among IDUs in Montenegro calls for increased and better designed programs to prevent its further spread and a potential HIV outbreak.


More than 20 million hepatitis C virus (HCV) carriers live in the countries of the Eastern Mediterranean. We determined HCV genotype distribution among chronically infected patients in Montenegro and investigated the phylodynamics and phylogeography of the most represented HCV subtypes. The HCV-NS5b sequences of the Montenegrin patients were compared with sequences isolated in different known localities of the Mediterranean area, Europe and Asia. A Bayesian approach was used in order to allow the simultaneous estimate of the evolutionary rate, time-scaled phylogeny, demography and ancestral spatial status. The most frequent HCV subtypes among the Montenegrin patients, were 1b (34.7%) and 3a (24.7%), but there was also a significant prevalence of 1a and 4d (19.5%). Subtype 3a was significantly more frequent among younger patients and intravenous drug users (IDUs), whereas subtype 1b was more frequently associated with iatrogenic exposure and older ages. The spatio-temporal analysis of the epidemic suggested that HCV-1b penetrated Europe at the beginning of the XX century, probably through Greece and Cyprus and in the 1920s reached Montenegro, where there was an exponential increase in the effective number of infections between the 1950s and 1970s. The phylogeographic and phylodynamic analysis of HCV 3a showed that its most probable origin was in the Indian sub-continent (Pakistan in our reconstruction) about 300 years ago. The evolutionary dynamics analysis showed that HCV-3a reached Montenegro more recently in the late 1970s and underwent multi-phasic growth still persisting. Our data suggest multiple introduction of HCV subtypes in the area, supported by different causes of dispersion: adverse social conditions and unsafe medical practices for HCV-1b and i.v. drug use for HCV-3a.

Slovenia


INTRODUCTION: In Slovenia national strategies to prevent hepatitis B virus (HBV) infection in children were introduced in the mid-nineties. The aim of the present study was to analyze the epidemiological characteristics of chronic hepatitis B infection in children in Slovenia after the introduction of mandatory
HBV vaccination of children and mandatory screening of pregnant women for HBV surface antigen (HBsAg) with consecutive active and passive immunization of newborns of HBsAg-positive mothers.

METHODS: Children from all regions of Slovenia whose blood samples tested positive for HBsAg at the national reference laboratory for viral hepatitis between January 1997 and December 2010 were included. Demographic, epidemiological and virological data were reviewed retrospectively. Statistical evaluation of the patients' characteristics was performed and possible trends during the observation period determined. RESULTS: Among 52 HBsAg-positive children, there were 22 (42.3%) girls and 30 (57.7%) boys. Among 40 children tested for HBeAg, 17 were positive (42.5%). The most frequent risk factor for acquiring HBV infection was “presence of HBV infection within the family” (24/35; 68.6%). A significant association between the presence of HBeAg and a viral load of >20,000 IU/ml was found (p=0.001). The difference in the proportion of children of Slovenian origin born before 1994 and after was statistically significant (p=0.039). A statistically significant negative linear trend of the number of diagnosed children in the observed period was found (p=0.006). CONCLUSIONS: Prevention strategies adopted in the mid-nineties have resulted in the elimination of chronic hepatitis B in children of Slovenian origin born in Slovenia.


BACKGROUND: National testing strategy, including monitoring and evaluation, is critical in responding to HIV, sexually transmitted infections, and viral hepatitis. Community-based voluntary counselling and testing contributes to early HIV diagnoses among key populations. Countries providing community-based testing, should integrate some core data on testing and linkage to care in these services into national surveillance and monitoring and evaluation systems. This study aimed to support the integration of community-based voluntary counselling and testing data into respective national surveillance and M&E systems for those infections. METHODS: Preliminary consensus on indicators for the integration of community-based voluntary counselling and testing data into respective national surveillance and monitoring and evaluation systems was reached. Pilot studies were conducted in Estonia, Poland, Serbia, Slovakia, Slovenia and Spain. After pilot activities were implemented, the final consensus on indicators was reached. An analysis of the facilitators and barriers faced during pilot studies was conducted to inform the final recommendations for implementation. RESULTS: The minimum set of six indicators to be integrated into national surveillance and monitoring and evaluation systems were: number of tests, number of clients tested, reactivity rate for tests and clients, positivity (active infection) rates for tests and clients, linkage to care rates for clients with reactive and/or positive test result, proportion of all new diagnoses in a country with first reactive test result at community-based voluntary counselling and testing service. Seven additional indicators were identified. Each indicator should be disaggregated by key population, sex and age group. A list of 10 recommendations for the collection and integration of community-based voluntary counselling and testing data into respective national surveillance and monitoring and evaluation systems for HIV, sexually transmitted infections and viral hepatitis was identified. CONCLUSIONS: Integration of some community-based voluntary counselling and testing monitoring and evaluation data into national surveillance and monitoring and evaluation systems in all pilot countries was achieved. The recommendations will support such integration in other European countries. European Centre for Prevention and Control of Diseases included questions from the minimum list of indicators into their Dublin Declaration questionnaire 2020 to contribute to evidence based community testing policies in European countries.


AIMS: To estimate the prevalence of anti-HBc-positive patients with functioning kidney graft, to detect the anti-HBc-positive patients in danger for hepatitis B virus (HBV) reactivation and to update Slovenian guidelines on hepatitis B follow-up, vaccination, introduction of chemoprophylaxis or treatment.

MATERIALS AND METHODS: The Slovenian national cohort of kidney transplant patients with functioning graft managed at the University Medical Center Ljubljana was included. In a cross-sectional study between March and September 2020, all included patients were screened for the presence of anti-HBc; all anti-HBc-positive patients were additionally tested for anti-HBs, HBsAg, and HBV DNA. RESULTS: Out of a total of 778 included patients, 72 were anti-HBc positive (9.2%). Eight patients (1%) presented with
asymptomatic chronic HBV infection: 6 were HBsAg-positive/HBV DNA-negative, and 2 were HBsAg-negative/HBV DNA positive. In one of the latter, HBsAg mutant variant P120QD144E was proven. By the time of the study, 12 anti-HBc-positive patients (16.6%) have already been receiving chemoprophylaxis. CONCLUSION: The prevalence of anti-HBc-positive patients in the national cohort of kidney transplant patients in Slovenia was 9.2%. Based on the specific combination of HBV markers (anti-HBc, anti-HBs, HBsAg, HBV DNA) we stratified patients into six subgroups. Algorithm on follow-up, hepatitis B vaccination, chemoprophylaxis, or treatment is presented for each of the specific subgroups.


BACKGROUND & AIMS: Prevention of hepatitis C virus (HCV) transmission among people who inject drugs (PWID) is critical for eliminating HCV in Europe. We estimated the impact of current and scaled-up HCV treatment with and without scaling up opioid substitution therapy (OST) and needle and syringe programmes (NSPs) across Europe over the next 10 years. METHODS: We collected data on PWID HCV treatment rates, PWID prevalence, HCV prevalence, OST, and NSP coverage from 11 European settings. We parameterised an HCV transmission model to setting-specific data that project chronic HCV prevalence and incidence among PWID. RESULTS: At baseline, chronic HCV prevalence varied from <25% (Slovenia/Czech Republic) to >55% (Finland/Sweden), and <2% (Amsterdam/Hamburg/Norway/Denmark/Sweden) to 5% (Slovenia/Czech Republic) of chronically infected PWID were treated annually. The current treatment rates using new direct-acting antivirals (DAAs) may achieve observable reductions in chronic prevalence (38-63%) in 10 years in Czech Republic, Slovenia, and Amsterdam. Doubling the HCV treatment rates will reduce prevalence in other sites (12-24%; Belgium/Denmark/Hamburg/Norway/Scotland), but is unlikely to reduce prevalence in Sweden and Finland. Scaling-up OST and NSP to 80% coverage with current treatment rates using DAAs could achieve observable reductions in HCV prevalence (18-79%) in all sites. Using DAAs, Slovenia and Amsterdam are projected to reduce incidence to 2 per 100 person years or less in 10 years. Moderate to substantial increases in the current treatment rates are required to achieve the same impact elsewhere, from 1.4 to 3 times (Czech Republic and France), 5-17 times (France, Scotland, Hamburg, Norway, Denmark, Belgium, and Sweden), to 200 times (Finland). Scaling-up OST and NSP coverage to 80% in all sites reduces treatment scale-up needed by 20-80%. CONCLUSIONS: The scale-up of HCV treatment and other interventions is needed in most settings to minimise HCV transmission among PWID in Europe.

LAY SUMMARY: Measuring the amount of HCV in the population of PWID is uncertain. To reduce HCV infection to minimal levels in Europe will require scale-up of both HCV treatment and other interventions that reduce injecting risk (especially OST and provision of sterile injecting equipment).


INTRODUCTION: Of the 350 million individuals chronically infected with hepatitis B virus (HBV) worldwide, approximately 15 to 20 million have been exposed to hepatitis D virus (HDV). This study determined for the first time the HDV prevalence in Slovenian patients with chronic HBV infection. In addition, a literature search was performed to identify all HDV prevalence studies from European countries. METHODS: A total of 1,305 HBsAg-positive serum samples, obtained from the same number of patients, were randomly selected from 2,337 patients referred to the Slovenian national reference laboratory for viral hepatitis between 1998 and 2015. All samples were retrospectively tested for the presence of total anti-HDV antibodies. Anti-HDV-positive patients were additionally tested for the presence of anti-HDV IgM antibodies, HDV antigen, and HDV RNA. RESULTS: Total anti-HDV antibodies were detected in three of the 1,305 patients tested (0.23%; 95% CI: 0.08-0.67%), of whom one patient had recovered from the past HDV infection and two patients had an ongoing chronic HDV infection. The literature search identified 36 peer-reviewed HDV prevalence studies published between 1983 and 2016 and originating from 21 European countries. CONCLUSIONS: The observed prevalence of HDV infection in Slovenia was among the lowest reported in Europe and worldwide. Due to the observed low
prevalence of HDV infection, routine diagnostic testing for HDV should not be considered in differential diagnosis of exacerbation of liver disease in Slovenian patients with chronic HBV infection.


Hepatitis E is an emerging zoonotic disease caused by hepatitis E virus (HEV). In this study, we investigated HEV presence in a wild boar (Sus scrofa) population of Slovenia. A total of 288 wild boar serum samples were collected throughout the country, and HEV infection was investigated by serology, using enzyme-linked immunosorbent assay (ELISA) and by HEV RNA detection using a real-time PCR assay. Antibodies against HEV were detected in 30.2% (87/288) of animals tested, whereas HEV RNA was detected in only one sample. This is the first evidence of HEV presence in the wild boar population in Slovenia, and these results suggest that these animals are part of the HEV epidemiological cycle in the country.


The majority of people infected with hepatitis C virus (HCV) are unaware of their infection. Assessment of the prevalence of HCV infection in the general population and in key populations at increased risk is needed for evidence-based testing policies. Our objectives were to estimate the prevalence of antibodies to HCV (anti-HCV), the prevalence of HCV viraemia (HCV RNA), and to describe HCV genotype distribution among pregnant women in Slovenia. Unlinked anonymous testing was performed on residual sera obtained from 31,849 pregnant women for routine syphilis screening during 1999, 2003, 2009, and 2013. Anti-HCV reactive specimens were tested for HCV RNA and HCV genotypes were determined. Annual prevalence of anti-HCV ranged between 0.09% (95% confidence interval (CI): 0.03–0.18) in 2009 and 0.21% (95% CI: 0.12–0.34) in 2003 and HCV RNA positivity between 0.06% (95% CI: 0.02–0.14) in 2009 and 0.14% (95% CI: 0.07–0.25) in 2003. We observed no statistically significant differences in anti-HCV or HCV RNA prevalence between age groups (<20, 20–29 and ≥30 years) in any year and no trend in time. Of 29 HCV active infections, 19 were with genotype 1 and 10 with genotype 3. HCV infection among pregnant women was rare suggesting a low burden in the Slovenian general population. Antenatal screening for HCV in Slovenia could not be recommended.


