Epidemiology of hepatitis C in Croatia in the European context

Tatjana Vilbic-Cavlek, Jasmina Kucinar, Bernard Kaic, Maja Vilbic, Nenad Pandak, Ljubo Barbic, Vladimir Stevanovic, Jasmina Vranes

Tatjana Vilbic-Cavlek, Department of Virology, Croatian National Institute of Public Health and School of Medicine University of Zagreb, Zagreb 10000, Croatia

Jasmina Kucinar, Department of Microbiology, Istria County Institute of Public Health, Pula 52100, Croatia

Bernard Kaic, Department of Epidemiology, Croatian National Institute of Public Health, Zagreb 10000, Croatia

Maja Vilbic, Vrapce University Psychiatric Hospital, Zagreb 10000, Croatia

Nenad Pandak, Department of Infectious Diseases, General Hospital “Dr Josip Bencevic”, Slavonski Brod 35000, Croatia and School of Medicine University of Osijek, Osijek 31000, Croatia

Ljubo Barbic, Vladimir Stevanovic, Department of Microbiology and Infectious Diseases with Clinic, Faculty of Veterinary Medicine University of Zagreb, Zagreb 10000, Croatia

Jasmina Vranes, Department of Microbiology, Public Health Institute “Dr Andrija Stampar” and School of Medicine University of Zagreb, Zagreb 10000, Croatia

Author contributions: Vilbic-Cavlek T made contributions to conception and design of the study, acquisition of the data, involved in drafting the manuscript; Kaic B and Vranes J made contributions to design, involved in drafting and revising the manuscript critically; Kucinar J, Vilbic M, Barbic L, Pandak N and Stevanovic V made contributions in acquisition of the data, involved in drafting the manuscript; all authors read and approved the final manuscript.

Conflict-of-interest statement: Authors reported no conflict of interests.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Tatjana Vilbic-Cavlek, MD, PhD, Department of Virology, Croatian National Institute of Public Health and School of Medicine University of Zagreb, Rockefellerova 12, Zagreb 10000, Croatia. tatjana.vilbic-cavlek@hzjz.hr
Telephone: +385-1-4863238

Received: April 21, 2015
Peer-review started: April 23, 2015
First decision: May 18, 2015
Revised: June 3, 2015
Accepted: July 18, 2015
Published online: August 28, 2015

Abstract

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
Hepatitis C virus (HCV) represents a major public health problem. The World Health Organization (WHO) estimates that about 2.8% or 170 million of world’s population has been infected with HCV, of whom 15 million people live in the WHO European region. In addition, 86000 hepatitis C-related deaths are reported per year in Europe\textsuperscript{[2-4]}. The HCV prevalence varies markedly in different regions and populations. Injecting drug users (IDUs) and recipients of blood transfusions prior to 1992 are traditionally identified risk groups for HCV infection\textsuperscript{[2-4,25-30]}. Variable HCV prevalence is reported in hemodialysis patients and prison populations\textsuperscript{[5-11]}. Transmission of HCV also occurs through occupational, perinatal and sexual exposures\textsuperscript{[12-14]}. However, the association between HCV transmission and high-risk sexual behavior is still controversial\textsuperscript{[15-17]}. Tattooing has emerged in recent years as an additional route of HCV transmission\textsuperscript{[18,19]}. In addition, some other unconventional risk factors for HCV transmission such as digestive endoscopy, abortions, acupuncture, beauty treatments, practice of contact sports and professional pedicure/manicure have been identified among HCV-seropositive persons\textsuperscript{[20]}. In this review, the prevalence, risk factors and HCV genotype distribution in different population groups in Croatia were analyzed in the context of HCV epidemiology in Europe (Table 1).

**HCV PREVALENCE AND TRANSMISSION RISK FACTORS IN CROATIA**

It is estimated that between 35000 and 45000 of the Croatian population is chronically infected with HCV\textsuperscript{[21,22]}. Prevalence of HCV infection in different population groups is presented in Figure 1.

**Polytransfused patients and plasma product recipients**

Before the introduction of routine HCV screening of blood/blood products in 1992, transfusion-associated HCV infections were common in Croatia. A study on 359 hemophilia patients in the period from 1993 to 1999 showed that 75.9% tested positive to anti-HCV antibodies, of whom all were infected through coagulation factor concentrates before 1990\textsuperscript{[23]}. In a pilot study conducted in 1992, serologic evidence of HCV infection was found in 24.1% polytransfused patients\textsuperscript{[24]}. With the current blood transfusion safety and the availability of recombinant clotting factors, these patients are no longer at risk for HCV infection\textsuperscript{[25]}. 

