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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

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.

Key words: Hepatitis C; Seroprevalence; Genotypes; Croatia; Europe

Core tip: As in other European countries, epidemiology of hepatitis C has changed in Croatia in last few decades. In addition, changes in the hepatitis C virus (HCV) genotype distribution were observed due to changes in prevailing routes of transmission. Although a decline in HCV prevalence was observed in some risk groups (polytransfused and hemodialysis patients), HCV prevalence is still high in injecting drug users (IDUs) (29%-65%), reaching 100% in older injectors and those reporting sharing injection equipment. In addition, a high HCV prevalence (8.3%-44%) was found in Croatian prisoners reflecting high proportion of IDUs within this population group. Since IDUs represent a group with the highest risk for HCV, strategies to reduce risk among IDUs should be considered.

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INTRODUCTION

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[1]. 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[2-4]. Variable HCV prevalence is reported in hemodialysis patients and prison populations[5-11]. Transmission of HCV also occurs through occupational, perinatal and sexual exposures[12-14]. However, the association between HCV transmission and high-risk sexual behavior is still controversial[15-17]. Tattooing has emerged in recent years as an additional route of HCV transmission[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[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[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[23]. In a pilot study conducted in 1992, serologic evidence of HCV infection was found in 24.1% polytransfused patients[24]. With the current blood transfusion safety and the availability of recombinant clotting factors, these patients are no longer at risk for HCV infection[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[26-30]. Seroprevalence rates among IDUs in therapeutic communities were significantly higher compared to outpatients (60.66% *vs* 41.86%)[28]. 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)[29]. HCV-positive IDUs started using heroin at a significantly younger age than HCV-negative IDUs

Table 1 Prevalence of anti-hepatitis C virus and hepatitis C virus-RNA in different population groups in Europe (2004-2014)