INTRODUCTION: Since the introduction of highly active antiretroviral therapy, chronic hepatitis C has become one of the leading causes of non-AIDS-related morbidity and mortality in patients with HIV infection. Two previous Slovenian nationwide studies published in 2002 and 2009 showed a very low prevalence of hepatitis C virus (HCV) infection among Slovenian HIV-infected individuals (14.5% and 10.7%, respectively). METHODS AND RESULTS: The presence of HCV infection was tested in 579/639 (90.6%) patients that were confirmed as HIV-positive in Slovenia by the end of 2013. Among them, 7.6% (44/579) of HIV-infected individuals were anti-HCV-positive, and 33/44 (75%) anti-HCV-positive patients were also HCV RNA-positive. HCV genotype 1 was most prevalent among HIV-infected patients (68%), followed by genotype 3 (20%), genotype 4 (8%), and genotype 2 (4%). Anti-HCV positivity was significantly higher in those that acquired HIV by the parenteral route (91.8%) than in those that acquired HIV by the sexual route (2.8%). DISCUSSION: Slovenia remains among the countries with the lowest prevalence of HCV infection in HIV-infected individuals. Because the burden of HIV among men who have sex with men in Slovenia is disproportionately high and increasing rapidly, the current favorable situation could change quickly and should be therefore monitored regularly.

Serbia
Fernández-López L, S Baros, M Niedźwiedzka-Stadnik, DV Staneková, M Rosińska, D Simic, V Jovanoic, M Hábeková, M Takáčová, I Wawer, P Wysocki, A Conway, I Klavs and J Casabona (2021). "Integration of
Background Analyses of temporal trends in immunisation coverage may help to identify problems in immunisation activities at specific points in time. These data are essential for further planning, meeting


BACKGROUND: Treating HCV in people with hemophilia prevents the development of end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC) and greatly increases the quality of life for people living with hemophilia. There are many obstacles in reaching the WHO goal of globally eradicating HCV by 2030, mainly its scale, complexity, and implementation. That is why many countries have implemented a micro-elimination strategy: a pragmatic elimination approach in populations with the most efficacy. The aim of this publication is to present the morbidity and mortality rates, the clinical course and treatment outcomes of chronic HCV infection in people with hemophilia (PwH), as well as to show an example of a successfully conducted HCV micro-elimination strategy among people with hemophilia in the Province of Vojvodina. METHODS: A retrospective, single-center study, performed using medical documentation of all registered PwH in the Clinical Center of Vojvodina from 1994. until 2020. It included 74 hemophilia patients, out of which 32 were patients with hemophilia and chronic HCV infection. RESULTS: The mean age of HCV-positive positive people with hemophilia (PwH) was 42.3 years, with the duration of infection of 30-35 years. Co-infection with HIV was observed in 6.25% of cases. Furthermore, 18.75% of patients had spontaneous HCV elimination, and 75% were treated with antiviral protocols. Cirrhosis developed in 21.87% with an incidence rate of 0.6 per 100 patient-years. After treatment with Pegylated IFN and ribavirin (RBV), 58.3% achieved SVR. Side effects of IFN-based therapy regimens were recorded in 20.8% of treated (PwH). In 37.5% PWH, DAA protocols were administered, and these patients achieved SVR. HCV- PwH have a statistically higher mortality rate than non-infected people with hemophilia. Among the HCV-positive PWH, hemophilia-related deaths were 6.25%, and HCV-related deaths were 9.37%. Currently, in the Registry of PWH in Vojvodina, there are no patients with active HCV infection.

CONCLUSION: The micro-elimination strategy in the subpopulation of PWH was successfully implemented in Vojvodina by hematologists and infectious diseases specialists in close collaboration.


Background Analyses of temporal trends in immunisation coverage may help to identify problems in immunisation activities at specific points in time. These data are essential for further planning, meeting
recommended indicators, monitoring, management and advocacy. Aim This study examined the trends of mandatory vaccination coverage in the period 2000-2017 in Serbia. Methods Data on completed immunisations were retrieved from annual national reports of the Institute of Public Health of Serbia during the period 2000-2017. To assess the trends of immunisation coverage, both linear and joinpoint regression analyses were performed. A probability \( p < 0.05 \) was considered significant. Results Over the period 2000-2017 linear regression analysis showed a significant decline in coverage with the primary vaccination against poliomyelitis, diphtheria, tetanus, pertussis and measles, mumps, rubella (MMR) \((p \leq 0.01)\). In the same period, coverage of all subsequent revaccinations significantly decreased, namely, first revaccination for pertussis \((p < 0.01)\); first, second and third revaccination against diphtheria, tetanus and poliomyelitis \((p < 0.01)\); and second dose against MMR before enrolment in elementary school \((p < 0.05)\). Although linear regression analysis did not show change in vaccination coverage trend against tuberculosis \((Bacillus Calmette-Guérin; BCG)\), hepatitis B \((\text{HepB3})\) in infants and diseases caused by Haemophilus influenzae type b \((\text{Hib3})\), the joinpoint regression analysis showed that the coverage declined for BCG after 2006, HepB3 after 2010 and Hib3 after 2008. Conclusion To achieve and keep optimum immunisation coverage, it is necessary to address barriers to immunisation, such as the availability of all vaccines and vaccine-hesitancy among parents and healthcare workers in Serbia.


BACKGROUND: Serbia has an intermediate estimated prevalence of chronic hepatitis C (CHC) infection, approximately 1.13%, with hepatitis C remaining one of the leading causes of liver-related morbidity and mortality in Serbia with impaired quality of life and overwhelming cost of treating its complications. As the availability of new treatment options and resources for screening remains limited, micro-elimination of CHC becomes a top priority. METHODS: Review of the available published data related to the clinical and epidemiological situation of the hepatitis C infection in Serbia, including the unpublished data from the databases of four major reference centres in Serbia (Clinical Center Serbia, Clinical Center Niš, Clinical Center Vojvodina and Clinical Center Kragujevac). RESULTS: Currently in Serbia, micro-elimination appears to be realistic in the patients with haemophilia, who represent a small, well-defined subpopulation, under constant monitoring by the healthcare system. Other feasible targets for micro-elimination of CHC infection in Serbia are patients on hemodialysis, prisoners and people who inject drugs. CONCLUSIONS: Micro-elimination is feasible in Serbia, especially in the subpopulation of patients with haemophilia. This may represent an initial step towards achieving the WHO objective to eliminate hepatitis C infection by 2030.


INTRODUCTION: Hepatitis E is considered an emerging human viral disease with many evidences of zoonotic nature of disease, and swine are the main reservoir of HEV. The aim of this study was to determine HEV seroprevalence in commercial pig farms, backyard pigs, slaughtered pigs and wild boars in the region of the city Belgrade. METHODOLOGY: A total of 405 sera samples: 150 samples from 3 commercial pig farms, 70 samples from backyard pigs, 119 samples from slaughtered pigs and 66 samples from wild boars of the region of the city Belgrade, Serbia were analysed by commercial ELISA test. RESULTS: The overall HEV seroprevalence in 3 commercial pig farms was 55.33% (83/150). All tested farms (farm A, B and C) were positive on the presence of anti-HEV antibodies, respectively 58% (29/50), 54% (27/50) and 54% (27/50). From 70 tested backyard pigs, 75.71% (53/70) were tested seropositive. In total, 26 backyard pig holdings were confirmed as positive to anti-HEV antibodies (81.25%). At slaughterhouse, 25% (8/32) weaned piglets and 20.69% (18/87) fattening pigs were tested positive on anti-HEV antibodies. Overall HEV seroprevalence in tested wild boar population was 52.25% (36/66). CONCLUSIONS: Detected very high seroprevalence of anti-HEV antibodies indicated an active circulation of HEV, being enzootic in the swine population, and wild boars, as well, in the region of the city Belgrade.


BACKGROUND: Chronic hepatitis C virus (HCV) infection, that is defined by active carriage of HCV RNA in the blood, is represents one of the major public health problems worldwide. In Serbia, the prevalence of
METHODS: The aim of our study was to evaluate the ability of noninvasive scores in order to define the degree of liver fibrosis, and to assess the effect of host and viral factors on fibrosis in chronic HCV patients. In a retrospective analysis a total of 814 patients with chronic HCV infection were included. Liver fibrosis scores were calculated, and in particular AST/ALT Score APRI, Forns Index, and FIB-4 score, and all of them compared with histological classification. RESULTS: We found that noninvasive biochemical scores of fibrosis, have a good performance especially to distinguish mild and moderate fibrosis to advanced fibrosis. In particular, we found that FIB-4 score is a useful screening tool to accurately exclude patients with advanced disease. CONCLUSIONS: Noninvasive liver fibrosis scores are efficient tools in the management and follow-up of HCV patients in clinical practice.


BACKGROUND: Globally, an estimated 257 million people are living with chronic hepatitis B (HBV) infection and an estimated 71 million people with the chronic hepatitis C virus (HCV). The true public health dimensions and impact of hepatitis epidemics are poorly understood. Case definitions are fundamental parts of disease surveillance, representing sets of standardised criteria used to assess whether or not a person has a certain disease. The study evaluated the sensitivity and specificity of hepatitis B and hepatitis C case definitions, current at the time of data collection, recommended by the European Commission (EC) and the Centers for Disease Prevention and Control (CDC). METHODS: The study involved 150 hospital referrals with suspected cases of hepatitis from a Serbian clinic during 2014/2015. Case definitions of hepatitis B and C were tested for their sensitivity, specificity, positive and negative predictive values. RESULTS: EC 2008 and the CDC 2012 case definitions for acute hepatitis B, and the CDC 2012 case definition for probable case of chronic hepatitis B have low sensitivity. Case definitions which rely on laboratory confirmation only have maximal sensitivity. EC case definitions showed maximal sensitivity and specificity for hepatitis C confirmed cases. The CDC case definition for chronic hepatitis C showed low sensitivity (36.8%) and low negative predictive value (65.6%) for probable cases and maximal sensitivity and specificity for confirmed cases. Hepatitis C case definitions requiring presence of clinical criteria have low sensitivity and high specificity, resulting from presence of infection and absence of any clinical manifestation, but have high positive and negative predictive values. CONCLUSION: Syndromic case definitions show low sensitivity and are of limited use. They highlight the importance of laboratory diagnostics (offering maximal sensitivity and specificity, and high positive and negative predictive values), as well as the need for universal case definitions, for confirmed cases only.


To assess the current hepatitis A virus (HAV) endemicity in the Autonomous Province of Vojvodina, Serbia, we examined the seroprevalence and susceptibility profiles of the general population. A serum bank of 3466 residual samples, collected in 2015-16 as per the specifications of the European Sero-Epidemiology Network 2 project (ESEN2), was tested for anti-HAV antibodies with an enzyme immunoassay. Relationships between anti-HAV positivity and demographic features of respondents were examined by univariable and multivariable analyses. Present-day HAV seroprevalence was compared with that obtained in 1978-79. Surveillance data for hepatitis A recorded between 2008 and 2017 were also analyzed. Age was the only demographic variable found to be independently associated with a HAV seropositive status. Seropositivity (17% overall vs. 79% in 1978-79) increased with age to a maximum of 90% in the elderly ≥60 years. Only 5% of subjects <30 years were seropositive, unlike the 44% of seropositives ≥30 years. The estimated age at midpoint of population immunity (AMPI) increased markedly from 14 years in the late 70s to 55 years in 2015-16. Meanwhile, disease incidence decreased noticeably in recent years (from 11 in 2008 to 2 per 100,000 population in 2017). In the ongoing pre-vaccine era, natural infection provides immunity for merely a third (31%) and two thirds (57%) of people in their 40s and 50s, respectively. Hence, the majority of people ≤40 years (94%) and middle-aged adults 40-49 years (69%) are susceptible to HAV. Older susceptible individuals, particularly those ≥50 years (24%), are prone to severe symptoms. Taken together, these changes reflect the epidemiological transition of Vojvodina and Serbia from high to very low HAV endemicity, thereby supporting the current national policy of immunization of only high-risk groups.


Milošević I, U Karić, I Pešić-Pavlović, G Stevanović, A Barač, M Smiljanić, A Arsenović, O Stevanović, M Donin-Nenezić and B Brmbolić (2018). "Successful treatment of chronic hepatitis C in a hemodialysis patient in Serbia. The patient infected with genotype 1a has been successfully treated with Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir and Ribavirin. There are only a few real world reports regarding this therapeutic option in hemodialysis patients.


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.


Despite the availability of a safe and effective vaccine since 1982, overall coverage of hepatitis B vaccination among healthcare workers (HCWs) has not reached a satisfactory level in many countries worldwide. The aim of this study was to estimate the prevalence of hepatitis B vaccination, and to assess the predictors of hepatitis B vaccination status among HCWs in Serbia. Of 380 randomly selected HCWs, 352 (92.6%) were included in the study. The prevalence of hepatitis B vaccination acceptance was 66.2%. The exploratory factor analyses using the vaccination-refusal scale showed that items clustered under ‘threat of disease’ explained the highest proportion (30.4%) of variance among those declining vaccination. The factor analyses model of the potential reasons for receiving the hepatitis B vaccine showed that ‘social influence’ had the highest contribution (47.5%) in explaining variance among those vaccinated. In the multivariate adjusted model the following variables were independent predictors of hepatitis B vaccination status: occupation, duration of work experience, exposure to blood in the previous year, and total hepatitis B-related knowledge score. Our results highlight the need for well-planned national policies, possibly including mandatory hepatitis B immunisation, in the Serbian healthcare environment.