**Injecting drug users**

IDUs represent the most common risk group for HCV infection in Croatia. There are several studies estimating prevalence of HCV infection among IDUs which showed positivity rate from 29% to 65%, according to geographical region\textsuperscript{[26-30]}. Seroprevalence rates among IDUs in therapeutic communities were significantly higher compared to outpatients (60.66% vs 41.86%)\textsuperscript{[26]}. Factors associated with an increased risk of HCV infection included age, duration of IDU and sharing injection equipment. A very high prevalence of 100% was observed among older injectors (40-49 years) compared to 46.5% in younger injectors (20-29 years)\textsuperscript{[26]}. HCV-positive IDUs started using heroin at a significantly younger age than HCV-negative IDUs.
<table>
<thead>
<tr>
<th>Study population/country</th>
<th>Study area</th>
<th>Sample size</th>
<th>Anti-HCV</th>
<th>HCV RNA</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraavenous drug users</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>Limburg, Antwerp</td>
<td>310</td>
<td>66.2%-84.4%</td>
<td>-</td>
<td>Mathé et al[44], 2005</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>Sofia</td>
<td>773</td>
<td>73.90%</td>
<td>-</td>
<td>Vassile et al[43], 2006</td>
</tr>
<tr>
<td>Croatia</td>
<td>Brod-Pozisina County</td>
<td>208</td>
<td>44.60%</td>
<td>-</td>
<td>Kolovrat et al[107], 2010</td>
</tr>
<tr>
<td>Croatia</td>
<td>Zadar County</td>
<td>327</td>
<td>59%</td>
<td>-</td>
<td>Medici et al[100], 2008</td>
</tr>
<tr>
<td>Croatia</td>
<td>Multicenter</td>
<td>76</td>
<td>51.30%</td>
<td>-</td>
<td>Vilibic-Cavlek et al[83], 2011</td>
</tr>
<tr>
<td>Croatia</td>
<td>Zagreb, Rijeka, Split</td>
<td>401</td>
<td>29%-46%</td>
<td>-</td>
<td>Kolarić et al[103], 2010</td>
</tr>
<tr>
<td>Greece</td>
<td>Multicenter</td>
<td>-</td>
<td>43.3%-41.3%</td>
<td>-</td>
<td>Raptopoulou et al[123], 2011</td>
</tr>
<tr>
<td>Hungary</td>
<td>Budapest</td>
<td>215</td>
<td>15%</td>
<td>-</td>
<td>Gyarmathy et al[79], 2011</td>
</tr>
<tr>
<td>Italy</td>
<td>Multicenter</td>
<td>1085</td>
<td>83.20%</td>
<td>-</td>
<td>Camoni et al[109], 2010</td>
</tr>
<tr>
<td>Lithuania</td>
<td>Vilnius</td>
<td>543</td>
<td>63.90%</td>
<td>68.30%</td>
<td>Stroffolini et al[115], 2012</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>Nationwide</td>
<td>300</td>
<td>80%</td>
<td>-</td>
<td>Gyarmathy et al[37], 2011</td>
</tr>
<tr>
<td>Romania</td>
<td>Bucharest</td>
<td>45</td>
<td>88.90%</td>
<td>57.80%</td>
<td>Sultan et al[107], 2011</td>
</tr>
<tr>
<td>Russia</td>
<td>St. Petersburg</td>
<td>387</td>
<td>94.60%</td>
<td>-</td>
<td>Pintilie et al[110], 2009</td>
</tr>
<tr>
<td>Spain</td>
<td>Barcelona</td>
<td>1132</td>
<td>88%</td>
<td>-</td>
<td>Muga et al[111], 2006</td>
</tr>
<tr>
<td>Sweden</td>
<td>Stockholm</td>
<td>310</td>
<td>86.50%</td>
<td>-</td>
<td>Norden et al[112], 2014</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Amsterdam</td>
<td>497</td>
<td>60%</td>
<td>69%</td>
<td>Lindenburg et al[113], 2011</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Multicenter</td>
<td>452</td>
<td>38.80%</td>
<td>-</td>
<td>Norden et al[112], 2013</td>
</tr>
<tr>
<td>Hemodialysis patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albania</td>
<td>Tirana</td>
<td>50</td>
<td>16.70%</td>
<td>56%</td>
<td>Vila Brumilda et al[117], 2008</td>
</tr>
<tr>
<td>Croatia</td>
<td>Zagreb</td>
<td>128</td>
<td>2.30%</td>
<td>-</td>
<td>Crnjaković-Palmovic et al[118], 2005</td>
</tr>
<tr>
<td>Estonia</td>
<td>Tallinn</td>
<td>357</td>
<td>3.40%</td>
<td>-</td>
<td>ICIPH[36], 2014</td>
</tr>
<tr>
<td>Germany</td>
<td>Multicenter</td>
<td>4718</td>
<td>7.70%</td>
<td>-</td>
<td>Saune et al[119], 2011</td>
</tr>
<tr>
<td>Germany</td>
<td>Multicenter</td>
<td>1633</td>
<td>5.80%</td>
<td>-</td>
<td>Klem et al[120], 2008</td>
</tr>
<tr>
<td>Italy</td>
<td>Sicily</td>
<td>320</td>
<td>6.25%</td>
<td>-</td>
<td>Li Cavoli et al[121], 2011</td>
</tr>
<tr>
<td>Romania</td>
<td>Multicenter</td>
<td>174</td>
<td>39.26%</td>
<td>-</td>
<td>Voiulescu et al[122], 2010</td>
</tr>
<tr>
<td>Serbia</td>
<td>Nationwide</td>
<td>5208</td>
<td>12.70%</td>
<td>-</td>
<td>Djukanovic et al[123], 2012</td>
</tr>
<tr>
<td>1Persons with high-risk sexual behavior</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td>Multicenter</td>
<td>821</td>
<td>4.60%</td>
<td>73.10%</td>
<td>Vilibic-Cavlek et al[124], 2009</td>
</tr>
<tr>
<td>(MSM)</td>
<td>Zagreb</td>
<td>360</td>
<td>3.00%</td>
<td>-</td>
<td>Bozicevic et al[125], 2009</td>
</tr>
<tr>
<td>Estonia</td>
<td>Tallinn</td>
<td>227</td>
<td>7.90%</td>
<td>-</td>
<td>Uuskula et al[126], 2008</td>
</tr>
<tr>
<td>Italy</td>
<td>Verona</td>
<td>345</td>
<td>0.90%</td>
<td>-</td>
<td>Zermiani et al[127], 2012</td>
</tr>
<tr>
<td>Moldova</td>
<td>Balti, Chisinau</td>
<td>397</td>
<td>1.2%-3.7%</td>
<td>-</td>
<td>Zobrabyan et al[128], 2013</td>
</tr>
<tr>
<td>Slovenia</td>
<td>Stockach</td>
<td>1908</td>
<td>0.50%</td>
<td>-</td>
<td>Blackhurst et al[129], 2013</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>London</td>
<td>2309</td>
<td>0.65%</td>
<td>-</td>
<td>Scott et al[130], 2010</td>
</tr>
<tr>
<td>(MSM)</td>
<td>London</td>
<td>1121</td>
<td>1.20%</td>
<td>-</td>
<td>Price et al[131], 2013</td>
</tr>
<tr>
<td>Prisoners</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td>Multicenter</td>
<td>3348</td>
<td>8.30%</td>
<td>-</td>
<td>Burek et al[132], 2010</td>
</tr>
<tr>
<td>France</td>
<td>Caen</td>
<td>190</td>
<td>11%</td>
<td>-</td>
<td>Vilibic-Cavlek et al[133], 2011</td>
</tr>
<tr>
<td>France</td>
<td>Nationwide</td>
<td>597</td>
<td>4.90%</td>
<td>-</td>
<td>Vermeul et al[134], 2009</td>
</tr>
<tr>
<td>France</td>
<td>Multicenter</td>
<td>60975</td>
<td>4.80%</td>
<td>79%</td>
<td>Semaille et al[135], 2013</td>
</tr>
<tr>
<td>Hungary</td>
<td>Multicenter</td>
<td>5957</td>
<td>5.20%</td>
<td>-</td>
<td>Roux et al[136], 2014</td>
</tr>
<tr>
<td>Ireland</td>
<td>Regional (Northern)</td>
<td>1185</td>
<td>1.10%</td>
<td>-</td>
<td>Danis et al[137], 2007</td>
</tr>
<tr>
<td>Italy</td>
<td>Multicenter</td>
<td>973</td>
<td>38%</td>
<td>-</td>
<td>Babudieri et al[138], 2005</td>
</tr>
<tr>
<td>Macedonia</td>
<td>Prilep, Bitola</td>
<td>200</td>
<td>20%</td>
<td>-</td>
<td>Jovanovska et al[139], 2014</td>
</tr>
<tr>
<td>Portugal</td>
<td>445</td>
<td>11%</td>
<td>-</td>
<td>-</td>
<td>Barros et al[140], 2008</td>
</tr>
<tr>
<td>Spain</td>
<td>Multicenter</td>
<td>370</td>
<td>22.70%</td>
<td>-</td>
<td>Saiz de la Hoyea et al[141], 2011</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Nationwide</td>
<td>10723</td>
<td>24.20%</td>
<td>-</td>
<td>Kirwan et al[142], 2011</td>
</tr>
<tr>
<td>HIV-infected patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td>Zagreb</td>
<td>120</td>
<td>15%</td>
<td>72.20%</td>
<td>Semé et al[143], 2007</td>
</tr>
<tr>
<td>Italy</td>
<td>Ancona</td>
<td>440</td>
<td>32.90%</td>
<td>-</td>
<td>Orsetti et al[144], 2013</td>
</tr>
<tr>
<td>Slovenia</td>
<td>Nationwide</td>
<td>356</td>
<td>10.70%</td>
<td>68.40%</td>
<td>Semé et al[145], 2009</td>
</tr>
<tr>
<td>Spain</td>
<td>Nationwide</td>
<td>579</td>
<td>7.60%</td>
<td>75%</td>
<td>Škamperle et al[146], 2014</td>
</tr>
<tr>
<td>Spain</td>
<td>Regional (Southern)</td>
<td>520</td>
<td>69%</td>
<td>71%</td>
<td>Cifuentes et al[147], 2012</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>London</td>
<td>1017</td>
<td>8.90%</td>
<td>-</td>
<td>Møbsen et al[148], 2005</td>
</tr>
<tr>
<td>Alcohol abusers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td>Istria County</td>
<td>167</td>
<td>2.40%</td>
<td>-</td>
<td>ICIPH[36], 2014</td>
</tr>
<tr>
<td>Germany</td>
<td>Hamburg</td>
<td>463</td>
<td>5.20%</td>
<td>-</td>
<td>Schmidt et al[149], 2013</td>
</tr>
<tr>
<td>Spain</td>
<td>Salamanca</td>
<td>396</td>
<td>3.53%</td>
<td>-</td>
<td>Novo-Veleino et al[150], 2013</td>
</tr>
<tr>
<td>Adult general population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulgaria</td>
<td>Plovdiv</td>
<td>2211</td>
<td>1.08%</td>
<td>-</td>
<td>Atanasova et al[151], 2014</td>
</tr>
</tbody>
</table>
and reported a longer history of IDU. Young IDUs were found to be at higher risk for HCV infection because of their high-risk behavior patterns. They are usually less critical toward drugs, less cautious, and more easily influenced by others[27]. The frequency of sharing injection equipment was the most important risk factor for HCV transmission in this risk group[27-29]. The HCV seroprevalence rates ranged from 27.3% in IDUs who reported sharing needles/syringes occasionally to 100% in those who always shared injection equipment[29].