Study population/country	Study area	Sample size	Anti-HCV	HCV RNA	Reference
Intravenous drug users					
Belgium	Limburg, Antwerp	310	66.2%-84.4%	-	Mathei *et al*[64], 2005
Bulgaria	Sofia	773	73.90%	-	Vassilev *et al*[65], 2006
Croatia	Brod-Posavina County	208	44.60%	-	Kolovrat *et al*[28], 2010
	Zadar County	327	59%	-	Medić *et al*[27], 2008
	Multicenter	76	51.30%	-	Vilibic-Cavlek *et al*[29], 2011
	Zagreb, Rijeka, Split	401	29%-65%	-	Kolarić *et al*[26], 2010
Greece	Multicenter	-	43.3%-61.3%	-	Raptopoulou *et al*[60], 2011
Hungary	Budapest	215	15%	-	Gyarmathy *et al*[66], 2011
Italy	Multicenter	1085	83.20%	-	Camoni *et al*[62], 2010
	-	1320	48.10%	-	Curcio *et al*[61], 2011
	Multicenter	543	63.90%	68.30%	Stroffolini *et al*[63], 2012
Lithuania	Vilnius	300	80%	-	Gyarmathi *et al*[66], 2011
Luxembourg	Nationwide	268	81.30%	-	Removille *et al*[67], 2011
Romania	Bucharest	45	88.90%	57.80%	Sultana *et al*[68], 2011
Russia	St. Petersburg	387	94.60%	-	Paintsil *et al*[3], 2009
Spain	Barcelona	1132	88%	-	Muga *et al*[2], 2006
Sweden	Stockholm	310	86.50%	-	Norden *et al*[58], 2013
The Netherlands	Amsterdam	497	60%	69%	Lindenburg *et al*[59], 2011
	Rotterdam	452	38.80%	-	Norden *et al*[58], 2013
United Kingdom	Multicenter	1058	27%-74%	-	Hickman *et al*[69], 2007
Hemodialysis patients					
Albania	Tirana	50	16.70%	56%	Vila Brunilda *et al*[79], 2014
Croatia	Zagreb	128	2.30%	-	Crnjaković-Palmović *et al*[34], 2005
	Istria County	157	3.40%	-	ICIPH[35], 2014
France	Multicenter	4718	7.70%	-	Saune *et al*[81], 2011
Germany	Multicenter	1633	5.80%	-	Kliem *et al*[83], 2008
Italy	Sicily	320	6.25%	-	Li Cavoli *et al*[82], 2011
Romania	Multicenter	174	39.26%	-	Voiculescu *et al*[78], 2010
Serbia	Nationwide	5208	12.70%	-	Djukanovic *et al*[80], 2012
[1]Persons with high-risk sexual behavior					
Croatia (MSM, CSW, STD)	Multicenter	821	4.60%	73.10%	Vilibic-Cavlek *et al*[17], 2009
(MSM)	Zagreb	360	3.00%	-	Bozicevic *et al*[92], 2009
Estonia (CSW)	Tallin	227	7.90%	-	Uuskula *et al*[99], 2008
Italy (CSW)	Verona	345	0.90%	-	Zermiani *et al*[100], 2012
Moldova (MSM)	Balti, Chisinau	397	1.2%-3.7%	-	Zohrabyan *et al*[95], 2013
Sweden (MSM)	Stockholm	1008	0.50%	-	Blaxhult *et al*[93], 2013
United Kingdom (MSM)	London	2309	0.65%	-	Scott *et al*[94], 2010
(MSM)	London	1121	1.20%	-	Price *et al*[91], 2013
Prisoners					
Croatia	Multicenter	3348	8.30%	-	Burek *et al*[37], 2010
	Multicenter	190	11%	-	Vilibic-Cavlek *et al*[18], 2011
France	Caen	597	4.90%	-	Verneuil *et al*[103], 2009
	Nationwide	60975	4.80%	79%	Semaille *et al*[102], 2013
	Multicenter	5957	5.20%	-	Roux *et al*[104], 2014
Hungary	Multicenter	4894	4.90%	-	Treso *et al*[9], 2012
Ireland	Regional (Northern)	1185	1.10%	-	Danis *et al*[113], 2007
Italy	Multicenter	973	38%	-	Babudieri *et al*[10], 2005
Macedonia	Prilep, Bitola	200	20%	-	Jovanovska *et al*[109], 2014
Portugal	-	445	11%	-	Barros *et al*[107], 2008
Spain	Multicenter	370	22.70%	-	Saiz de la Hoya *et al*[110], 2011
United Kingdom	Nationwide	10723	24.20%	-	Kirwan *et al*[106], 2011
	Scotland	5187	19%	-	Taylor *et al*[108], 2013
HIV-infected patients					
Croatia	Zagreb	120	15%	72.20%	Seme *et al*[38], 2007
Italy	Ancona	440	32.90%	-	Orsetti *et al*[118], 2013
Slovenia	Nationwide	356	10.70%	68.40%	Seme *et al*[114], 2009
	Nationwide	579	7.60%	75%	Škamperle *et al*[117], 2014
Spain	Regional (Southern)	520	69%	71%	Cifuentes *et al*[119], 2012
United Kingdom	London	1017	8.90%	-	Mohsen *et al*[115], 2005
Alcohol abusers					
Croatia	Istria County	167	2.40%	-	[2]ICIPH[35], 2014
Germany	Hamburg	463	5.20%	-	Schmidt *et al*[123], 2013
Spain	Salamanca	396	3.53%	-	Novo-Veleiro *et al*[126], 2013
Adult general population					
Bulgaria	Plovdiv	2211	1.08%	-	Atanasova *et al*[136], 2014