INTRODUCTION: Medical students are mainly exposed to needle stick and sharp object injuries in the course of their clinical activities during studying. They are at high risk due to their undeveloped skills, restricted clinical experience, lack of knowledge and risk perception. The objectives of this study were to determine the prevalence of needle stick injuries of the fourth and final year medical students, and to estimate their knowledge about blood-borne pathogens disease transmission and standard precautions.

METHODS: This cross-sectional study was conducted at the Faculty of Medicine, in February 2014. The students were invited to self-administer a questionnaire of 26 closed questions prepared for this study.

RESULTS: The questionnaire was filled in and returned by 637 students. The prevalence of needle sticks and sharp object injuries was 29.5%. Needle stick injuries were the most common type of accidents, more frequent among the fourth compared to the sixth year students (p=0.002). The majority of accidents occurred in patient rooms (53%) and the emergency department (15%). 54% of participants reported an accident to the responsible person. Students without accidents had a significantly better perception of risk (3.79 vs. 3.35; p<0.05). Out of the total participating students, only 16.6% (106/637) received all three doses of Hepatitis B vaccination, while 16.2% were partially vaccinated. CONCLUSIONS: There is a need for additional theoretical and practical education of our students on blood exposure via accidents, raising the awareness of the necessity of hepatitis B vaccination, and introducing the unique/comprehensive procedure for accident reporting for students and healthcare workers in the entire country.


INTRODUCTION: About one quarter of human immunodeficiency virus (HIV) infected persons in Serbia have also been found to be hepatitis C virus (HCV) co-infected. In the general population, HCV genotype 1 has been shown to be the most prevalent one. Here, we present the first study on the distribution of HCV genotypes among HIV/HCV co-infected patients in Serbia, in relation to epidemiological and clinical features. MATERIAL AND METHODS: The study included HIV/HCV co-infected and a group of HCV mono-infected patients in the period 1998-2012, with collection of epidemiological, clinical, and behavioral data using a standardized questionnaire. The HCV genotyping to the level of pure genotype was performed by reverse hybridization. RESULTS: Intravenous drug use (IDU) was found to be significantly more prevalent among the co-infected patients (p < 0.01). HCV genotype 1 was detected in 87% of patients with mono-infection, compared to 46.3% of patients with co-infection (p < 0.01); genotypes 3 and 4 were significantly more common among co-infected patients (6% and 5%, vs. 27% and 25%, respectively). Multivariate logistic regression confirmed IDU, infection with non-1 HCV genotype and HCV viral load over 5 log to be predictors of HIV co-infection. CONCLUSIONS: The HCV genotypes 3 and 4 were found to be significantly more prevalent among HIV/HCV co-infected patients in Serbia, compared to HCV mono-infected patients, but also more prevalent compared to the European HIV/HCV co-infected cohort. History of IDU represents an independent predictor of HCV genotypes 3 and 4 infection, with important implications for treatment.


The goal of this study was to identify host and viral factors affecting the response to pegylated interferon/ribavirin (PEG-IFN/RBV) treatment in patients with chronic hepatitis C genotype 1b. Baseline characteristics of the patients and sequences within the p7 region were analyzed in pre-treatment serum samples from 53 individuals with chronic hepatitis C genotype 1b and related to the outcome of therapy. We found a significant correlation between age and response to therapy (p < 0.001). Furthermore, the pre-treatment viral load was closely associated with the stage of liver fibrosis (p < 0.001). The presence of fewer than 4 mutations and age above 40 were significantly associated with non-response (NR) (p < 0.001). Our findings may be useful for estimating the likelihood of achieving a sustained virologic response (SVR) in patients who are chronically infected with hepatitis C virus genotype 1b.


BACKGROUND: Chronic ethyl alcohol consuming is well known independent negative predictor of unfavorable natural course and therapy outcome of Chronic Hepatitis C (CHC) infection. OBJECTIVE: The aim of the present study was to clarify the impact of alcohol consumption on fibrosis rate progression in patients with CHC and Sustained Virologic Response (SVR) rates in patients undergoing treatment with
INTRODUCTION: The triple therapy which consists of one of the protease inhibitor plus pegylated interferon and ribavirin. METHOD: This cross sectional retrospective study included 807 CHC patients underwent liver biopsy and hospitalized at Clinical center of Vojvodina, Novi Sad, Serbia. According to the alcohol consumption equal or greater than 50 g/day prior to liver biopsy, patients were divided into two groups. We compared demographic, clinical, virologic and histopathological markers of CHC, as well as response to antiviral therapy. RESULTS: We find statistically significant differences (p=0.001) in gender, but not in age (p=0.081), estimated duration of the CHC (p=0.470) and hepatitis C genotype (p=0.545) between two groups. Among patients with CHC who consume alcohol ≥50 g/day there were significantly higher incidence of intravenous drug users (p=0.000). Binary logistic regression showed that the only independent predictors of moderate to severe fibrosis (fibrosis ≥2) were age (p=0.000) and alcohol use (p=0.027). There was not statistically significant difference in SVR rate between two groups (p=0.810). CONCLUSION: We believe that this good result in treatment outcome was the consequence of proper selection of patients based primarily on regulations of Republic of Serbia on the necessity of abstinence from the use of alcohol and psychoactive substances at least one year before starting antiviral therapy.


INTRODUCTION: Seroprevlence of chronic hepatitis C viral infection in correctional facilities ranges from 16% to 49%. However, there are only very limited data available on the course of hepatitis C viral infection and outcomes oftreatment with pegylated interferon plus ribavirin in correctional settings. The aim of this study was to assess the feasibility and effectiveness of use of pegylated interferon plus ribavirin treatment in the Serbian correctional setting. MATERIAL AND METHODS: The study sample consisted of the patients with hepatitis C hospitalized in the Special Hospital for Prisoners in Belgrade (Serbia) during 2007-2013. Health authorities approved treatment for 32 patients out of 76 treatment-naive patients referred to this institution. The patients (N=32) received 180 mcg pegylated interferon alfa-2a once a week plus oral ribavirin in dosage of 800 mg or 1000/1200 mg/day for 24 or 48-week treatment. All patients who completed therapy were assessed at the end of an additional 24-week treatment-free period for a sustained virological response. RESULTS: Sustained virological response was achieved in 53.8% of hepatitis C viral infection genotype 1 patients and in 73.3% and 66.6% of patients with hepatitis C viral infection genotype 3 and 4, respectively. One patient with mixed genotype (1, 2) did not achieve sustained virological response. The overall safety profile of the treatment regimen was very good. The incidence of influenza-like symptoms and depression were low. A serious adverse event was recorded only in 6.4% of patients. CONCLUSION: The results showed that pegylated interferon alfa-2a plus ribavirin given once a week was well tolerated among prisoners and the regimen had the same adherence and effectiveness as in general population.


INTRODUCTION: The triple therapy which consists of one of the protease inhibitor plus pegylated interferon and ribavirin (P/R) is the standard of care for the treatment of chronic hepatitis C virus (HCV) genotype 1 (G1) infection both in treatment-naive and experienced patients. OBJECTIVE: The aim of this study was to analyze the efficacy and tolerability of this regimen in hospital practice in Serbia. METHODS: From July 2012 to October 2012, 20 previously treated patients with advanced fibrosis and HCV G1 infection were included in the triple antiviral regimen in six referral centers in Serbia. All patients were treated with response guide therapy (RGT) regime according to the boceprevir treatment protocol. During the 4-week lead-in period all patients received peginterferon plus ribavirin. After the lead-in period boceprevir was added in the dosage of 800 mg three times a day orally. The subsequent treatment varied according to virologic response and fibrosis. During the therapy HCV RNA level was measured at week 4, 8, 12, 24 of the treatment for the assessment of virologic response profile. All patients who completed therapy were assessed at the end of the treatment and at the end of an additional 24-week treatment-free period for a sustained virological response (SVR). RESULTS: The total of 20 patients with advanced fibrosis was treated. Among patients with an undetectable HCV RNA level at week 8 the rate of SVR was 100%. No patient with decrease in the HCV RNA level < 1 log 10 IU/ml at treatment week 4 achieved SVR. The overall rate of SVR was 55%. The safety profile of the treatment regimen was good. Anemia was reported in 25% of patients. There was no life-threatening treatment adverse event. CONCLUSION: Boceprevir in combination with P/R achieved fairly good SVR rates in patients that were most difficult to treat who failed on dual therapy and was effective among patients with cirrhosis.
For the first time in Serbia, a small surveillance study was conducted in order to estimate the presence and frequency of occurrence of selected human [adenoviruses (HAdV), noroviruses, (NoV GI, NoV GII) and hepatitis A virus (HAV)], animal [porcine adenovirus (PAdV) and bovine polyomavirus (BPyV)] and zoonotic [hepatitis E virus (HEV)] viruses in selected surface waters. In total, 60 surface water samples were collected in two sampling occasions at 30 locations, with each sampling time being separated by 1-5 months. In addition, six sewage effluent samples were collected at one sampling site per each of the three tested town sewage systems, in two sampling occasions with 2 months intervals, before their discharge into the surface waters. The most prevalent virus found was HAdV which was detected in 43.33 % samples. NoV GI was found in 40 % samples. NoV GI was found in 10 % samples, and PAdV, BPyV and HEV were detected in 5 (8.33 %), 4 (6.67 %) and 2 (3.33 %) samples, respectively. HAV was not found in any of analysed surface waters or urban sewage samples. The obtained results confirm the presence of pathogenic enteric viruses of both human and animal origin in surface waters in Serbia indicating the existence of diverse contamination sources.


BACKGROUND: The epidemiological characteristics of hepatitis C virus (HCV) infection have not yet been described in Serbia. AIMS: To determine the prevalence of anti-HCV-positive individuals among first-time blood donors and the risk factors for hepatitis C transmission. METHODS: A multicentre case-control study nested within a prospective cohort study was conducted at 10 main transfusion centres in Serbia in 2013 and 27,160 blood donors who gave blood for the first time were included. Blood donors with confirmed anti-HCV positivity and seronegative controls were enrolled to determine the risk factors.

RESULTS: Of 27,160 blood donors 52 were anti-HCV-positive; seroprevalence was 0.19%. By univariate analysis, marital status, educational level, drug use, previous transfusion, tattooing, non-use of condoms and number of sexual partners, were risk factors for hepatitis C. In the final multivariate analysis, three factors remained independently predictive: drug use, tattooing and previous blood transfusion. In total, 87.5% of cases had at least one of the risk factors for HCV transmission; 20.9% presumed that they knew when the infection occurred. CONCLUSION: HCV seroprevalence in Serbia is higher than in developed European countries. Preventive measures need to be directed towards drug use and tattooing facilities. The admission questionnaire for blood donors should be improved.


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We report a comprehensive approach for outbreak investigations, including cluster analysis (Bernoulli model), an algorithm to build inferential models, and molecular techniques to confirm cases. Our approach may be an interesting tool to best exploit the large amount of unsystematically collected information available during outbreak investigations in healthcare settings.


INTRODUCTION: Hepatitis E virus (HEV) infection is rarely reported in industrialized countries, but recent studies have revealed quite variable seroprevalence rates among European populations, including blood donors. In Serbia, very limited data about HEV seroprevalence are available. This study aimed to determine the prevalence of anti-HEV IgG antibodies and HEV RNA in the sera of volunteer blood donors in Serbia. METHODOLOGY: Serum samples from 200 volunteer blood donors were tested for the presence of anti-HEV IgG by enzyme-linked immunosorbent assay (ELISA) using ORF-2 HEV genotype 3 recombinant proteins as antigen, and for the presence of HEV RNA by nested reverse transcriptase polymerase chain reaction (RT-PCR). RESULTS: In total, 15% of the volunteer blood donors were seropositive. The prevalence increased with age; 21.5%, 14.2%, and 5.4% HEV seroprevalence rates were found in individuals older than 51 years, between 31 and 50 years, and in those younger than 30 years of age, respectively. However, no HEV RNA was detected in any of the individuals analyzed. CONCLUSIONS: The prevalence of anti-HEV IgG among blood donors as representatives of the general population is quite high in Serbia compared to data from many European countries. One of the reasons for this could
be the high prevalence of HEV among Serbian pigs and the traditional consumption of piglet meat in the country. The relatively high HEV seroprevalence found among Serbian blood donors indicates the need for further investigation.