**Hemodialysis patients**

Hemodialysis patients also represent a risk group for HCV infection. In a pilot study conducted in 1992, 44% of hemodialysis patients showed anti-HCV antibodies[24]. A similar seropositivity rate (38%) was noted in 1994[21]. Two regional surveys from north-west Croatia (1997) and north Adriatic Coast (2003) reported prevalence rates of 26.1% and 23%, respectively[22,23]. A low prevalence (2.3%) was noted in 2005 in a Dialysis Center at one Zagreb hospital[34].

More recent data from Istria County (2007-2013) showed a similar prevalence of 3.2%[35].

**Persons with high-risk sexual behavior**

Persons with high-risk sexual behavior (persons with multiple sexual partners, men who have sex with men (MSM), commercial sex workers (CSW), persons with a history of sexually transmitted diseases (STDs)) showed a higher HCV prevalence (4.6%) compared to the Croatian general population (0.9%)[36]. In a multicenter study from 7 cities (Zagreb, Split, Rijeka, Zadar, Osijek, Slavonski Brod and Dubrovnik) conducted during 2003-2006, the highest seroprevalence rate (8.5%) was found in patients with a history of STD compared to 6.5% in persons with multiple sex partners, 4.0% in CSW/clients of CSW and 2.9% in MSM. Among STD markers, a prior HBV infection and hepatitis B vaccine were shown to be risk factors associated with higher HCV prevalence. No other factors reflecting risky sexual behavior such as sexual orientation and number of sexual partners as well as number of risk behaviors correlated with HCV seropositivity.

---

<table>
<thead>
<tr>
<th>Country</th>
<th>Region</th>
<th>City</th>
<th>IDUs</th>
<th>HCV Prevalence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Croatia</td>
<td>Primorje-Gorski Kotar</td>
<td>Zagreb</td>
<td>785</td>
<td>3.70%</td>
<td>Ticac et al[20], 2010</td>
</tr>
<tr>
<td>France</td>
<td>Multicenter</td>
<td>Paris</td>
<td>14416</td>
<td>0.84%</td>
<td>Meffre et al[39], 2010</td>
</tr>
<tr>
<td>Germany</td>
<td>Berlin, Frankfurt</td>
<td>28809</td>
<td>2.4%-3.5%</td>
<td>68%</td>
<td>Vermehren et al[44], 2012</td>
</tr>
<tr>
<td>Greece</td>
<td>Crete</td>
<td>876</td>
<td>2.20%</td>
<td>-</td>
<td>Drosis et al[43], 2013</td>
</tr>
<tr>
<td>Italy</td>
<td>Regional (Southern)</td>
<td>2195</td>
<td>2.60%</td>
<td>-</td>
<td>Cozzolongo et al[33], 2009</td>
</tr>
<tr>
<td>Kosovo</td>
<td>-</td>
<td>1287</td>
<td>0.50%</td>
<td>-</td>
<td>Quaglio et al[33], 2008</td>
</tr>
<tr>
<td>Latvia</td>
<td>Multicenter</td>
<td>1459</td>
<td>2.4%</td>
<td>71.40%</td>
<td>Tolmane et al[41], 2011</td>
</tr>
<tr>
<td>Macedonia</td>
<td>Skopje</td>
<td>4000</td>
<td>0.40%</td>
<td>-</td>
<td>Kiprijanovska et al[42], 2013</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Amsterdam</td>
<td>1364</td>
<td>0.60%</td>
<td>-</td>
<td>Baaten et al[39], 2007</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Arnhem, Nijmegen</td>
<td>2200</td>
<td>0.20%</td>
<td>-</td>
<td>Slavenburg et al[45], 2008</td>
</tr>
<tr>
<td>Croatia</td>
<td>Zagreb County</td>
<td>200</td>
<td>0.50%</td>
<td>-</td>
<td>Vilibic-Cavlek et al[32], 2009</td>
</tr>
<tr>
<td>Greece</td>
<td>Piraeus</td>
<td>5497</td>
<td>0.80%</td>
<td>-</td>
<td>Panagopoulos et al[46], 2004</td>
</tr>
<tr>
<td>Poland</td>
<td>Warsaw</td>
<td>544</td>
<td>2.02%</td>
<td>-</td>
<td>Aniszewska et al[47], 2009</td>
</tr>
<tr>
<td>Russia</td>
<td>Cheboksary</td>
<td>150</td>
<td>3%</td>
<td>-</td>
<td>Asratian et al[48], 2009</td>
</tr>
<tr>
<td>Spain</td>
<td>Madrid</td>
<td>157</td>
<td>1%</td>
<td>-</td>
<td>Santiago et al[49], 2012</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Multicenter</td>
<td>9557</td>
<td>0.71%</td>
<td>-</td>
<td>Prasad et al[50], 2007</td>
</tr>
</tbody>
</table>

1Persons with high-risk sexual behavior: Men who have sex with men-MSM, commercial sex workers-CSW, persons with sexually transmitted diseases-STDs; 2Istria County Institute of Public Health, Pula, Croatia. ICIPH: Istria County Institute of Public Health; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; IDU: Injecting drug users; STDs: Sexually transmitted diseases; CSW: Commercial sex workers; MSM: Men who have sex with men.
was detected in 73.1% anti-HCV positive persons, but was also found in three seronegative cases ("window period").