Croatia	Primorje-Gorski Kotar County	785	3.70%	-	Tićac *et al*[39], 2010
	Zagreb	451	2.20%	-	Serdar *et al*[40], 2013
	Multicenter	1950	0.90%	-	Vilibic-Cavlek *et al*[36], 2014
France	Paris	14416	0.84%	-	Meffre *et al*[133], 2010
Germany	Berlin, Frankfurt	28809	2.4%-3.5%	68%	Vermehren *et al*[144], 2012
Greece	Crete	876	2.20%	-	Drositis *et al*[145], 2013
Italy	Regional (Southern)	2195	2.60%	-	Cozzolongo *et al*[150], 2009
Kosovo	-	1287	0.50%	-	Quaglio *et al*[142], 2008
Latvia	Multicenter	1459	2.40%	71.40%	Tolmane *et al*[146], 2011
Macedonia	Skopje	4000	0.40%	-	Kiprijanovska *et al*[140], 2013
The Netherlands	Amsterdam	1364	0.60%	-	Baaten *et al*[138], 2007
	Arnhem, Nijmegen	2200	0.20%	-	Slavenburg *et al*[137], 2008
Norway	Oslo	-	0.55%	-	Vik *et al*[143], 2008
Poland	Multicenter	1652	0.90%	-	Ganczak *et al*[135], 2009
Romania	Nationwide	13460	3.23%	91%	Gheorghe *et al*[147], 2010
Spain	Multicenter	-	0.6%-1.6%	-	Munoz-Gamez *et al*[132], 2013
Pregnant women					
Croatia	Zagreb County	200	0.50%	-	Vilibic-Cavlek *et al*[17], 2009
	Istria County	930	1.30%	-	Kucinar *et al*[41], 2014
Greece	Piraeus	5497	0.80%	-	Panagopoulos *et al*[159], 2004
Poland	Warszaw	544	2.02%	-	Aniszewska *et al*[161], 2009
Russia	Cheboksary	150	3%	-	Asratian *et al*[163], 2009
Spain	Madrid	157	1%	-	Santiago *et al*[154], 2012
Switzerland	Multicenter	9057	0.71%	-	Prasad *et al*[153], 2007
Healthcare workers					
Bosnia and Herzegovina	Tuzla	1699	0.40%	73.40%	Ahmetagić *et al*[50], 2006
Italy	Regional (Central)	733	1.8%-4.7%	-	Catalani *et al*[176], 2004
Poland	Warsaw	961	1.70%	19%	Slusarczyk *et al*[175], 2012
	Multicenter	414	1.40%	-	Ganczak *et al*[135], 2012
	Lodz	520	0.80%	-	Rybacki *et al*[173], 2013
Blood donors					
Albania	Nationwide	52727	0.60%	-	Durro *et al*[182], 2010
Bosnia and Herzegovina	Tuzla	16082	0.08%	91.10%	Ahmetagić *et al*[177], 2009
Croatia	Multicenter	155634	0.04%	-	Grgičević *et al*[23], 2006
	Multicenter	-	0%-0.009%	-	Transfusion medicine newsletter[44]
Italy	Regional (South)	17912	0.50%		Sommese *et al*[181], 2014

[1]Persons with high-risx sexual behavior: Men who have sex with men-MSM, commercial sex workers-CSW, persons with sexually transmitted diseases-STD; [2]Istria 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.

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[31]. Two regional surveys from north-west Croatia (1997) and north Adriatic Coast (2003) reported prevalence rates of 26.1% and 23%, respectively[32,33]. 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) show a higher HCV prevalence (4.6%)[17] 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 gonorrhea 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. HCV-RNA

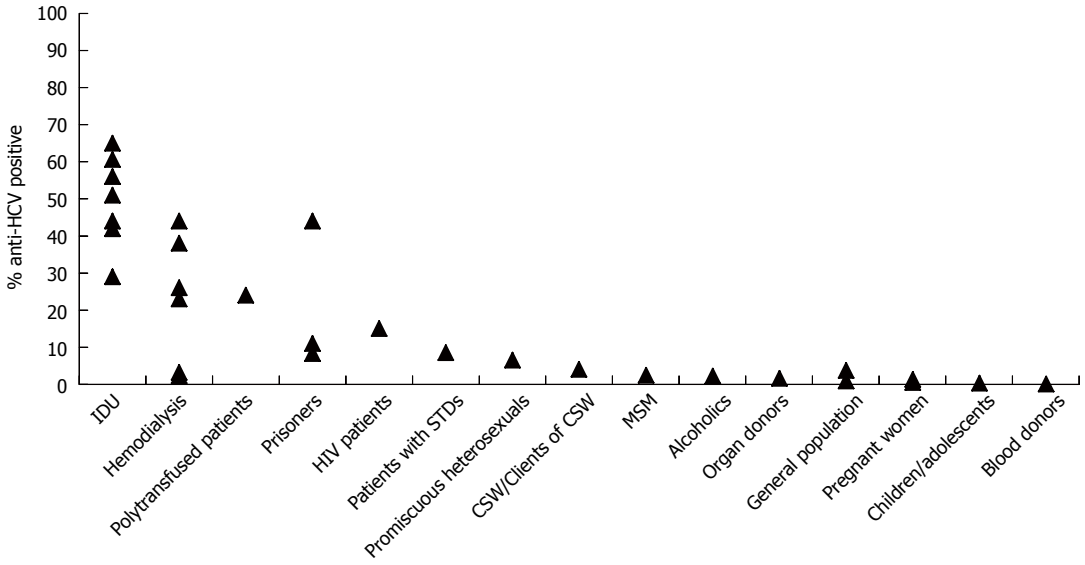

Figure 1 Hepatitis C virus seroprevalence among different population groups in Croatia. IDU: Injecting drug users; STDs: Sexually transmitted diseases; CSW: Commercial sex workers; MSM: Men who have sex with men.

was detected in 73.1% anti-HCV positive persons, but was also found in three seronegative cases ("window period")[17].