PURPOSE: The Roma constitute a large ethnic minority in Serbia, and are one of the poorest and most marginalized groups in Europe. Roma youth may be at high risk for hepatitis C, HIV, and other sexually transmitted infections, but little is known about the prevalence of these infectious diseases, HIV-related knowledge, and risky sexual behaviors in this vulnerable population. METHODS: We used a respondent-driven sampling to conduct biobehavioral surveys of Roma youth (aged 15-24 years) in Belgrade and Kragujevac, and to document HIV-related knowledge and risky sexual behaviors, health-seeking behaviors, and seroprevalence of HIV, hepatitis C virus (HCV), and syphilis. RESULTS: Four hundred eleven Roma youth participated in this study. One participant had HIV, four had HCV, and none had syphilis. Risky sexual behaviors were highly prevalent, especially among male subjects: 36.2% (Belgrade) and 45.1% (Kragujevac) had sexual debut before the age of 15 years; 53.9% (Belgrade) and 61.1% (Kragujevac) had more than one sexual partner in the past year; 11.5% (Belgrade) and 4.6% (Kragujevac) reported engaging in commercial sex; and 4.0% (Belgrade) and 3.2% (Kragujevac) reported having anal sex with other men. Among female subjects aged <25 years, 33.5% (Belgrade) and 25.7% (Kragujevac) reported having an abortion. One-quarter of all participants answered all five HIV knowledge questions correctly. CONCLUSIONS: Fortunately, the current prevalence of HIV, HCV, and syphilis is low; however, the high prevalence of reported risky behaviors suggests that Roma youth in Serbia are at high risk of contracting sexually transmitted infections.


Exposure to blood-borne infections (HIV, hepatitis B, hepatitis C) poses a serious risk to health care workers (HCWs). The aim of this cross-sectional study was to determine the level of knowledge and attitudes on occupational exposure in primary health care. In 2009, a total of 100 health care workers from the Primary Health Care Centre in Inđija, Autonomous Province of Vojvodina, Serbia were included in the study. The results suggested that the health care workers who participated in the survey possess basic knowledge about blood-borne virus transmission routes. Most incorrect answers were related to the transmission of blood-borne viruses by tears, saliva, urine and stool. This study also demonstrated that health workers tend to unrealistically estimate the risk of HIV infections. As for the level of education about the prevention and control of blood-borne infections, 49 % of the participants had never had any education on this topic, while 22 % had been educated during the last five years. Around 75 % consider education on blood-borne infection and protective measures at work unnecessary.


BACKGROUND: Pegylated interferon alfa plus ribavirin protocol is currently considered the most efficient hepatitis C treatment. However, no evidence of costs comparison among common viral genotypes has been published. OBJECTIVES: We aimed to assess core drivers of hepatitis C medical care costs and compare cost effectiveness of this treatment among patients infected by hepatitis C virus with genotypes 1 or 4 (group I), and 2 or 3 (group II). PATIENTS AND MATERIALS: Prospective bottom-up cost-effectiveness analysis from societal perspective was conducted at Infectious Diseases Clinic, University Clinic Kragujevac, Serbia, from 2007 to 2010. There were 81 participants with hepatitis C infection, treated with peg alpha-2a interferon plus ribavirin for 48 or 24 weeks. Economic data acquired were direct inpatient medical costs, outpatient drug acquisition costs, and indirect costs calculated through human capital approach. RESULTS: Total costs were significantly higher (P = 0.035) in group I (mean ± SD: 12,751.54 ± 5,588.06) compared to group II (mean ± SD: 10,580.57 ± 3,973.02). In addition, both direct (P = 0.039) and indirect (P < 0.001) costs separately were significantly higher in group I compared to group II. Separate comparison within direct costs revealed higher total cost of medical care (P = 0.024) in first compared to second genotype group, while the similar tendency was observed for total drug acquisition (P = 0.072). CONCLUSION: HCV genotypes 1 and 4 cause more severe clinical course require more care
and thus incur higher expenses compared to HCV 2 and 3 genotypes. Policy makers should consider willingness to pay threshold differentially depending upon HCV viral genotype detected.


BACKGROUND: Hepatitis B virus (HBV) genotypes influence disease progression and treatment outcome. OBJECTIVES: To determine natural history and treatment outcome in patient chronically infected with HBV. STUDY DESIGN: A cohort study included 162 treatment naive patients with chronic HBV infection in order to analyze factors influencing natural history of infection and survival. RESULTS: Genotype A was far less prevalent, detected in 14.2%. The prevalence of HBeAg+ serology of 60.8% among patients infected with genotype A was significantly higher than 30.9% recorded among those with genotype D (P=0.02). Even though patients from two genotypes subgroups had significantly different prevalence of HBeAg serology, their viral loads were similar at the time of diagnosis (2.90 log10 and 3.31 log10 HBV DNA IU/μl plasma, for genotypes A and D, respectively). The analyses of viral loads across three serologic patterns of chronic HBV infection were: for HBeAg+/HBeAb+, HbeAg-/HBAb+, and both “e” antigen and antibodies negative: 4.24, 2.67 and 2.69 log10 IU/ml of HBV DNA IU/μl, respectively (P=0.01). Mean time to liver cirrhosis was 23.2±3.4 years and 15.±8.4 years, for genotypes A and D, respectively (P=0.01). The overall estimated mean survival of patients with chronic HBV infection was 28.4 years, and was influenced by the stage of liver disease, but not by gender, age above 40, viral genotype and lamivudine therapy. CONCLUSIONS: Patients infected with genotype D had more rapid progression to ESLD regardless of levels of viral replication. All clinical and laboratory differences between genotypes did not affect survival of patients with chronic hepatitis B, regardless of lamivudine therapy.


INTRODUCTION: Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide. Pegylated interferon alfa-2a or 2b (PEG IFN alfa-2a or 2b) and ribavirin (RBV) represent a standard treatment of chronic hepatitis C (CHC). Sustained virological response (SVR), defined as continued undetectable HCV RNA 24 weeks after completion of treatment, is universally considered as an indicator of treatment efficacy. OBJECTIVE: The aim of this study was to determine efficacy and safety of PEG IFN alfa-2a and RBV treatment in patients with CHC in Serbia. METHODS: One hundred seventy-six patients with CHC were included in this multicenter trial from 8 reference centers in Serbia. The patients were treated with standard PEG IFN alfa-2a and RBV protocol. We performed the following virological testing: anti-HCV (ELISA), HCV RNK (quantitative PCR), HCV genotype (type-specific PCR), HBsAg, anti-HBs, anti-HBc and anti-HIV (ELISA). Histological activity and the degree of fibrosis were determined according to the Metavir scoring system. Potential predictors for achieving SVR were evaluated using multivariable logistic regression analysis. RESULTS: Of the treated patients with CHC 65.9% were male, and 60.2% of them aged over 40 years. Of the treated patients 68.2% had infection over 5 years, 63% had HCV RNA >400.000 IU/mL, 76.1% had HCV G1/4, and 60.1% had a mild to moderate liver fibrosis. SVR was achieved in 78.9% of patients (G1/4 79.1%; G2/3 78.1%). The factors that indicated a poorer efficacy of the treatment were age >40 (p<0.05), high basal viremia (p=0.013), and the reduction of PEG IFN alfa-2a and RBV doses, with interruption of therapy (p<0.001). Of the treated patients 45.9% had adverse affects (G1/4 50.8%; G2/3 29.7%). CONCLUSION: Treatment of CHC with PEG IFN alfa-2a and RBV was efficient in 78.9% of patients. The safety profile of therapy was satisfactory. Longer therapy increases the possibility of the development of adverse affects. No life-threatening adverse effects were recorded in our patients.


INTRODUCTION: Health workers and medical students are at occupational risk of blood-borne diseases during the accidents, that is, via percutaneous injury or entry of blood or body fluids through the mucosa or injured skin. OBJECTIVE: to review and analyze the knowledge, attitudes and perception of risks of bloodborne diseases of the clinical course students and health workers as well as the frequency of accidents. MATERIAL AND METHODS: Cross-sectional study was carried out among the students of the Faculty of Medicine in Belgrade, and health workers of the Clinical Center of Serbia. The subjects responded anonymously to questionnaire specially designed for the study. RESULTS: Both students and
Health workers were aware, in a high percentage, of the fact that the risk of hepatitis B spread was about 30%. Significantly more students gave affirmative reply that blood as biological material was a potential hazard of HIV infection spread (p = 0.001), and significantly more students knew that HIV would not be spread by sweat (p = 0.001). Hepatitis B vaccination was administered only to 24.1% of students and 71.4% of health workers. About 10% of students and 65.5% of health workers experienced some accident. There was no significant difference of accidents between nurses/technicians and physicians (p > 0.05), as well as of accidents and a total length of service (p > 0.05). The majority of accidents occurred during the use of needle/sharp object (in 27.3% of students and 33.1% of health workers). About 40% of students and slightly over a half of the workers reported the accidents to appropriate authorities. Additional education in this field is considered necessary by 73% of students. CONCLUSION: During the studies and via continuous medical education it is necessary to upgrade the level of knowledge on prevention of accidents, what would, at least partially, influence their reduction.


BACKGROUND/AIM: Military personnel is a population group at special risk of exposure to sexually transmitted diseases (STD). In peacetime, STD infection rates among service members are generally 2 to 5 times higher than among civilian population. In time of conflict, the differences can be 50 or more times greater. This study describes sexual behavior as a risk factor for STD in the Armed Forces of Serbia.

METHODS: The sample of 5,617 voluntary blood donors from the Armed Forces of Serbia gave blood and filled World Health Organization Questionnaire about sexual behavior within January 2007 – December 2008 period. The mandatory testing of voluntary blood donors was performed in the Institute of Transfusiology Military Medical Academy in Belgrade, by the specific immunoenzyme tests and polymerase chain reaction tests for HIV, hepatitis B, C and syphilis. Statistical analysis of data was done using Stat for Windows 93, USA, 1996. RESULTS: We identified 36 soldiers with some form of STDs. This study showed that 1,668 (29.7%) tested soldiers reported always using condoms, 1,725 (30.72%) almost always, 1,238 (20.04%) sometimes, 495 (8.81%) almost never and 490 (8.73%) never. Among the sample, 449 (7.99%) soldiers reported sexual contacts with partners with high risk of sexual behavior, whilst 22 (0.37%) of them reported homosexual and bisexual contacts. CONCLUSION: This study reported STDs found in voluntary blood donors among the service members of the Armed Forces of Serbia, but none of them was identified to be HIV positive. Soldiers with the most frequent risk behavior were reported to be those with inconsistent condom use. In the future, the STD Control and Prevention Program should be more intensively conducted among the members of the Armed Forces of Serbia.

Croatia


The aim of this paper is to introduce the digitalization process and its effects on better reach of the target population. Progress in the digitalization and e-health tools worldwide enables new opportunities in prevention, diagnostics and treatment for people living with HIV (PLHIV) and people in the risk of HIV infection, hepatitis C (HCV) and other sexually transmitted infections (STIs), especially in the context of the COVID-19 pandemic. The system already used for voluntary counselling and testing (VCT) at the CheckPoint Centre Zagreb run by the non-governmental organization (NGO) Croatian Association for HIV and Viral Hepatitis (CAHIV) was upgraded and adapted (due to the COVID-19 prevention epidemiological measures) and developed for implementation of the pilot project of feasibility and acceptability of home HIV self-testing (HIVST) among men who have sex with men (MSM) in Zagreb. A special feature of the HIVST mobile application enables an innovative approach in collecting clients’ test result feedback. This paper presents the method of use digitalization of the VCT and HIVST activities to support and increase availability of screening testing. Described procedures of new technologies application in VCT services and preliminary results of the HIVST pilot project indicate that technology-delivered interventions can contribute and improve access and utilisation of HIV/STI prevention and care services.

BACKGROUND: The HIV pandemic impacts the lives of millions and despite the global coordinated response, innovative actions are still needed to end it. A major challenge is the added burden of coinfections such as viral hepatitis, tuberculosis and various sexually transmitted infections in terms of prevention, treatment and increased morbidity in individuals with HIV infection. A need for combination prevention strategies, tailored to high-risk key populations arises and technology-based interventions can be a valuable asset. The COVID-19 pandemic challenged the delivery of existing services and added stress to existing public health and clinical structures but also highlighted the potential of exploiting existing infrastructures.