**Prison population**

Incarcerated persons accounted for 0.4% of a total Croatian population, among which IDUs comprise about 25%-30%. In a prison population, the overall HCV prevalence is reported to be 8.3%-44%[18,26,37]. HCV seropositivity in prisons also correlates significantly to IDU. HCV infection is most prevalent among IDUs (42%-52%) and relatively high among highly promiscuous persons (4.9%)[18,37]. Significant differences in seropositivity were found in prisoners who reported unprotected sexual activity compared to prisoners who used condoms (22% vs 4%). A history of tattoos was another risk factor associated with higher anti-HCV positivity in this population group. HCV-infected prisoners were significantly more likely to have a history of a tattoo exposure (27%) than HCV-uninfected prisoners (8%). However, it is not clear whether tattooing is a real risk factor for HCV transmission since many of anti-HCV positive prisoners reported other potential exposure to HCV (sharing injection equipment or risk sexual behavior). In addition, higher seroprevalence rates were found in prisoners who were unemployed and in those who resided in urban areas[18].

**Human immunodeficiency virus-infected patients**

One study addressed HCV prevalence in human immunodeficiency virus (HIV)-infected Croatian patients. Among 120 patients tested from 1985 to 2002, 15% were found to be anti-HCV positive and 72.2% of them were found to be viremic. A significant difference in the HCV prevalence was detected among blood and sexual exposure risk groups (66.7% vs 6.6%) with the highest prevalence reported in hemophiliacs (100%) and IDUs (58.3%)[38].

**Alcohol abusers**

Prevalence of HCV in alcohol abusers in Croatia is largely unknown. Regional data showed that HCV prevalence in alcoholic patients is higher compared to the Croatian general population. Among 167 consecutive samples from alcoholic patients tested at the Istria County Institute of Public Health between 2007 and 2013, four were confirmed positive for HCV antibodies (2.4%)[35].

**General population**

Two studies on the HCV prevalence were conducted in the Croatian general population. The 2011-2012 study included adult population undergoing routine preoperative check-up from 4/21 counties located in the Croatian mainland. Results of the study suggest that HCV is uncommon in both urban and rural general population. Eighteen of 1930 (0.9%) tested participants were found positive to HCV. No difference in seropositivity was found between genders and age groups[36]. An earlier study (2006-2007) from a Primorje-Gorski Kotar County, located on the north Adriatic coast, reported anti-HCV prevalence of 3.7% using enzyme-linked immunosorbent assay (ELISA). Age distribution of HCV-positive cases showed that majority of patients belong to the 21-30 age group (44%) and 31-40 age group (19%)[39]. Differences in the seroprevalence rates among the Croatian general population most probably reflect the methodological differences (line immunoassay-LIA and ELISA, selection of study participants) in these surveys.

In the period from 2002-2011, occupational exposures were monitored in one Zagreb hospital. Of 451 source patients, 2.2% were infected with
HCV. Majority of accidents were reported at surgical departments (63%), followed by departments of internal medicine (22.6%), and other departments such as dialysis, different laboratories, neurology, psychiatry and radiology[40].

**Pregnant women**
A few Croatian studies addressed HCV prevalence in pregnant women. Two regional studies (Zagreb County, 2003-2006 and Istria County, 2011-2012) showed HCV prevalence rates of 0.5% and 1.3%, respectively[17,41]. The Istrian study analyzed risk factors and revealed that 83.3% of seropositive women reported a history of IDU and 8.3% reported a former relationship with an IDU. HCV seropositivity increased with age from 0.3% to 3.1%, starting with 26-30 age group[41]. A prevalence of 49% was found in pregnant IDUs from Split region[32].

**Children and adolescents**
There is no published HCV prevalence research involving children in Croatia. In a group of 297 children and adolescents (up to 18 years) from Istria County tested in the period from 2007 to 2014, only one (0.3%) showed anti-HCV antibodies on two repeated testing. In one 6-mo-old child, anti-HCV antibodies were detected at initial testing while at age of 18 mo the result was negative (data from the Microbiology Service, Istria County Institute of Public Health). Mother’s history of IDU was reported in both cases.

**Organ/blood donors**
Since 2006, the Croatian Institute of Transfusion Medicine has been providing mandatory testing of organ donors for bloodborne pathogens. Among 642 organ donor plasma samples tested between 2006 and 2012, 1.6% were found to be anti-HCV positive[43]. Blood donors represent a group with the lowest seroprevalence of HCV infection in Croatia. The frequency of confirmed positive donors continuously declined from 1.38% in 1992 to 0.035% in 1999[23,24], and thereafter remained stable. In the last decade (2004-2013), the anti-HCV seropositivity is reported to be 0%-0.009%[41].

**EPIDEMIOLOGY OF HCV INFECTION IN CROATIA IN THE CONTEXT OF HCV EPIDEMIOLOGY IN EUROPE**

**Polytransfused patients and plasma product recipients**
Hemophilia patients who received clotting factor concentrates and recipients of blood transfusion before 1990 both represent high-risk groups for HCV infection. As expected, patients requiring multiple transfusions have a high prevalence of HCV infection. The prevalence of HCV among hemophiliacs correlates with the amount and type of product transfused. Nearly all hemophiliacs exposed to untreated commercial clotting factor concentrates before anti-HCV screening are HCV positive, while among those treated with cryoprecipitates, the anti-HCV positivity was about 66%[14]. Similar to seroprevalence in other European studies (59%-97%)[45-49], a Croatian study from 1990s showed a high HCV seropositivity in hemophilia patients (75.9%)[23]. Seroprevalence rate of 24.1% in Croatian polytransfused patients is within the range of the majority other studies (3%-21%)[48-52]. With the implementation of mandatory anti-HCV and HCV RNA screening of blood/blood donations, the risk of transfusion-associated hepatitis C has virtually been eliminated[53]. Rare cases of HCV transmission were reported from recently infected donors with serum HCV RNA level below the detection limit[54,55]. However, many European countries are facing the consequences of the past epidemic of transfusion-associated hepatitis C. In several European studies, patients with transfusion-associated HCV infection account for 20%-30% of patients older than 50 years with advanced chronic hepatitis, cirrhosis and hepatocellular carcinoma[25,56,57].