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[42].

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%)[44].

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%[4]. 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[61-63], 62.6% in Belgium[64], 73% in Bulgaria[65], 80% in Lithuania[66], 81.3% in Luxembourg[67], 86.5% in Sweden[58], 88% in Spain[2], 88.9% in Romania[68] and 94.6%-96% in Russia[3,65]. 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[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[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[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%)[76]. A similar trend was observed among hemodialysis patients in Croatia. HCV seroprevalence declined from 44% in 1992[24] to 23% in 2003[33]. More recent regional data showed low and stable seroprevalence rates in Croatian hemodialysis patients (2.3%-3.2%)[34,35]. There was no significant change in Germany (7%-6%) and Spain (5%-12%) by 2000[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[77]. In contrast, Poland showed not only stable, but also very high HCV prevalence (42%-44%)[76]. In addition, a high prevalence rate was found in Romania (39.26%)[78]. Some more recently published studies showed prevalences of 16.7% in Albania[79], 12.7% in Serbia[80], 7.7% in France[81], 6.25% in Italy[82] and 5.8% in Germany[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[83,84]. Additional risks factors include IDU and a history of kidney transplantation[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[85,86]. However, the risk for sexual partners is significantly higher when the risk factor for the index case is IDU[87-89]. In the last decade HCV infection has emerged as a STD in some European countries, expecially 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[90]. Another study conducted among British MSM showed an overal 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%)[91]. Two Croatian studies found a higher prevalence in HCV seropositivity in HIV-negative MSM (2.9% and 3%)[17,92] compared to the general population (0.9%)[36] but these diferences 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)[90,91,93-95]. 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%)[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[96,97]. In persons with multiple sex partners, there is an increased probability of having sex with an infectious partner[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[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[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[101]. The HCV seropositivity is reported to be 4.9% in Hungary[9], 4.8%-5.2% in France[102-104], 7%-24.2% in England and Wales[105,106], 11% in Portugal[107], 19% in Scotland[108], 20% in Macedonia[109], 22.7% in Spain[110] and 38% in Italy[10]. Different studies showed association between the HCV seroprevalence and history of IDU. Among prisoners who reported IDU, rates vary from 60.2% in Ukrainian[8], 69% in Portugese[107], 74.7% in Italian[10] to a high 87% among Danish prisoners[11]. In three Croatian studies conducted among prison population the seroprevalence ranged from 4.9% ih highly promiscuous persons to 52% in IDUs[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 HIV/HCV 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%[89,115]. 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%)[38] 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[130]. 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%)[35] 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%)[137,138], 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[149,150] 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%)[36]. Italian authors reported a bimodal distribution of HCV with the highest prevalence in subjects over 75 years of age[149]. 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%)[36].

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 (0.71%)[153] and Spain (1%-1.44%)[154,155]. Lower prevalence rates were reported in northern Europe (United Kingdom; 0.19%-0.22%[156], Scotland: 0.3%-0.4%[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[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%)[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)[41]. HCV prevalence in Croatian pregnant IDUs (49%)[42] is similar to the overall prevalence among IDUs (51%)[27,29].

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[164-166]. The prevalence reported in Croatian children and adolescents (0.3%) is within the European range (0.05%-0.4%)[167,168]. Vertical (mother-to-child) transmission and adolescent high-risk behaviors (IDU) are now the major routes of HCV transmission in developed countries[169]. The average risk for vertical transmission is about 4% per birth[4,14]. Perinatal transmission is confined almost always to women with detectable HCV RNA[167]. Factors predisposing to HCV transmission are higher maternal viral load at the time of delivery, maternal history of IDU and untreated HIV infection[14]. Breastfeeding carries no further risk of HCV transmission[4,170].

Occupationally exposed groups

Occupational HCV transmission has been reported among healthcare workers (HCWs) who have sustained contaminated needle stick injuries[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[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)[50,174]. However, a Belgian study showed higher rates in three larger metropolitan hospitals (1.3%-2.3%)[174]. Three studies conducted in Poland showed prevalence rates 0.8%-1.7%[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[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[143], 0.08%-0.26% in Bosnia and Herzegovina[177,178], 0.16%-0.32% in Germany[179], 0.4% in Hungary[180], 0.5% in Italy[181], 0.6% in Albania[182] and 0.3%-1.5% in Romania[183]. After 2000, HCV seroprevalence in Croatian blood donors was continuously very low (0.009%-0.03%)[44]. 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[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%)[184-186]. The most commonly detected subtype is 1b (37.4%)[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[184]. Another study conducted in north-east Croatia (2009-2011) detected genotype 1 in 79.8% and genotype 3 in 12.9% patients[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[184,187].