Molecular epidemiology of hepatitis C virus (HCV) is exceptionally complex due to the highly diverse HCV genome. Genetic diversity, transmission dynamics, and epidemic history of the most common HCV genotypes were inferred by population sequencing of the HCV NS3, NS5A, and NS5B region followed by phylogenetic and phylodynamic analysis. The results of this research suggest high overall prevalence of baseline NS3 resistance associate substitutions (RAS) (33.0%), moderate prevalence of NS5A RAS (13.7%), and low prevalence of nucleoside inhibitor NS5B RAS (8.3%). Prevalence of RAS significantly differed according to HCV genotype, with the highest prevalence of baseline resistance to NS3 inhibitors and NS5A inhibitors observed in HCV subtype 1a (68.8%) and subtype 1b (21.3%), respectively. Phylogenetic tree reconstructions showed two distinct clades within the subtype 1a, clade I (62.4%) and clade II (37.6%). NS3 RAS were preferentially associated with clade I. Phylogenetic analysis demonstrated that 27 (9.0%) HCV sequences had a presumed epidemiological link with another sequence and classified into 13 transmission pairs or clusters which were predominantly comprised of subtype 3a viruses and commonly detected among intravenous drug users (IDU). Phylodynamic analyses highlighted an exponential increase in subtype 1a and 3a effective population size in the late 20th century, which is a period associated with an explosive increase in the number of IDU in Croatia.


BACKGROUND: Maximising access to testing by targeting more than one infection is effective in identifying new infections in settings or populations. Within the EU funded Joint Action INTEGRATE, this paper examined the feasibility and impact of expanding integrated testing for HIV, hepatitis C (HCV), chlamydia, gonorrhoea and/or syphilis in four community-based pilots through targeted interventions in Croatia, Italy and Poland and the Spring European Testing Week since community settings are key in detecting new infections and reaching key populations. METHODS: Pilots led by local INTEGRATE partners prioritised testing for other infections or key populations. The Croatian pilot expanded testing for men who have sex with men to syphilis, chlamydia and gonorrhoea. Italian partners implemented a HIV and HCV testing/information event at a migrant centre. A second Italian pilot tested migrants for HIV and HCV through outreach and a low-threshold service for people who use drugs. Polish partners tested for HIV, HCV and syphilis among people who inject drugs in unstable housing via a mobile van. Pilots monitored the number of individuals tested for each infection and reactive results. The pilot Spring European Testing Week from 18 to 25 May 2018 was an INTEGRATE-driven initiative to create more testing awareness and opportunities throughout Europe. RESULTS: The Croatian pilot found a high prevalence for each infection, chlamydia and gonorrhoea respectively, 2.1%, 12.4% and 6.7%. The Italian migrant centre pilot found low proportions who were previously tested for HIV (24%) or HCV (11%) and the second Italian pilot found an HCV prevalence of 6.2%, with low proportions previously tested for HIV (33%) or HCV (31%). The Polish pilot found rates of being previously tested for HIV, HCV and syphilis at 39%, 37%, and 38%, respectively. Results from the Spring European Testing Week pilot showed it was acceptable with increased integrated testing, from 50% in 2018 to 71% in 2019 in participants.

CONCLUSIONS: Results show that integrated testing is feasible and effective in community settings, in reaching key populations and minimising missed testing opportunities, and the pilots made feasible because of the European collaboration and funding. For sustainability and expansion of integrated community testing across Europe, local government investment in legislation, financial and structural support are crucial.


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technical solutions for interventions regarding infectious diseases. In this paper we report the design process, results and evaluation findings from the pilots of ‘RiskRadar’-a web and mobile application aiming to support combination prevention, testing and linkage to care for HIV, viral hepatitis, various sexually transmitted infections and tuberculosis. METHODS: RiskRadar was developed for the INTEGRATE Joint Action’s aim to improve, adapt and pilot innovative digital tools for combination prevention. RiskRadar was designed iteratively using informed end-user-oriented approaches. Emphasis was placed on the Risk Calculator that enables users to assess their risk of exposure to one or more of the four disease areas, make informed decisions to seek testing or care and adjust their behaviours ultimately aiming to harm/risk reduction. RiskRadar has been piloted in three countries, namely Croatia, Italy and Lithuania. RESULTS: RiskRadar has been used 1347 times across all platforms so far. More than 90% of users have found RiskRadar useful and would use it again, especially the Risk Calculator component. Almost 49.25% are men and 29.85% are in the age group of 25-34. The application has scored 5.2/7 in the User Experience Questionnaire, where it is mainly described as “supportive” and “easy-to-use”. The qualitative evaluation of RiskRadar also yielded positive feedback. CONCLUSIONS: Pilot results demonstrate above average satisfaction with RiskRadar and high user-reported usability scores, supporting the idea that technical interventions could significantly support combination prevention actions on Sexually Transmitted Infections.


In patients with chronic liver disease (CLD), hepatitis E virus (HEV) may lead to decompensation and death. We tested 438 CLD patients (71.0% male; age 23-84 years) for HEV-IgG antibodies. Reactive samples were tested for HEV-IgM antibodies using ELISA. IgM positive samples were tested for HEV RNA using RT-PCR. HEV-IgG antibodies were found in 15.1% of patients, whereas 4.5% of IgG positive patients had detectable IgM antibodies. Not a single patient tested HEV RNA positive. Seroprevalence increased with age, from 9.7% (<45 years) to 17.4% (>60 years, p = 0.368). There was no difference in HEV-IgG seropositivity related to gender, level of education, geographic region, area of residence, liver disease, or hepatocellular carcinoma presence. Previous exposure to HEV was detected in 15.1% of patients, corresponding with the data from other endemic European regions. Despite the high local exposure, we did not find any evidence of acute or chronic hepatitis E among CLD patients.


Hepatitis E virus (HEV) is the most common cause of viral hepatitis globally. The first human case of autochthonous HEV infection in Croatia was reported in 2012, with the undefined zoonotic transmission of HEV genotype 3. This narrative review comprehensively addresses the current knowledge on the HEV epidemiology in humans and animals in Croatia. Published studies showed the presence of HEV antibodies in different population groups, such as chronic patients, healthcare professionals, voluntary blood donors and professionally exposed and pregnant women. The highest seroprevalence in humans was found in patients on hemodialysis in a study conducted in 2018 (27.9%). Apart from humans, different studies have confirmed the infection in pigs, wild boars and a mouse, indicating the interspecies transmission of HEV due to direct or indirect contact or as a foodborne infection. Continued periodical surveys in humans and animals are needed to identify the possible changes in the epidemiology of HEV infections.


BACKGROUND: Country level policies and practices of testing and care for HIV, viral hepatitis and sexually transmitted infections are lagging behind European recommendations on integration across diseases. Building on previous experiences and evidence, the INTEGRATE Joint Action arranged four national stakeholder meetings. The aim was to foster cross-disciplinary and cross-disease collaborations at national level as a vehicle for strengthened integration of testing and care services. This article presents the methodology and discusses main outcomes and recommendations of these meetings. METHODS: Local partners in Croatia, Italy, Lithuania and Poland oversaw the planning, agenda development and identification of key persons to invite to ensure that meetings addressed main challenges and issues of the respective countries. Invited national stakeholders represented policy and
public health institutions, clinical settings, testing sites and community organisations. National experts and experts from other European countries were invited as speakers and facilitators. Main topic discussed was how to increase integration across HIV, viral hepatitis and sexually transmitted infections in testing and care policies and practice; tuberculosis was also addressed in Lithuania and Italy. RESULTS: The agendas reflected national contexts and the meetings provided a forum to engage stakeholders knowledgeable of the national prevention, testing and care systems in interaction with international experts who shared experiences of the steps needed to achieve integration in policies and practice. The evaluations showed that participants found meetings relevant, important and beneficial for furthering integration. Of the respondents 78% agreed or strongly agreed that there was a good representation of relevant national stakeholders, and 78% that decision/action points were made on how to move the agenda forward. The importance of securing participation from high level national policy makers was highlighted. Outcomes were nationally tailored recommendations on integrated policies and strategies, diversification of testing strategies, stigma and discrimination, key populations, cost effectiveness, surveillance and funding. CONCLUSIONS: Shifting from single to multi-disease approaches require collaboration among a broad range of actors and national multi-stakeholder meetings have proven excellent to kick-start this. Face-to-face meetings of key stakeholders represent a unique opportunity to share cross-sectoral perspectives and experiences, identify gaps in national policies and practices and agree on required next steps.


Several arboviruses have emerged in Croatia in recent years. Tick-borne encephalitis is endemic in continental counties; however, new natural micro-foci have been detected. Two autochthonous dengue cases were reported in 2010. West Nile virus emerged in 2012, followed by emergence of Usutu virus in 2013. Although high seroprevalence rates of Toscana virus have been detected among residents of Croatian littoral, the virus remains neglected, with only a few clinical cases of neuroinvasive infections reported. Lymphocytic choriomeningitis virus is a neglected neuroinvasive rodent-borne virus. So far, there are no reports on human clinical cases; however, the seroprevalence studies indicate the virus presence in the Croatian mainland. Puumala and Dobrava hantaviruses are widely distributing rodent-borne viruses with sporadic and epidemic occurrence. Hepatitis E virus is an emerging food-borne virus in Croatia. After the emergence in 2012, cases were regularly recorded. Seropositivity varies greatly by region and population group. Rotaviruses represent a significant healthcare burden since rotavirus vaccination is not included in the Croatian national immunization program. Additionally, rotaviruses are widely distributed in the Croatian ecosystem. A novel coronavirus, SARS-CoV-2, emerged in February 2020 and spread rapidly throughout the country. This review focuses on emerging and neglected viruses of zoonotic importance detected in Croatia.


Viral hepatitis B is a global public health problem affecting nearly two billion subjects; 3.3% of whom are from the WHO (World Health Organization) Eastern Mediterranean Region (EMRO). It induces both acute and chronic hepatic disorders with subsequent liver cirrhosis and hepatocellular carcinoma (HCC) in a considerable percentage of patients based on the age of exposure. In this review, hepatitis B virus (HBV) and HCC prevalence, distribution and prevalence of different genotypes, and male/female infection frequencies in relation to the vaccination status in the Mediterranean countries were reported. Study Design. This systematic review describes the prevalence of hepatitis B infection, genotype distribution of hepatitis B virus, and prevalence and incidence of hepatocellular carcinoma in Mediterranean countries belonging to three different continents: Southern Europe (Spain, France, Italy, Croatia, and Greece), North Africa (Morocco, Algeria, Tunisia, Libya, and Egypt), and the Near East region (Syria, Lebanon, Turkey, Israel, and Palestine). We tried to collect new data from electronic databases: PubMed, ScienceDirect, ResearchGate, Google Scholar, and public health reports between 1980 and 2019. For each publication, we recorded reference, publication year, study characteristics (date, locations, sample size, and study population), and participant characteristics (population group, year, age, and sex). No language limitation was imposed, and articles or reports from non-peer-reviewed sources were not considered for this analysis. The main keywords were HBV prevalence, hepatitis B infection, HBV genotype, and HCC. Inclusion and Exclusion Criteria. Healthy population-based studies included the following sample...
Nakitanda AO and E Duffell (2020). "Late presentation to care is the major obstacle to receiving treatment for chronic hepatitis C (CHC). Our Care in Patients with Chronic Hepatitis C during a 10-Year Period in Croatia." Infect Dis Rep 12(3): 74-81.

BACKGROUND: Viral hepatitis is a leading cause of mortality globally, comparable to that of HIV and TB. Most hepatitis deaths are related to liver cirrhosis and hepatocellular carcinoma (HCC) associated with chronic hepatitis B and C infections. To examine the progress towards the elimination goals set in the global health sector strategy for viral hepatitis, we aimed to assess the impact of mortality-indicative morbidity. METHODS: We retrieved inpatients and day cases hospital discharges data from the Eurostat hospital activities database, and analysed ICD-10 and ICD-9 specific codes related to primary HCC and non-alcohol related cirrhosis registered by European Union/European Economic Area (EU/EEA) countries and United Kingdom (UK) for 2004 to 2015. RESULTS: In 2015, 20 countries (45.7% of total EU/EEA/UK population) reported 13,236 (Range 0-6294) day cases and 36,012 (4-9097) inpatients discharges of HCC. Romania, Croatia, Luxembourg and UK reported increasing day cases discharge rates between 2004 and 2015; while HCC inpatients discharge rates increased overall during this period. There were 13,865 (0-5918) day cases and 56,176 (3-29,118) inpatients discharges reported for cirrhosis across the 20 countries in 2015. Over the 12 years, day cases discharge rates for cirrhosis increased in Romania, Croatia and UK. Though higher than for day cases, cirrhosis inpatients discharge rates remained stable. CONCLUSIONS: The hospital burden of HCC and cirrhosis is high, with considerable inpatient load including sustained increasing trends in HCC discharge rates. Further interpretation in light of local health system contexts, and more robust harmonised data are needed to better understand the impact of the viral hepatitis epidemic in the region.