**Injecting drug users**
IDU is one of the most efficient routes for HCV transmission[4]. The prevalence of HCV infection among IDUs varies, although rates are continuously very high in most European countries. Recent studies have demonstrated HCV seroprevalence of 38.8%-60% in the Netherlands[58,59], 43.3%-61.7% in Greece[60], 48.1%-83.2% in Italy[60-63], 62.6% in Belgium[64], 73% in Bulgaria[65], 80% in Lithuania[66], 81.3% in Luxembourg[67], 86.5% in Sweden[59], 88% in Spain[68], 88.9% in Romania[68] and 94.6%-96% in Russia[3,45]. In Croatia, there are considerable geographical variations in HCV prevalence among IDUs (29%-65%)[26-30] similar to those observed in the United Kingdom (24%-74%)[69]. The efficiency of IDU in HCV transmission might be due to prolonged virus survival in contaminated syringes. A study from Doerrbecker et al[70] addressed HCV inactivation and stability profiles on inanimate surfaces to mimic viral cross-transmissions among IDUs. Viral infectivity on inanimate surfaces was detectable in the presence of serum for up to five days. Paintsil et al[71] analyzed the survival of HCV in syringes and the duration of potential infectiousness. The results of their study showed that HCV survived for up to 63 d in high void volume syringes. Besides syringes, sharing of drug injection paraphernalia such as drug preparation containers, cotton filters and rinse water poses a risk of transmitting the HCV[72]. HCV on a spoon as cooker can survive temperatures up to 65 ℃, confirming that virus survival on cookers could also be a potential source of HCV aside from syringes[70]. Other notable risk factors associated with increased risk of being HCV-infected in IDUs population include older age, unemployment, longer history of IDU and higher
number of rehabilitation treatment episodes\textsuperscript{[14,61]}.  

**Hemodialysis patients**

The prevalence of HCV among hemodialysis patients varies widely between geographic areas as well as between centers within the same country. In the 1990s, high prevalence rates (20%-50%) in most of European dialysis population were attributed to frequent blood transfusions\textsuperscript{[5-7,73,74]}. The introduction of sensitive ELISA tests for screening of blood and organ donations, use of erythropoietin in treatment of anemia and improvement in infection control practices have greatly decreased HCV infection among haemodialysis patients\textsuperscript{[25,75]}. A European multicenter study suggested a decline in HCV seroprevalence among hemodialysis patients in majority, but not in all European countries. From 1991 to 2000, anti-HCV prevalence decreased in France (42% to 30%), Sweden (16% to 9%), Italy (28% to 16%), Hungary (26% to 15%) and Belgium (13.5% to 6.8%) and tended to decrease in the United Kingdom (7% to 3%)\textsuperscript{[76]}. A similar trend was observed among hemodialysis patients in Croatia. HCV seroprevalence declined from 44% in 1992\textsuperscript{[24]} to 23% in 2003\textsuperscript{[33]}. More recent regional data showed low and stable seroprevalence rates in Croatian hemodialysis patients (2.3%-3.2%)\textsuperscript{[34,35]}. There was no significant change in Germany (7%-6%) and Spain (5%-12%) by 2000\textsuperscript{[76]}. However, another Spanish study from Cordoba showed a decrease in the HCV prevalence from 24% in 1992 to 9.2% by the end of 2002\textsuperscript{[77]}. In contrast, Poland showed not only stable, but also very high HCV prevalence (42%-44%)\textsuperscript{[76]}. In addition, a high prevalence rate was found in Romania (39.26%)\textsuperscript{[78]}. Some more recently published studies showed prevalences of 16.7% in Albania\textsuperscript{[79]}, 12.7% in Serbia\textsuperscript{[80]} 7.7% in France\textsuperscript{[81]}, 6.25% in Italy\textsuperscript{[82]} and 5.8% in Germany\textsuperscript{[83]}. The number of blood transfusions and the length of time on dialysis are the most important risk factors for HCV acquisition in hemodialysis patients\textsuperscript{[83,84]}. Additional risks factors include IDU and a history of kidney transplantation\textsuperscript{[84]}.  

**Persons with high-risk sexual behavior**

The role of sexual transmission in epidemiology of HCV infection is still controversial. In the past, sexual transmission has been considered a relatively inefficient route for HCV transmission. A risk of HCV transmission is extremely low among stable monogamous heterosexual partners\textsuperscript{[85,86]}. However, the risk for sexual partners is significantly higher when the risk factor for the index case is IDU\textsuperscript{[87-89]}. In the last decade HCV infection has emerged as a STD in some European countries, especially among HIV-positive MSM. A recently published Dutch study showed an increase in HCV seroprevalence in HIV-positive MSM from 5.6% in 1995 to 20.8% in 2008. *Chlamydia trachomatis* infection, IDU, unprotected anal intercourse and older age were variables independently associated with HCV infection\textsuperscript{[90]}. Another study conducted among British MSM showed an overall seroprevalence of 2.1%. The prevalence in HIV-negative MSM (1.2%) was higher, but not significantly higher, than that in the general population (0.67%). However, the prevalence was significantly higher in HIV-positive MSM (7.7%). Moreover, HCV infection was more common in MSM with a history of syphilis than in those without such history (12.2% vs 1.7%) and those who reported casual unprotected anal intercourse in the previous year than in those who did not report such intercourse (4.1% vs 1.2%)\textsuperscript{[91]}. Two Croatian studies found a higher prevalence in HCV seropositivity in HIV-negative MSM (2.9% and 3%)\textsuperscript{[17,92]} compared to the general population (0.9%)\textsuperscript{[93]} but these differences did not reach statistical significance. Similar findings were reported from other European studies among MSM that have controlled for IDU (Sweden, the Netherlands, United Kingdom, Moldova)\textsuperscript{[50,91,93-95]}. Among Croatian persons with high-risk sexual behavior, the highest HCV seropositivity rates were detected in patients with a history of STD (8.5%) and persons with multiple sex partners (6.5%)\textsuperscript{[17]}. Association between HCV seroprevalence and multiple sex partners was observed in several studies. However, the number of partners associated with infection risk varied among studies, ranging from one partner in the previous month to more than 50 partners in the previous year or lifetime\textsuperscript{[96,97]}. In persons with multiple sex partners, there is an increased probability of having sex with an infectious partner\textsuperscript{[98]}. In Croatian CSW and their clients, a prevalence of 4.0% was found. A higher prevalence of 7.9% was reported in Estonian CSW\textsuperscript{[99]}. In contrast, prevalence of HCV in Italian CSW was as low as 0.9%, lower than in the general Italian population. The low HCV prevalence reflects the low prevalence of IDU in the analyzed cohort\textsuperscript{[100]}.  