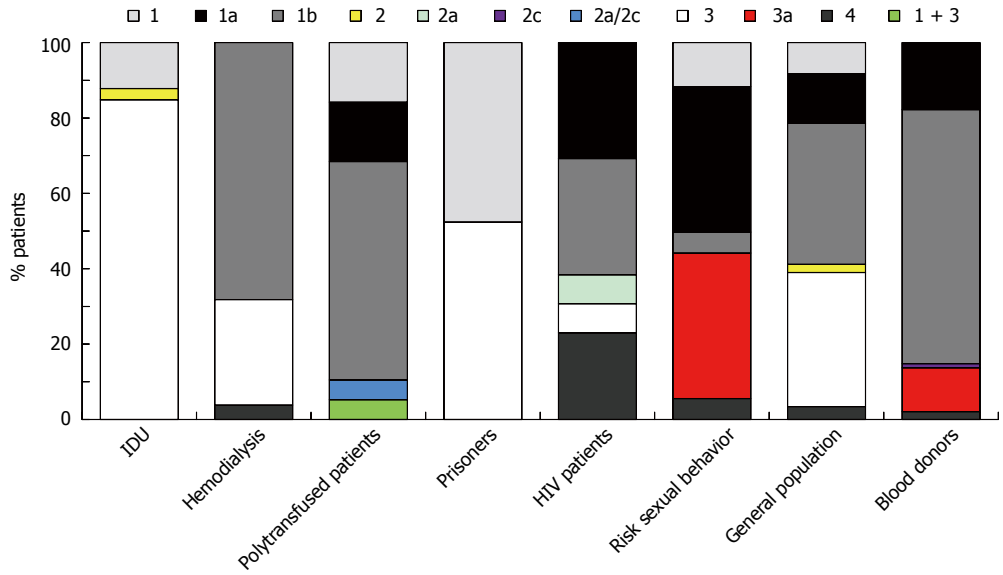

Figure 2 Hepatitis C virus genotypes distribution in Croatia. IDU: Injecting drug users; HIV: Human immunodeficiency virus.

A history of blood transfusion before 1992 was an independent predictor of HCV infection caused by genotype 1[187]. 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[32]. Genotype 3 is predominant in Croatian IDUs (60.5%-83.9%)[184,185]. The most prevalent subtypes in this population group are 3a (60.5%) and 1a (23.7%)[184]. A study among Croatian male prisoners showed an equal distribution of genotype 3 (52.4%) and genotype 1 (47.6%)[185]. 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%)[17].

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[4]. 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[188]. In southern Italy, genotype 2c is commonly found[189,190]. 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[4]. Other HCV genotypes such as genotype 5 and 6 are more geographically restricted. Genotype 5 was found in restricted areas of Belgium, Spain, France and Greece and is mainly transmitted by blood transfusion[191]. Genotypes/subtypes 1a and 3/3a are the most commonly identified in IDUs in Europe[9,138,192-196]. Genotypes 1b and 2 are linked to blood transfusion and unsafe medical procedures[197]. 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[198]. 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[199,200]. 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[200,201]. In Italy, genotype 1b appears to be the most frequent (30.7%-60%), with genotype 2 following (21.3%-34.8%)[200].

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[4]. 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 hepacivirus 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 supported by recent studies that have described related hepaci and pegiviruses in diverse animal species. In contrast to ongoing focus on primate for HCV origins, a virus related to HCV was described in domestic dogs in 2011[205]. In an effort to further investigate the host range of canine hepacivirus, serology-based approach was utilized to screen for the presence of the virus in mammalian species[206]. Serological evidence of hepacivirus infection was detected in horses with high prevalence while viral RNA was found in 7.8% seropositive horses. Equine hepacivirus (EHcV) is the most closely related animal hepacivirus to HCV described to date. Different studies confirmed EHcV infection in horses[207-209] and repeated sampling of viremic horses demonstrated viral persistence over at least 6-mo period and viral loads comparable to those observed in HCV infection[206]. Similar to HCV infections in humans, acute and chronic stages of EHcV infection in horses with viral RNA detectable predominantly within the liver was confirmed[210]. Several recently published studies demonstrated hepaciviruses and pegiviruses in rodents and bats[211-213].

Detection of multiple novel hepaciviruses in diverse mammalian species has highlighted the importance of further research to define distribution of hepaciviruses 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.

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