Late presentation to care is the major obstacle to receiving treatment for chronic hepatitis C (CHC). Our aim was to analyze the prevalence and trends of late presenters (LP) at first consultations in Croatia during a 10-year period. This retrospective cross-sectional study included all adult CHC patients (n = 854) entering specialist medical care at the University Hospital for Infectious Diseases Zagreb between 2009 and 2018. LP was defined as liver stiffness measurement ≥ 9.5 kPa or biopsy METAVIR F ≥ 3. During the study period, mean patients' age increased from 37 to 52 years while HCV genotype distribution...
changed leading to the replacement of genotype 1b with 1a (g1b 32% to 21%; g1a 19% to 38%). A total of 320 (37.4%) were LP; they were older (47.5, IQR 40.5-57.6), and more commonly infected with g1b (34.1%) and g3 (42.5%). The prevalence of LP significantly increased from 31.9% in 2009 to 46.5% in 2018. Late presentation for care of CHC is increasing in Croatia suggesting a gap of diagnosing strategies in patients over 50 years.


Recently an increase has been reported in the number of HBV transmissions from anti-HBc positive blood donors that were repeatedly negative in HBsAg and nucleic acid testing using the most sensitive tests available. The aim of the study was to show the effect of anti-HBc antibody testing performed in 2006 on permanent deferral of voluntary blood donors (VBDs), and to estimate occult hepatitis B infection (OBI) rate in this population after the introduction of mandatory molecular testing in the 2013-2016 period. More than 30,000 blood donations collected during the 2005-2007 period and more than 14,000 VBDs having donated blood during the 2013-2016 period after the introduction of molecular testing from eastern Croatia were included in the study. Serologic testing was performed with HBsAg assay throughout the study period, and anti-HBc assay was only performed in 2006. As part of the confirmatory algorithm testing, all HBsAg positive and unclear results were tested with molecular tests. Anti-HBc prevalence among VBDs in 2006 was 1.5%, with a rate of 1:197, whereas HBsAg prevalence was stable from 2005 to 2007 (0.04%, 0.1% and 0.1%, respectively). The calculated OBI rate from 2013 to 2016 was 1:30,250. Ten of 161 (12.4%) VBDs had serologic anti-HBc-only pattern. Anti-HBc testing in 2006 resulted in statistically more deferrals of VBDs compared to 2005 and 2007, and to the rest of Republic of Croatia. The strategy of universal anti-HBc testing of VBDs in addition to the existing HBsAg and molecular screening could be an additional measure to prevent HBV transmission by blood and blood components.


BACKGROUND: To fulfill epidemiological data and investigate possible interspecies transmission, this study shall attempt to sequence representative HEV strains of human, swine and wild boar origin collected from 2010 to 2017 in Croatia. METHODS: In total, 174 anti-HEV antibody positive human sera samples; 1419 blood or faeces samples of swine, as well as 720 tissue and/or blood samples of wild boar originating from different counties (18 in total) in Croatia were tested for the presence of HEV RNA. RESULTS: HEV RNA was detected in 26 human sera samples (14.9%; 95% CI 10.4-21.0%), HEV RNA was detected in 216 tested swine (15.2%; 95% CI 13.5-17.1%), regardless of age, farm breeding system or geographical origin. Viral RNA was also detectable in faeces samples which prove that swine actively participate in shedding HEV into the environment. Of the total of 720 tested wild boar samples, 83 were HEV RNA positive (11.5, 95% CI 9.4-14.1%) originating from six counties. According to the sequence analysis all strains have shown to be members of Orthohepevirus A genotype HEV-3, regardless of host. The genotyping results confirm grouping of sequences into four subtypes of HEV strains of which subtypes 3a and 3c belong to the general cluster 3abchij, and were predominately detected during the study, while subtypes 3e and 3f fall within cluster 3efg. Strains within subtypes 3a and 3e were found in humans, swine and wild boars; subtype 3c strains were derived from humans and swine, whereas subtype 3f strains were found only in humans. Strains belonging to subtypes 3a and 3c were derived during the entire investigated period and may be considered endemic in Croatia, whereas strains within subtypes 3e and 3f were detected sporadically indicating the possibility of newly imported infections. CONCLUSIONS: All detected strains show to be genetically highly related to strains found in humans and/or animals from other European Countries, indicating that trade of live animals or wild boar movement increases the risk of HEV infection spread. Furthermore, homologous strains found in different investigated species within this study indicate interspecies transmission of HEV and/or an existence of an accessible mutual source of infection.

The backbone of current treatment for chronic Hepatitis C virus (HCV) infection are direct-acting antivirals targeting viral nonstructural proteins (NS3, NS4A, NS5A, NS5B). To date, there are six NS5A inhibitors approved for treatment of chronic HCV infection. The presence of drug-associated resistance substitutions is mainly due to fast error-prone replication, showing differential frequency between genotypes and subtypes. The aim of this study was to determine the frequency of baseline resistance to NS5A protein inhibitors in patients with genotype 1 HCV in Croatia. Resistance-associated substitutions (RAS) were detected by Sanger sequencing of HCV NS5A region amplified from 84 patients followed by phylogenetic analysis and analysis with Geno2Pheno algorithm. The frequency of NS5A RAS was 14.3% and highly dependent on viral subtype. The overall frequency of NS5A RAS was higher in patients infected with HCV subtype 1b (24.2%) than in those infected with HCV subtype 1a (7.8%). Overall, three resistance-conferring mutations were detected (Q30R, M28T and Y93H) along with two mutations (M28V and L31I) that cause reduced susceptibility to NS5A inhibitors. Analysis of the sequences showed two distinct subtype 1a clades with RAS detected in 4.3% (1/23) clade I and 10.7% (3/28) clade II sequences. Only a few distinct NS5A RAS were detected suggesting a high degree of homogeneity of the viral population. High frequency of clinically relevant NS5A RAS in Croatia suggest that the analysis of frequency and patterns of resistance mutations in local populations and evaluation of their possible clinical impact could be beneficial.


HIV and sexually-transmitted diseases (STDs) represent a significant public health problem worldwide. We analyzed the seroprevalence and risk factors for HIV, hepatitis B and syphilis in populations with high-risk behaviors in Croatia. During a three-year period, a total of 443 men who have sex with men (MSM) / bisexual persons, sex workers (SW) / clients of SW, persons with multiple sexual partners, and persons with a history of STD were tested for the presence of HIV, hepatitis B virus (HBV), and Treponema pallidum (syphilis) antibodies within the framework of second generation HIV surveillance. Participants were recruited from 11 Croatian counties, the vast majority among clients of voluntary counselling and testing centers. The overall prevalence of HIV, HBsAg, anti-HBc, and syphilis was 1.4%, 2.6%, 12.1%, and 3.4%, respectively. HBV and syphilis seroprevalence differed significantly between, genders with higher prevalence among men (anti-HBc 3.4% vs. 0.9%, P=0.004; syphilis 3.4% vs. 0%, P=0.049), as well as between age groups, with a steady increase according to age. Participants with a history of STD were more often seropositive than participants who did not report STD (HBsAg 8.2% vs. 1.0%, P=0.002; anti-HBc 32.4% vs. 6.4%, P<0.001; syphilis 12.0% vs. 1.7%, P<0.001). Syphilis seroprevalence was higher in homo / bisexual persons (12.2%) compared with heterosexual persons (1.2%, P<0.001). Logistic regression showed that history of STD was a significant risk factor for hepatitis B (HBsAg AOR=6.229, 95% CI=1.491-26.022; anti-HBc AOR=5.872, 95% CI=2.899-11.896) and syphilis seropositivity (AOR=5.572, 95% CI=1.751-17.726), while homo / bisexual behavior was associated with syphilis seropositivity (AOR=12.820, 95% CI=3.688-44.557). Our results highlight the importance of continuing STDs screening and prevention in at-risk populations.


OBJECTIVE: Hepatitis C virus (HCV) genotyping is an important part of pre-treatment diagnostic algorithms as it guides the choice of therapeutic regimens. The aim of this study was to analyse the distribution of HCV genotypes in patients with chronic hepatitis C from Croatia in the period 2008-2015. METHODS: The study enrolled 3,655 anti-HCV positive patients with available results of HCV genotyping from the three largest national HCV genotyping laboratories. RESULTS: The majority of HCV-infected individuals enrolled in the study were male (70.7%). Analysis of age distribution in a subset of 2,164 individuals showed a mean age of 40.9 years (SD 11.77 years). Croatian patients were mostly infected with HCV genotype 1 (56.6%), followed by genotype 3 (37.3%), genotype 4 (4.2%) and genotype 2 (1.8%). Genotype 1 subtyping in a subset of 1,488 patients showed 54% (803/1,488) of 1b infections and 46% (685/1,488) of 1a infections. Percentages of genotype 1 were the highest in Central/Northwestern and
Eastern Croatia and the lowest in the Central/Southern Adriatic Region. Genotype 3 was most frequently found in the Central/Southern Adriatic Region (49.1%) but represented only 17.5% of infections in Eastern Croatia (p < 0.001). CONCLUSIONS: The results of this nine-year retrospective analysis on the distribution of HCV genotypes and subtypes in 3,655 HCV-infected individuals from Croatia showed that the majority of infections can be attributed to genotypes 1 and 3 with absence of major changes in the molecular epidemiology of the two most frequent HCV genotypes infection in Croatia in the past 20 years.


BACKGROUND: We assessed correlates of anti-hepatitis C (anti-HCV) positivity and utilization of needle and syringe exchange programs (NSEP) and opioid agonist treatment (OAT) among people who inject drugs (PWID) in two Croatian cities. METHODS: We conducted a cross-sectional study using respondent-driven (RDS) sampling among PWID in Rijeka (N=255) and Split (N=399). We used RDS-weighted population estimates and multivariable logistic regression to explore correlates of anti-HCV positivity and NSEP and OAT utilization. RESULTS: Seventy-eight percent (78.0%) of PWID in Rijeka and 61.5% in Split received anti-HCV treatment. In Rijeka, PWID who utilized NSEP and, in Split, those who were ever imprisoned, had higher odds of anti-HCV positivity. In Rijeka, PWID on OAT were more likely to use non-sterile injecting equipment and to inject for longer than 10 years. PWID enrolled in NSEP were more likely than half of PWID reported misuse of OAM in the past month, while out of PWID enrolled in OAT, 65.4% in Rijeka and 88.7% in Split injected OAM in the month prior to the survey. CONCLUSIONS: Key findings of the paper point to the need to scale up HCV testing and treatment, improve access to NSEP and the quality of OAT provisions in order to prevent its misuse among PWID.

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Several genes and their single nucleotide polymorphisms (SNPs) are associated with hepatitis C infection among intravenous drug users in Croatia.

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BACKGROUND: Several genes and their single nucleotide polymorphisms (SNPs) are associated with either spontaneous resolution of hepatitis C infection or better treatment-induced viral clearance. We tested a cohort of intravenous drug users (IVDU) diagnosed with chronic hepatitis C virus (HCV) for treatment response and its association with the SNPs in the interleukin-6 (rs1800795-IL6) and the interleukin-28B (rs12979860-IL28B) genes. METHODS: The study included 110 Croatian IVDU positive for hepatitis C. The patients were treated by standard pegylated-interferon/ribavirin and followed throughout a period of...
four years, during which sustained virological response (SVR) was determined. All data were analysed with statistical package SPSS 19.0 (IBM Corp, Armonk, NY, USA) and PLINK v1.07 software. RESULTS: Patients showed a significantly better response to treatment according to the number of copies of the C allele carried at rs1800795-IL6 (P = 0.034). All but one of the patients with CC genotype achieved SVR (93%), whereas the response rate of patients with GG genotype was 64%. The association of rs1800795-IL6 with SVR status remained significant after further adjustment for patients’ age, fibrosis staging, and viral genotype (OR 2.15, 95% CI 1.16-4.68, P = 0.019). Distributions of allele frequencies at the locus rs12979860-IL28B among the study cohort and the underlying general population were suggestive of a protective effect of CC genotype in acquiring chronic hepatitis C in the Croatian IDU population. DISCUSSION: The rs1800795-IL6 polymorphism is associated with positive response to treatment in IDU patients positive for HCV infection. A protective role of rs12979860-IL28B CC genotype in acquiring chronic hepatitis C is suggested for Croatian IDU population.