**Prison population**

Since IDUs constitute a substantial proportion of prison population in many European countries, HCV prevalence rates among prisoners are higher than in the general population\textsuperscript{[101]}. The HCV seropositivity is reported to be 4.9% in Hungary\textsuperscript{[9]}, 4.8%-5.2% in France\textsuperscript{[102-104]}, 7%-24.2% in England and Wales\textsuperscript{[105,106]} 11% in Portugal\textsuperscript{[107]}, 19% in Scotland\textsuperscript{[108]}, 20% in Macedonia\textsuperscript{[109]}, 22.7% in Spain\textsuperscript{[110]} and 38% in Italy\textsuperscript{[110]}. Different studies showed association between the HCV seroprevalence and history of IDU. Among prisoners who reported IDU, rates vary from 60.2% in Ukrainian\textsuperscript{[8]}, 69% in Portuguese\textsuperscript{[107]}, 74.7% in Italian\textsuperscript{[112]} to a high 87% among Danish prisoners\textsuperscript{[113]}. In three Croatian studies conducted among prison population the seroprevalence ranged from 4.9% in highly promiscuous persons to 52% in IDUs\textsuperscript{[18,26,37]}. Some studies suggested that tattooing and piercing are risk factors HCV infections, especially those done...
in nonprofessional settings\(^{19,111}\). In contrast, a Dutch study showed no evidence for an increased HCV seroprevalence among persons with multiple tattoos and/or piercings. The authors suggested that this might be due to the introduction of hygiene guidelines for tattoo and piercing shops in combination with the low observed prevalence HCV in the general population\(^{112}\). Compared to similar studies, the prevalence of HCV among prisoners in Northern Ireland is lower (1.1%) than in other European countries (only 11% of Irish prisoners reported ever injected drugs)\(^{113}\).

**HIV-infected patients**

With the increased life expectancy of HIV-infected patients due to highly active antiretroviral therapy, HCV has recently emerged as an important pathogen in these patients\(^{114}\). Prevalence of HCV/HIV coinfection varies substantially according to route of transmission. About 50%-90% of HIV positive IDUs are co-infected with HCV\(^{15,115,116}\), whereas the co-infection rate in HIV positive MSM is 3.5%-7%\(^{69,116}\). In Europe, prevalence of HIV/HCV coinfection is reported to be 7.6%-10.7% in Slovenia\(^{38,117}\), 8.9% in the United Kingdom\(^{115}\), 32.2% in Italy\(^{118}\) and 58%-69% in Spain\(^{119}\). The reported prevalence in Croatian HIV-infected patients (15%)\(^{30}\) is within the European range. HIV infection appears to adversely affect the outcome of hepatitis C, leading to increased viral persistence, higher levels of viremia, and accelerated progression of HCV-related liver disease\(^{120,121}\).

**Alcohol abusers**

It is traditionally assumed that the prevalence of HCV infection in alcohol-dependent individuals is higher than in the general population, but the modes of transmission are not clearly understood\(^{122-124}\). Higher risk for trauma and accidents requiring blood transfusion could be a potential reason for a higher HCV prevalence in alcoholics\(^{125}\). Additionally, risky sexual behavior and IDU could be confounding factors for HCV seropositivity in this population\(^{126}\). A wide range of prevalence has been reported which could be related to a different distribution of risk factors among studies. Several earlier European studies showed prevalence rates of 14% in Sweden\(^{127,128}\), 24.3% in Spain\(^{129}\) and 31.7% in Italy\(^{110}\). History of IDU was reported by 58%-88.7% Swedish HCV-positive alcoholic patients. The prevalence of blood transfusions, number of hospital admissions, duration of alcohol dependence or presence of tattooing were not shown to be factors of importance for the HCV transmission\(^{127,128}\).

Two recently published studies showed lower prevalence rates. A Spanish study analyzed a total of 396 patients with diagnosis of alcohol abuse/alcohol dependence consecutively attended at the alcoholism unit and found 3.53% to have chronic HCV infection. Variables independently associated with HCV infection were female gender, current or past IDU and the presence of alcoholic liver disease\(^{126}\). In a German study, anti-HCV antibodies were found in 5.3% alcohol-dependent patients. A history of IDU or nonprofessional tattooing emerged as potential risk factors\(^{123}\). Data from Norway (Oslo County) showed a prevalence of 4.4% in alcoholics\(^{131}\). HCV prevalence in Croatia was reported to be lower (2.4%)\(^{33}\) compared to European data. However, these data are limited to a small number of tested subjects and probably do not reflect the prevalence of all alcoholic population.

**General population**

Data from the European countries indicate significant variations in HCV seroprevalence, even within the same country. It seems that HCV seroprevalence in the Croatian adult general population (0.9%)\(^{36}\) echoes the prevalence rates of many European countries (Spain 0.6%-1.6%\(^{132}\), France 0.84%\(^{133}\), Belgium 0.87%\(^{134}\), Poland 0.9%\(^{135}\) and Bulgaria 1.08%\(^{136}\). Lower prevalence rates were reported in the Netherlands (0.2%-0.6%)\(^{117,138}\), Sweden (0.37%)\(^{139}\), Macedonia (0.4%)\(^{140}\), Greece (0.5%)\(^{141}\), Kosovo (0.5%)\(^{142}\) and Norway (0.55%-0.7%)\(^{131,143}\). A German study conducted among adult population in two metropolitan emergency departments (Berlin, Frankfurt) during 2008-2010 found higher prevalence rates (2.4% and 3.5%, respectively). Authors suggested that a high HCV prevalence may be partly explained by the urban study setting as well as the fact that high-risk populations such as IDU and homeless people were not excluded from the study. Additionally, some other risk groups (e.g., patients with coagulation disorders or liver transplant candidates) may even have been overrepresented which may have accounted for selection bias\(^{144}\). Similar HCV prevalence rates was found in the Cretan (2.2%)\(^{145}\) and the Latvian general population (2.4%)\(^{146}\). A high overall seroprevalence rate (3.23%) was reported in a Romanian nationwide study (2006-2008), with significant differences between the main geographical regions (2.63%-4.25%) as well as between counties (0.56%-7.19%)\(^{147}\). Italy has a particular south-to-north prevalence gradient, with very high prevalence in south and central Italy (7.3% and 6.1%) and lower in the north (2.6%)\(^{4,148,149}\).

The majority of European studies showed no difference in HCV seropositivity between genders\(^{148,150}\) or a higher prevalence in males\(^{77,146,151}\). In contrast, a Romanian study has found higher HCV prevalence among females (3.51%) compared to males (2.85%)\(^{147}\). There was no significant difference in the HCV seropositivity between males (1.2%) and females (0.7%) in the Croatian population\(^{36}\).

Although in some European regions age-specific seroprevalence generally increases with age\(^{76,150,152}\), no difference in HCV prevalence was found among...
different age groups in Croatia (0.7%-1.7%)\textsuperscript{[26]}. Italian authors reported a bimodal distribution of HCV with the highest prevalence in subjects over 75 years of age\textsuperscript{[49]}. Seroprevalence of anti-HCV could be considered bimodal in Croatian patients as well, with the highest prevalence in the 30-39 age group (1.7\%)\textsuperscript{[26]}.

**Pregnant women**

Prevalence of HCV in pregnant women is similar to that in the general age-matched population. HCV seroprevalence in the Croatian pregnant women (0.5%-1.3\%) is comparable to that reported in Switzerland (0.7\%)\textsuperscript{[53]} and Spain (1%-1.44\%)\textsuperscript{[154,155]}. Lower prevalence rates were reported in northern Europe (United Kingdom: 0.19%-0.22\%)\textsuperscript{[156]}, Scotland: 0.3%-0.4\%\textsuperscript{[157]}, while Italy, Greece, Poland, Slovakia and Russia reported higher HCV seropositivity (1.9\%, 0.8-1.95\%, 2.02\%, 2.2\% and 3\%, respectively)\textsuperscript{[158-163]}. In a Polish study, the most commonly identified risk factors were history of blood products transfusion before 1992 (24\%), hospitalization with surgical procedures (23\%) and IDU (15\%)\textsuperscript{[161]}. In a Croatian study, all but one HCV seropositive pregnant women reported current or past IDU or a former relationship with an IDU (83.3\% and 8.3\%, respectively)\textsuperscript{[41]}. HCV prevalence in Croatian pregnant IDUs (49\%)\textsuperscript{[42]} is similar to the overall prevalence among IDUs (51\%)\textsuperscript{[17,20]}.

**Children and adolescents**

Before 1992, the mode of HCV acquisition in children was blood transfusion. Higher prevalence rates of 10%-20\% have been reported in children with other potential exposures such as hemodialysis, malignancy and surgery for congenital heart disease\textsuperscript{[164-166]}. The prevalence reported in Croatian children and adolescents (0.3\%) is within the European range (0.05%-0.4\%)\textsuperscript{[167,168]}.

Vertical (mother-to-child) transmission and adolescent high-risk behaviors (IDU) are now the major routes of HCV transmission in developed countries\textsuperscript{[169]}. The average risk for vertical transmission is about 4\% per birth\textsuperscript{[4,14]}. Perinatal transmission is confined almost always to women with detectable HCV RNA\textsuperscript{[167]}. Factors predisposing to HCV transmission are higher maternal viral load at the time of delivery, maternal history of IDU and untreated HIV infection\textsuperscript{[14]}. Breastfeeding carries no further risk of HCV transmission\textsuperscript{[4,170]}.

**Occupationally exposed groups**

Occupational HCV transmission has been reported among healthcare workers (HCWs) who have sustained contaminated needle stick injuries\textsuperscript{[4]}. Prevalence studies among HCWs indicate the low risk for HCV infection associated with occupational exposures. The HCV prevalence among HCWs was not found to significantly differ from that of the general population\textsuperscript{[171-173]}. However, some differences in the prevalence among regions are observed. Very low overall HCV prevalences were reported in Bosnian and Herzegovinian and Belgian HCWs (0.4% and 0.41\%, respectively)\textsuperscript{[160,174]}. However, a Belgian study showed higher rates in three larger metropolitan hospitals (1.3%-2.3\%)\textsuperscript{[174]}. Three studies conducted in Poland showed prevalence rates 0.8%-1.7\%\textsuperscript{[135,173,175]}.

Higher HCV prevalence was found in Italy. A study conducted in Pistoia (central Italy) analyzed samples from 511 HCWs engaged in direct clinical task and 222 clerical/nurse school attendees, of whom 3.8\% and 1.8\% were seropositive to HCV\textsuperscript{[176]}. There are no published data on the HCV prevalence in the Croatian HCWs.

**Blood donors**

Blood donors’ studies showed a decreasing trend in HCV prevalence across time. Data from European countries showed prevalence of 0.13\% in Norway\textsuperscript{[143]}, 0.08%-0.26\% in Bosnia and Herzegovina\textsuperscript{[177,178]}, 0.16%-0.32\% in Germany\textsuperscript{[179]}, 0.4\% in Hungary\textsuperscript{[180]}, 0.5\% in Italy\textsuperscript{[181]}, 0.6\% in Albania\textsuperscript{[182]} and 0.3%-1.5\% in Romania\textsuperscript{[183]}. After 2000, HCV seroprevalence in Croatian blood donors was continuously very low (0.009%-0.03\%)\textsuperscript{[40]}. Since blood donors represent a strictly controlled group, it is expected that the HCV prevalence is lower than in the general population.

**HCV GENOTYPES DISTRIBUTION IN CROATIA**

HCV RNA was detected in 72.2%-82.7\% Croatian HCV infected patients\textsuperscript{[17,32,38]}. Prevalence of HCV genotypes varies by different population groups (Figure 2) as well as by regions. In the general population, genotype 1 is the most widely distributed (60.4%-79.8\%), followed by genotype 3 (12.9%-47.9\%)\textsuperscript{[184-186]}. The most commonly detected subtype is 1b (37.4\%)\textsuperscript{[184]}. In a 10-year study (1995-2006) conducted in four geographical regions (two regions in Croatian mainland and two regions located on the Adriatic Coast), genotype 1 was predominant in three regions (north-west/north-east continental and north coastal area) with prevalence rates 60.4%-76.1\% while in a south coastal area, the prevalence of both genotype 1 and genotype 3 was similar (46.9\% and 47.9\%, respectively). In other regions, genotype 3 was found in 18.3%-32.4\% patients\textsuperscript{[184]}. Another study conducted in north-east Croatia (2009-2011) detected genotype 1 in 79.8\% and genotype 3 in 12.9\% patients\textsuperscript{[187]}. The difference in genotype 3 prevalence between regions could be attributed to different populations. The first study included residents of Split, second largest Croatian city with a large number of IDUs in whom genotype 3 is the most prevalent. Percentage of genotypes 2 and 4 was very low in both studies (0.8%-2.2\% and 3.4%-6.5\%, respectively), while genotypes 5 and 6 were not detected\textsuperscript{[184,187]}.
A history of blood transfusion before 1992 was an independent predictor of HCV infection caused by genotype 1. Genotype 1, subtypes 1a and 1b were detected in majority of Croatian polytransfused patients with HCV infection (12%, 12% and 44%, respectively) (data from the Department of Infectious Diseases, General Hospital “Dr Josip Bencevic”, Slavonski Brod). In hemodialysis patients, subtype 1b was detected in 75% patients (33.3% received more than two blood transfusions) and type 3 in 20.8% patients. Genotype 3 is predominant in Croatian IDUs (60.5%-83.9%) and in Croatian male prisoners showed an equal distribution of genotype 3 (52.4%) and genotype 1 (47.6%). A study among Croatian male prisoners showed an equal distribution of genotype 3 (52.4%) and genotype 1 (47.6%). In persons with high-risk sexual behavior, genotype 1 is the most commonly detected (55.6%) followed by genotype 3 (38.9%). The HCV subtypes distribution is the following: 1a (38.9%), 3a (38.9%) and 1b (5.6%).