BACKGROUND: There are limited data on HIV and hepatitis C virus (HCV) epidemiology among people who inject drugs (PWID) in Croatia. This study aims to provide data on HIV and HCV prevalence and sexual and injecting risk behaviours among PWID in Zagreb, Split, and Rijeka. METHODS: Using respondent-driven sampling (RDS) we recruited from November 2014 to February 2015 a total of 176 PWID in Zagreb, 255 in Rijeka and 399 in Split. Participants provided biological specimens for HIV and HCV testing and completed a behavioural questionnaire. RESULTS: The proportion of female PWID ranged from 19.5% in Zagreb to 26.0% in Split. In the month before the survey, 2.5% of PWID in Split, 5.6% in Rijeka and 8.0% in Zagreb reported sharing non-sterile needles and syringes. Many PWID injected opioid substitution therapy (OST) in the month before the survey (57.0% in Zagreb and 57.5% in Split and Rijeka, respectively). Among PWID who had a casual sexual partner in the past 12 months (ranging from 39.2% in Split to 44.4% in Rijeka) condom use was low. Although HIV prevalence was low (0.2% in Rijeka and Zagreb, 0.3% in Split), HCV antibody prevalence was considerable (29.1% in Zagreb, 31.5% in Rijeka, 38.3% in Split). HIV and HCV testing coverage in the past 12 months was insufficient (6.8% and 7.0% in Split; 13.2% and 13.5% in Zagreb; 20.2% and 21.5% in Rijeka, respectively). CONCLUSION: We found a low-level HIV epidemic and a sizable HCV epidemic among PWID in Zagreb, Split and Rijeka. Presence of high-risk injecting and sexual behaviours together with inadequate HIV and HCV testing coverage call for development of a comprehensive approach to harm reduction and introduction of needle and syringe exchange programmes in prisons, as well as strengthening sexual health interventions.


AIM: To develop a new method of health-economic analysis based on a marginal approach. METHODS: We tested the research hypothesis that a detailed comparative a priori incremental cost-effectiveness analysis provides the necessary input for budget impact analysis about the proper order of introduction of new therapies, and thus maximizes the cost-effectiveness bounded by the total budget constraint. For the analysis we chose a combination therapy for the treatment of hepatitis C virus (HCV) genotype 1 (GT1) infection, which was approved by the European Medicine Agency in 2015. We used the incremental cost-effective approach to assess the increase in the percentage of patients achieving sustained virological response (SVR) and the expenditure per additional SVR modulated by the new therapy's market entrance dynamics. Patient subpopulations were differentiated by their response to previous treatment, presence of cirrhosis, and HCV GT1 subtype. Final parameters were estimated by Monte Carlo simulations. RESULTS: The new combination therapy had high efficacy, shorter duration, and was better tolerated than alternative interventions. The research hypothesis was confirmed: gradual introduction of the new therapy on the market, based on a priori incremental cost-effectiveness analysis, would result in average increase in successfully treated patients by 20%-40%, while additional costs would approximately be between 8%-40%, i.e., 721000-52000 per additional patient achieving SVR. CONCLUSION: We showed the new combination therapy to be cost-effective for certain patient subpopulations, especially for experienced cirrhotic HCV GT1 patients. Results of the analysis are in agreement with the latest recommendations for HCV patients' treatment in Croatia. This economic
evaluation could serve as a starting point for negotiations between pharmaceutical industry and insurance companies.


Hepatitis E is attributed great attention as an emerging worldwide-distributed zoonosis. The clinical presentation varies from severe fulminant in underdeveloped to milder forms of diagnostically unrecognized hepatitis cases in developed countries. Chronic hepatitis E is more often described in subjects with transplanted solid organs and HIV disease. The diagnosis of hepatitis E is established by determination of anti-HEV IgM and IgG with Western blot confirmation and detection of HEV RNA. In Croatia, the first case of indigenous disease caused by HEV genotype 3 (HEV-3) was detected in 2012. In this paper we present current knowledge on hepatitis E supplemented by own results obtained at the University Hospital for Infectious Diseases in Zagreb and guidelines for diagnosis and treatment of immunocompetent and immunocompromised individuals. In the period from 2011-2014, HEV was tested in 1107 patients, of whom 117 (10.6%) had anti-HEV antibodies. Acute HEV infection was diagnosed in 25 (2.3%) patients. Considering the prevalence of antibodies we can conclude that HEV diagnostics should be included in the diagnostic panel for patients with elevated aminotransferases.


Hepatitis E has become an emerging infection in many European countries. We analysed the prevalence of hepatitis E virus (HEV) infection in selected population groups in Croatia. Overall HEV IgG seropositivity was 5.6%, while 1.9% participants showed IgM antibodies suggestive of recent infection. No IgM-positive sample was positive for HEV RNA. HEV IgG antibodies were most prevalent in alcohol abusers (8.9%) and war veterans (8.6%), compared with 6.1% among injecting drug users and 2.7% in healthcare professionals. No individual with high-risk sexual behaviour tested HEV seropositive. HEV IgG positivity increased significantly with age from 1.8% to 2.3% in individuals younger than 40 years to 11.3% in individuals older than 50 years (P = 0.023). The mean age of HEV-positive participants was significantly higher than that of HEV-negative participants (50.9 ± 11.8 years versus 41.2 ± 11.8 years, P = 0.008). Seroprevalence rates were significantly higher in residents of suburban and rural areas compared with residents of urban areas (14.5% versus 2.5%, P = 0.003). Additionally, an increasing prevalence of HEV IgG antibodies was observed from 1.8% in participants living in families with two household members to 12.1% in those living with more than four members (P = 0.046). Gender, marital status, educational level, sexual orientation, source of drinking water, history of blood transfusions, surgical procedures, tattooing and travelling were not associated with HEV seroprevalence. Logistic regression showed that living in suburban/rural areas was the main risk factor for HEV seropositivity (OR = 6.67; 95%CI = 1.89-25.0; AOR = 7.14, 95%CI = 1.89-25.0).


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.

Chronic infection with hepatitis C virus (HCV) is caused by an inadequate immune response. Experimental data suggest that the impaired activation of Toll-like receptors (TLRs) 2 and 4 contributes to chronic infection. We assessed the distribution of three single-nucleotide polymorphisms (SNPs) in the TLR2 (Arg753Gln) and TLR4 (Asp299Gly/Thr399Ile) genes in individuals from north-east Croatia and their effect on the outcome of antiviral therapy. The study consisted of 60 chronically infected patients and 40 healthy subjects. TLR polymorphisms were determined by the PCR-based melting curve analysis. HCV genotyping was performed using the Linear Array Hepatitis C Virus Genotyping Test. Thirty-three patients were treated with standard interferon and ribavirin therapy, and their viral load was evaluated at weeks 28 and 53 after the beginning of therapy. The majority of chronic infections were caused by genotype 1 (77%), followed by genotypes 3 (15%) and 4 (7%). Patients with genotype 1 had higher viral loads than patients infected with other genotypes (P = 0.0428). Healthy individuals and patients with chronic infection had similar frequencies of TLR2-Arg753Gln and TLR4-Asp299Gly/Thr399Ile SNPs. Heterozygous and homozygous TLR4-Asp299Gly/Thr399Ile polymorphisms correlated with higher viral loads and delayed responses to antiviral therapy. We have provided the first evidence that TLR4 polymorphisms influence the success of antiviral therapy in our region. This suggests that therapeutic strategies should be adjusted not only according to HCV genotype but also to individual TLR polymorphism(s).


Hepatitis E is becoming a growing health concern in European countries as an increase of sporadic human cases of unknown origin has been recorded lately. Its causative agent, Hepatitis E virus (HEV), is known to have zoonotic potential and thus the role of domestic and wild animals in the chain of viral spread should be considered when investigating risk factors and the epidemiology of the disease. A comprehensive survey based on viral RNA detection was carried out in Croatia including blood, spleen and liver samples originating from 1816 different domestic and wild animals and digestive gland samples from 538 molluscs. A high HEV prevalence was detected in domestic pigs (24.5%) and wild boars (12.3%), whereas cattle, molluscs, ruminant and carnivore wildlife samples tested negative. Molecular characterization of both ORF1 and ORF2 genomic regions confirmed the phylogenetic clustering of the obtained sequences into genotype 3, previously reported in Europe. Furthermore, our results proved the presence of identical sequence variants in different samples, regardless of their origin, age or habitat of the host, suggesting transmission events between domestic swine, as well as between domestic swine and wild boars in the country. Moreover, a close genetic relationship of Croatian animal strains and known human HEV strains from GenBank opens the question of possible cross-species HEV transmission in Croatia, especially in the areas with an intensive swine production.


We analyzed prevalence, risk factors and hepatitis C virus (HCV) genotype distribution in different population groups in Croatia in the context of HCV epidemiology in Europe, with the aim to gather all existing information on HCV infection in Croatia which will be used to advise upon preventive measures. It is estimated that 35000-45000 of the Croatian population is chronically infected with HCV. Like in other European countries, there have been changes in the HCV epidemiology in Croatia over the past few decades. In some risk groups (polytransfused and hemodialysis patients), a significant decrease in the HCV prevalence was observed after the introduction of routine HCV screening of blood/blood products in 1992. Injecting drug users (IDUs) still represent a group with the highest risk for HCV infection with prevalence ranging from 29% to 65%. Compared to the prevalence in the Croatian general population (0.9%), higher prevalence rates were found in prison populations (8.3%-44%), human immunodeficiency virus-infected patients (15%), persons with high-risk sexual behavior (4.6%) and alcohol abusers (2.4%). Low/very low prevalence was reported in children and adolescents (0.3%) as well as in blood donors (0%-0.009%). In addition, distribution of HCV genotypes has changed due to different routes of transmission. In the general population, genotypes 1 and 3 are most widely distributed (60.4%-79.8% and 12.9%-47.9%, respectively). The similar genotype distribution is found in groups with high-risk sexual behavior.
Genotype 3 is predominant in Croatian IDUs (60.5%-83.9%) while in the prison population genotypes 3 and 1 are equally distributed (52.4% and 47.6%). Data on HCV prevalence and risk factors for transmission are useful for implementation of preventive measures and HCV screening.


We assessed hepatitis E virus (HEV) seroprevalence in patients with hepatic disorders as well as in human immunodeficiency virus (HIV)-infected patients and emphasised the issue of possible non-specific anti-HEV seroresponse and need for combining diagnostic methods for hepatitis E diagnosis. Over a two-year period, from March 2011 to February 2013, we determined anti-HEV immunoglobulin M (IgM) and IgG by enzyme immunoassays (EIA; Mikrogen, Germany) in 504 hepatitis patients negative for acute viral hepatitis A-C. Furthermore, 88 samples from randomly selected consecutive HIV-infected patients were also analysed. All EIA reactive samples were additionally tested by line immunoblot assays (LIA; Mikrogen, Germany). HEV nested reverse transcription polymerase chain reaction (RT-PCR) was carried out in 14 anti-HEV IgM LIA-positive patients. Anti-HEV IgM or IgG were detected in 16.9 % of patients by EIA and confirmed by LIA in 10.7 % [95 % confidence interval (CI) 8.3-13.7 %] of hepatitis patients. HEV RNA was detected in five patients. The agreement between EIA and LIA assessed by Cohen's kappa was 0.47 (95 % CI 0.55-0.75) for IgM and 0.83 (95 % CI 0.78-0.93) for IgG. Anti-HEV IgM and IgG seroprevalence in HIV-infected patients was 1.1 %, respectively. Our findings show a rather high HEV seroprevalence in patients with elevated liver enzymes in comparison to HIV-infected patients. Discordant findings by different methods stress the need to combine complementary methods and use a two-tier approach with prudent interpretation of reactive serological results for hepatitis E diagnosis.


BACKGROUND: Healthcare workers (HCWs) are at an increased risk of exposure to and transmission of infectious diseases. Vaccination lowers morbidity and mortality of HCWs and their patients. To assess vaccination coverage for influenza and hepatitis B virus (HBV) among HCWs in Croatian hospitals, we conducted yearly nationwide surveys. METHODS: From 2006 to 2011, all 66 Croatian public hospitals, representing 43-60% of all the HCWs in Croatia, were included. Statistical analysis was performed using the Kruskal-Wallis analysis of variance, Dunn's multiple comparison analysis and the chi-square test, as appropriate. RESULTS: The median seasonal influenza vaccination coverage rates in pre-pandemic (2006-2008) seasons were 36%, 25% and 29%, respectively. By occupation, influenza vaccination rates among physicians were 33 ± 21%, 33 ± 22% among graduate nurses, 30 ± 34% among other HCWs, 26 ± 21% among housekeeping and the lowest, 23 ± 17%, among practical nurses (p < 0.01). In 2009-2010 season, seasonal influenza vaccination coverage was 30%, while overall vaccination coverage against pandemic influenza was fewer than 5%. Median vaccination coverage in the post-pandemic seasons of 2010-2011 and 2011-2012 decreased to 15% and 14%, respectively (reduction of 24% and 35%, respectively, p < 0.0001). Meanwhile, the median mandatory HBV vaccination coverage was 98%, albeit with considerable differences according to work setting (range 19-100%) and occupation (range 4-100%). CONCLUSIONS: We found substantial year-on-year variations in seasonal influenza vaccination rates, with reduction in post pandemic influenza seasons. HBV vaccination is satisfactory compared to seasonal influenza vaccination coverage, although substantial variations by occupation and work setting were observed. These findings highlight the need for national strategies that optimize vaccination coverage among HCWs in Croatian hospitals. Further studies are needed to establish the potential role of mandatory vaccination for seasonal influenza.