HCV GENOTYPES DISTRIBUTION IN EUROPE

Understanding the HCV genotypes distribution is important as a part of a molecular clue for the spread of HCV. It is well-documented that genotype distribution is associated with the mode of transmission. Available data indicate that genotypes 1 and 3 account for the majority of HCV infections in Europe. The most frequent subtype is 1b, detected in many countries in Central (Albania, Bosnia and Herzegovina, the Czech Republic, Hungary, Montenegro, Romania), Western (Austria, France, Greece, Italy, Portugal, Spain) and Eastern Europe (Belarus, Estonia, Lithuania, Latvia and Russia) with a wide range of prevalences (27.2%-92.6%, 29.7%-57.5% and 58.8%-87.7%, respectively). In Finland, Luxembourg, Norway and Switzerland, both subtypes 1b and 1a were equally prevalent, while in Denmark, Sweden and United Kingdom, subtype 1a is more commonly reported. The prevalence rates of genotype 3 varied from 6.6%-44.6% in Central, 3.6%-46.0% in Western and 9.2%-38.5% in Eastern Europe. In southern Italy, genotype 2c is commonly found. Genotype 4 prevalence is rising in Europe (detected in significant proportions in France, Germany, Greece, Italy, Poland, Portugal, Spain, Sweden and Switzerland) reflecting immigration patterns in these areas. Other HCV genotypes such as genotype 5 and 6 are more geoographically restricted. Genotype 5 was found in restricted areas of Belgium, Spain, France and Greece and is mainly transmitted by blood transfusion. Genotypes/subtypes 1a and 3/3a are the most commonly identified in IDUs in Europe. Genotypes 1b and 2 are linked to blood transfusion and unsafe medical procedures.

There are some regional differences in HCV genotypes among hemodialysis patients. Subtype 1b seems to be most frequent in the Netherlands and France while in Italian hemodialysis patients subtypes 2a and 3a predominated. In the general population, genotypes 1 and 3 are the most commonly detected in majority of European countries with the prevalences reported to be 45.1%-79.3% and 19.7%-35.1%, respectively. HCV genotype 1 is even more prevalent in Hungarian (85.5%) and almost exclusively present in Romanian (93.4%-99.1%) patients with chronic HCV infection. In Italy, genotype 1b appears to be the most frequent (30.7%-60%), with genotype 2 following (21.3%-34.8%).

FUTURE CHALLENGES

Over the past few decades, there have been remarkable...
changes in hepatitis C epidemiology. The prevalence of genotypes has evolved with time due to changes in the predominant route of transmission\(^{19}\). However, challenges in HCV prevention remain. Since IDUs still represent a group with the highest risk of HCV transmission, strategies to reduce risk among IDUs should be considered.

From an epidemiological point of view, one of the main challenges regarding HCV infection is to identify infected individuals in order to offer timely treatment. In the last five years, an average of 200 newly discovered HCV infected persons per year are reported to the Reference Centre for Epidemiology, Croatian National Institute of Public Health. Based on a seroprevalence rate of 0.9% in the general population, we must assume that only a small part of the estimated 40000 Croatian HCV-positive citizens are aware of their HCV infection. This discrepancy emphasizes the need to provide testing for HCV infection to a larger proportion of the population.

Another challenge is to identify routes of transmission in individual cases of HCV infection. In routine reports on surveillance of communicable diseases, the country is expected to report the most probable route of infection to WHO and to the European Centre for Disease Prevention and Control (ECDC). In order to meet these requirements, HCV infection as a reportable disease under enhanced surveillance, which anticipates collecting additional information for each case of HCV infection using a standardized questionnaire, in this case, information on the most probable route of infection. A large quantity of information exists on patients with HCV, including clinical, epidemiological, behavioral information, laboratory parameters, but is scattered among different sections of the health system and should be collected at one place and linked to an individual patient. Ideally, a registry of HCV infected persons should be set up, which would not only allow to collect and record all the relevant information on each individual, but would also allow monitoring progression of infection as well as treatment outcomes of patients under treatment.

The origin of HCV is a challenge which has been target of virologists, epidemiologists and geneticists for years but has remained obscure. The majority of recent emerging infections in human populations represent zoonoses transmitted from wild animals and possibility of HCV cross-species transmission from animal species must be taken into consideration\(^{202,203}\).

Although higher primates are susceptible to experimental infection, HCV naturally infects only humans\(^{203}\). Recently, a novel hepatitis virus infecting a wild non-human primate, the black-and-white colobus (Colobus guereza), an Old world monkey from Uganda was discovered\(^{204}\). Animal origin of HCV is additionally published studies demonstrated hepaciviruses and pegiviruses in rodents and bats\(^{211-213}\).

Detection of multiple novel hepacviruses in diverse mammalian species has highlighted the importance of further research to define distribution of hepacviruses and their host range. Discovery of zoonotic source for the HCV would be an important step in understanding host relationship and adaptation and enhance the ability to study pathogenesis and immune response using susceptible animal models.

REFERENCES


Makris M, Preston FE, Triger DR, Underwood JC, Choo QL, Kuo...


Savchenko VG, Garmaeva TTs, Kulikov SM, Filatov FP, Sudarikov AB, Mikhaillova EA. [Efficacy and safety of transfusion therapy in hematological patients]. *Ter Arkh* 2006; **78**: 12-18 [PMID: 16944745]


Kretzschmar E, Chudy M, Nübling CM, Ross RS, Kruse F. First case of hepatitis C virus transmission by a red blood cell concentrate after introduction of nucleic acid amplification technique screening in Germany: a comparative study with various assays. *Vox Sang* 2007; **92**: 297-301 [PMID: 17456153]


Kirwan P, Evans B, Brant L. Hepatitis C and B testing in English prisons is low but increasing. J Public Health (Oxf) 2011; 33: 197-204 [PMID: 21345883 DOI: 10.1093/pubmed/fdr011]


Taylor A, Munro A, Allen E, Dunleavy K, Cameron S, Miller L,


909. Nishioka Sde A, Gyorskos TW, Joseph L, Collet JP, Maclean JD. Tattooing and risk for transfusion-transmitted diseases: the role of the type, name and design of the tattoos, and the conditions in which they were performed. *Epidemiol Infect* 2002; 128: 63-71 [PMID: 11895092]


143 Vik IS, Skauk K, Dalgud O, Steen TW, Hoddevik G. [Hepatitis C—a health problem also in Norway]. *Tidsskr Nor Laegeforen* 2010; **130**: 563-566 [PMID: 18313199]


159 Mogul D, Schwarz KB. Hepatitis C viral infection in children. *Clin Liver Dis 2011; 1*: 77-80 [DOI: 10.1002/clld.64]


Vilibic-Cavlek T et al. Epidemiology of hepatitis C in Croatia


Kapoor A, Simmonds P, Gerold G, Qaisar N, Jain K, Henriques