Infection with non-1 genotype in Croatia is detected in 41.2% of patients with chronic hepatitis C. Since the last treatment guidelines for hepatitis C patients, little has been changed. With today’s standard of care, sustained viral response can be achieved in 43% to 85% of non-1 CHC patients, which is not satisfactory at all. The lowest cure rate is usually found among patients with genotype 3 and 4 infection. The grouping of genotype 2 and genotype 3 patients to “easy to treat” genotypes was an unfortunate consequence of their underrepresentation in previous large registration clinical trials. Careful re-examination of the data obtained shows clearly enough that patients with genotype 3 infection respond
Hepatitis E is a viral zoonotic disease infecting swine worldwide. Since pigs represent a likely animal reservoir for the hepatitis E virus, the epidemiology of naturally occurring hepatitis E was investigated in Croatian swine herds. Nearly all tested animals were seropositive for antibodies against the hepatitis E virus (55/60, 91.7%). Active infection was detected in all age groups by RT-PCR of viral RNA in serum (8/60, 13.3%) and bile samples (3/37, 8.1%), which was further confirmed by histopathological findings of characteristic lesions in the livers of the infected animals. Three new strains of hepatitis E virus were isolated from Croatian pig herds. Phylogenetic analysis using median-joining networks clustered those less to treatment than genotype 2 patients. They sometimes behave more like patients with genotype 1 infection. Small progress is found in treatment approach and viral kinetics might be a useful tool for tailoring therapy to improve efficacy. Rapid virologic response is the best parameter to predict success of therapy. For patients who achieve a rapid viral response, consideration of shortened therapy (< 24 weeks) may be reasonable although sustained viral response is still slightly higher with 24 weeks of therapy. Nevertheless, the presence of poor prognostic factors (high viral load, advanced fibrosis, obesity, increased age, insulin resistance and liver non-viral steatosis) may discourage a shortened course of therapy. Extending therapy (> 24 weeks) in patients who do not achieve a rapid viral response would be beneficial, particularly in patients with genotype 3 infection and poor prognostic factors, but formal recommendation should be confirmed in prospective trials. New data suggest a prognostic role for IL28B polymorphisms mostly in genotype 3 patients not achieving a rapid viral response and these could also be considered for improved tailoring of therapy. In conclusion, new treatments are urgently needed for non-1 genotype chronic hepatitis C patients. So far, telaprevir and boceprevir have failed to show a satisfactory activity in these genotypes. Evaluation of many promising molecules such as second generation of protease inhibitors or NS5B nucleos(t)ide inhibitors, NS5A inhibitors, cyclophilin inhibitors or their combinations with or without pegylated interferon or ribavirin is still in progress.


Understanding the country-specific epidemiology of disease, which may vary greatly among countries, is crucial for identifying the most appropriate preventive and control measures. An overview of the local epidemiology of viral hepatitis in Croatia is given in this paper. The overall prevalence of hepatitis B in Croatia is low (less than 2% HBsAg carriers in the general population). Hepatitis B incidence and prevalence began to decline significantly following the introduction of universal hepatitis B vaccination in 1999. Information on HBsAg seroprevalence is derived from routine testing of certain subpopulations (pregnant women, blood donors) and seroprevalence studies mostly targeted at high-risk populations. Universal childhood vaccination against hepatitis B remains the main preventive measure. We recommend testing for immunity one to two months after the third dose of hepatitis B vaccine for health-care workers. The incidence and prevalence of hepatitis C have also been declining in the general population. The main preventive measures are ensuring safety of blood products, prevention of drug abuse, and harm reduction programs for intravenous drug users. Hepatitis A incidence has declined dramatically since fifty years ago, when thousands of cases were reported annually. In the last five years, an average of twenty cases have been reported per year. The reduction of hepatitis A is a consequence of improved personal and community hygiene and sanitation. Hepatitis D has not been reported in Croatia. The risk of hepatitis D will get to be even smaller as the proportion of population vaccinated against hepatitis B builds up. Hepatitis E is reported only sporadically in Croatia, mostly in persons occupationally in contact with pigs and in travelers to endemic countries. In conclusion, Croatia is a low prevalence country for hepatitides A, B and C. Hepatitis D has not been reported to occur in Croatia and there are only sporadic cases of hepatitis E. Since hepatitis A is a rare disease occurring sporadically, which is a consequence of improved sanitation and hygiene, hepatitides B and C are the main causes of viral hepatitis in Croatia. The introduction of universal mandatory hepatitis B vaccination of schoolchildren in 1999 resulted in a decrease in the incidence of hepatitis B, which is most pronounced in adolescents and young adults, and further decrease in the incidence and prevalence is expected as the pool of susceptible individuals decreases through vaccination. The incidence of hepatitis C is decreasing as well. In spite of a relatively favorable epidemiological situation, hepatitis B and C are still a significant public health burden with an estimated 25,000 persons chronically infected with HBV and about 40,000 persons chronically infected with HCV in Croatia.


Hepatitis E is a viral zoonotic disease infecting swine worldwide. Since pigs represent a likely animal reservoir for the hepatitis E virus, the epidemiology of naturally occurring hepatitis E was investigated in Croatian swine herds. Nearly all tested animals were seropositive for antibodies against the hepatitis E virus (55/60, 91.7%). Active infection was detected in all age groups by RT-PCR of viral RNA in serum (8/60, 13.3%) and bile samples (3/37, 8.1%), which was further confirmed by histopathological findings of characteristic lesions in the livers of the infected animals. Three new strains of hepatitis E virus were isolated from Croatian pig herds. Phylogenetic analysis using median-joining networks clustered those
Croatian strains with isolates from various parts of the world, indicating their likely origin in international trade. Similarity to human isolates implies a zoonotic potential of Croatian strains, which raises a public health concern, especially in the light of the high prevalence of hepatitis E in the herds studied.

Other


Inclusion body hepatitis (IBH) is an economically important disease of chickens, with a worldwide distribution, caused by Fowl Aviadenoviruses (FAdVs). Currently, the increased number of cases, the virulence of the isolate strains, as well as the lack of cross-species protection highlight that detailed in-field data are fundamental for the development of successful control strategies. This case report provides a detailed clinicopathological investigation of an unusual IBH outbreak in a commercial broiler farm in the region of Macedonia, Greece. The farm consisted of 64,000 birds, originated from the same breeder stock and placed in three different houses (Flock A-C). At 20 days of age, a sudden increase in daily mortality was recorded in Flock A. It is worth mentioning that, although all flocks were serologically (indirect ELISA) and molecularly (RT-PCR) positive for FAdV, the mortality rate, attributed to IBH, was much higher in Flock A compared to others. The clinical manifestation included non-specific symptoms such as depression, inappetence, yellowish mucoid diarrhea, and lack of uniformity. At necropsy, typically, enlarged, pale, and friable livers were dominant, while sporadically lesions were recorded in the pancreas, kidneys, skeletal muscles, and lymphoid organs. The histopathological examination of liver samples showed multifocal inflammation, necrosis, and the presence of basophilic/eosinophilic inclusion bodies in hepatocytes. In addition, the loss of the architecture of pancreatic lobules and the presence of fibrosis and foci of mononuclear cell aggregates were suggestive of chronic pancreatic inflammation. PCR analysis confirmed the presence of FAdV, belonging to species E, serotype FAdV-8b. Performance and financial calculations revealed that IBH increased Feed Conversion Ratio (FCR), feed cost/chick as well as feed cost/kg live weight, whereas the Livability (%) and the European Production Efficiency Factor (EPEF) were decreased in the most severely affected flocks (Flock A). This study is the first report of the detection and identification of FAdV serotypes associated with IBH in commercial broiler flocks in Greece. However, there is still a lack of information about the circulating FAdV serotypes in the country, and therefore epidemiological studies are needed to establish control strategies for IBH.


After the 2016 Balkan route border closures, vaccination of refugee children in Greece was mainly performed by non-governmental organisations. Activities varied between camps, resulting in heterogeneity of vaccination coverage (VC). In April 2017, the European programme ‘PHILOS - Emergency health response to refugee crisis’ took over vaccination coordination. Interventions were planned for the first time for refugee children in the community and unaccompanied minors at safe zones. From April 2017-April 2018, 57,615 vaccinations were performed against measles-mumps-rubella (MMR) (21,031), diphtheria-tetanus-pertussis (7,341), poliomyelitis (7,652), pneumococcal disease (5,938), Haemophilus influenzae type b (7,179) and hepatitis B (8,474). In April 2018, the vaccination status of children at camps (reception and identification centres and community facilities such as hostels/hotels were excluded) was recorded and VC for each disease, stratified by dose, nationality and camp size, was calculated. More than 80% of the children received the first MMR dose, with VC dropping to 45% for the second dose. For all other vaccines, VC was < 50% for the first dose in children aged 0-4 years and < 25% for the second dose. Despite challenges, PHILOS improved planning and monitoring of vaccination activities; however, further efforts towards improving VC in refugee children are needed.


OBJECTIVES: to evaluate the epidemiology of hepatitis B infection in pregnant women living in the Marche Region (Central Italy), according to the Country of origin. DESIGN: cross sectional observational
study conducted from May 2011 to April 2012, which involved 13 of the 15 birthing centres in the Marche region. SETTING AND PARTICIPANTS: serological data of hepatitis B infection were obtained during the execution of mandatory prenatal screening. The total number of pregnant women was of 10,232 of which 7,669 were Italian (74.9%) and 2,563 were foreign (25.1%). MAIN OUTCOME MEASURES: rate of adherence to prenatal serologic screening and prevalence of hepatitis B infection in Italian and foreign pregnant women. The 95% confidence intervals were calculated using the exact method for proportions. The test for proportions was applied to make comparisons between groups (significance level: 0.05). RESULTS: the rate of adherence to prenatal serologic screening and the overall prevalence of hepatitis B infection in pregnancy were 98.6% and 0.8%, respectively. In foreign women, compared to native ones, differences of adherence to screening and the prevalence of infection were significant (96.7% vs. 99.3% and 2.7% vs. 0.2%). The highest prevalence was observed in pregnant women who came from the Western Pacific Region, Eastern Europe, and Africa (7.0%, 4.0%, and 3.3%, respectively). More than half of the cases of pregnant women, positive for hepatitis B surface antigen, were originating in Albania and China (60.6%). The prevalence of hepatitis B infection was significantly higher in pregnant women from China (8.1%), Albania (7.7%), Ukraine (7.2%), and Senegal (6.1%). CONCLUSIONS: the study emphasises the need to organise targeted interventions to facilitate access to prenatal screening programmes to foreign women for better control of hepatitis B infection in the Marche Region.


Hepatitis B virus (HBV), is the leading cause of liver diseases infecting an estimated 240 million persons worldwide. The HBV prevalence rates are variables between different countries, with an high level of endemicity in the south-eastern part of Europe. Seven main HBV-D subgenotypes have been described until now (D1-D7). Turkey, seems to have played an important role in the penetration of HBV-D1 in the Mediterranean area. The importance of Turkey in the European epidemiology of HBV is also suggested by the observation that the highest spread of HBV infection in the Continent are reported in Turkey with Romania, Bulgaria, Greece, Albania and some southern regions of Italy. In this paper the molecular epidemiology and the epidemiological history of HBV-D in Turkey was studied, by characterizing 34 new Turkish isolates and performing a phylogeographic reconstruction. By using a phylodynamic and phylogeographic Bayesian approach, the analysis suggested that HBV-D1 originated in Turkey about in the early 1940s. The large prevalence of D1 in comparison to the other subgenotypes in Turkey confirms the importance of this Country as epidemiological reservoir of HBV-D1 dispersion. The phylogeny suggests that after each initial introduction of the virus in a specific population, separate transmission clusters have been evolving along independent phylogenetic lineages. Better characterization and continuous monitoring of such groups are going to be crucial to understand in detail the epidemiology of HBV-D1 subgenotype in Turkey and to assess the efficacy of prevention, vaccination and therapy in controlling the epidemic.
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