

Epidemiology of hepatitis E in South-East Europe in the "One Health" concept

Anna Mrzljak, Petra Dinjar-Kujundzic, Lorena Jemersic, Jelena Prpic, Ljubo Barbic, Vladimir Savic, Vladimir Stevanovic, Tatjana Vilibic-Cavlek

ORCID number:

Author contributions: Mrzljak A and Dinjar-Kujundzic P made contributions to conception and design of the study, acquisition of the data, involved in drafting the manuscript. Jemersic L, Prpic J, Barbic L, Savic V and Stevanovic V made contributions in acquisition of the data, involved in drafting the manuscript. Vilibic-Cavlek T made contributions to design, involved in drafting and revising the manuscript critically. All authors read and approved the final manuscript.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

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Manuscript source: Invited manuscript

Received: March 11, 2019

Peer-review started: March 11, 2019

First decision: May 9, 2019

Anna Mrzljak, Department of Medicine, Merkur University Hospital; School of Medicine, University of Zagreb, Zagreb 10000, Grad Zagreb, Croatia

Petra Dinjar-Kujundzic, Department of Medicine, Merkur University Hospital, Zagreb 10000, Grad Zagreb, Croatia

Lorena Jemersic, Jelena Prpic, Vladimir Savic, Croatian Veterinary Institute, Zagreb 10000, Grad Zagreb, Croatia

Ljubo Barbic, Vladimir Stevanovic, Faculty of Veterinary Medicine, University of Zagreb, Zagreb 10000, Grad Zagreb, Croatia

Tatjana Vilibic-Cavlek, Department of Virology, Croatian Institute of Public Health; School of Medicine, University of Zagreb, Zagreb 10000, Grad Zagreb, Croatia

Corresponding author: Anna Mrzljak MD, PhD, Assistant Professor, Department of Medicine, Merkur University Hospital, Zajceva 19, Zagreb 10000, Grad Zagreb, Croatia.

anna.mrzljak@mef.hr

Telephone: +385-1-2431390

Fax: +385-1-2431393

Abstract

The significance of hepatitis E virus (HEV) as an important public health problem is rising. Until a decade ago, cases of HEV infection in Europe were mainly confined to returning travelers, but nowadays, hepatitis E represents an emerging zoonotic infection in many European countries. The aim of this manuscript is to perform a systematic review of the published literature on hepatitis E distribution in humans, animals and environmental samples ("One Health" concept) in the South-Eastern European countries. Comparison of the available data showed that the anti-HEV seroprevalence in the South-Eastern Europe varies greatly, depending on the population studied, geographical area and methods used. The IgG seroprevalence rates in different population groups were found to be 1.1%-24.5% in Croatia, up to 20.9% in Bulgaria, 5.9%-17.1% in Romania, 15% in Serbia, up to 9.7% in Greece and 2%-9.7% in Albania. Among possible risk factors, older age was the most significant predictor for HEV seropositivity in most studies. Higher seroprevalence rates were found in animals. HEV IgG antibodies in domestic pigs were detected in 20%-54.5%, 29.2%-50%, 38.94%-50% and 31.1%-91.7% in Serbia, Bulgaria, Romania and Croatia, respectively. In wild boars seroprevalence rates were up to 10.3%, 30.3% and 31.1% in Romania, Slovenia and Croatia, respectively. A high HEV RNA prevalence in wild boars in some

Revised: May 16, 2019
Accepted: May 31, 2019
Article in press: June 1, 2019
Published online: July 7, 2019

P-Reviewer: Komatsu H, Sergi C
S-Editor: Ma RY
L-Editor: A
E-Editor: Ma YJ



countries (Croatia and Romania) indicated that wild boars may have a key role in the HEV epidemiology. There are very few data on HEV prevalence in environmental samples. HEV RNA was detected in 3.3% and 16.7% surface waters in Slovenia and Serbia, respectively. There is no evidence of HEV RNA in sewage systems in this region. The available data on genetic characterization show that human, animal and environmental HEV strains mainly belong to the genotype 3.

Key words: Hepatitis E virus; "One-Health"; Humans; Animals; Environment; South-East Europe

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Core tip: In South-East Europe, the hepatitis E virus (HEV) prevalence as in other parts of Europe varies greatly, depending on the studied population, geographical area and methods used. Seroprevalence rates were found to be 0%-36% in humans and 10.3%-54.5% in animals. Human studies showed sporadic detection of HEV RNA in patients with acute hepatitis and in transplant population. HEV RNA was detected in up to 31.6% pigs and 16.7% environmental samples. Studies on phylogenetic characterization in human, animal and environmental samples showed that HEV strains from the south-eastern European countries mainly belong to the genotype 3.

Citation: Mrzljak A, Dinjar-Kujundzic P, Jemersic L, Prpic J, Barbic L, Savic V, Stevanovic V, Vilibic-Cavlek T. Epidemiology of hepatitis E in South-East Europe in the "One Health" concept. *World J Gastroenterol* 2019; 25(25): 3168-3182

URL: <https://www.wjgnet.com/1007-9327/full/v25/i25/3168.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v25.i25.3168>

INTRODUCTION

Hepatitis E represents an important public health problem in many parts of the world. The World Health Organization estimates that 20 million hepatitis E virus (HEV) infections occur worldwide leading to an estimated 3.3 million symptomatic cases and 44000 deaths related to hepatitis E. Until a decade ago, cases of HEV infection in Europe were mainly confined to travelers returning from endemic areas, whereas nowadays, hepatitis E is endemic in many European countries. It is estimated that 5%-15% of all acute hepatitis infections of unknown origin in Europe are caused by HEV^[1]. The seroprevalence ranges from 0.6% to 52.5%, depending on the population group tested and geographical region. In addition to differences in seroprevalence rates between countries, there are also differences in HEV seropositivity within the same country^[2]. Changes in HEV epidemiology could be explained by the confirmation of zoonotic nature of the disease. To date, three zoonotic HEV genotypes have been confirmed to infect humans. In addition to well-known HEV-3 and HEV-4 genotypes, a new genotype HEV-7 has also been recently described to infect humans^[3,4]. Domestic pigs and wild boars represent the most important animal reservoirs for HEV-3 and HEV-4 worldwide with usually high seroprevalence rates ranging between 23%-100%^[5]. However, zoonotic transmission of HEV has also been reported from some other animal reservoirs such as rabbits, deer and camels^[3,6-8]. In addition, HEV must be considered as a food-borne pathogen as well, since food-borne cases of hepatitis E in humans are increasingly reported. Food-borne HEV-3 and HEV-4 infections due to consumption of undercooked meat and meat products from infected animal reservoirs have been repeatedly described^[4,6,9-11]. Furthermore, HEV-3 has also been found in mollusks and human consumption of contaminated shellfish has been implicated as the cause of sporadic cases of acute hepatitis E^[12,13]. Other types of food such as berry fruit have rarely been suspected to act as vehicles for HEV transmission after environmental contamination with animal feces^[14,15].

In this manuscript, a bibliographic review of the literature on hepatitis E was performed with the aim of gathering the latest data regarding the prevalence, risk factors and HEV genotype distribution in the South-East Europe in the multi-disciplinary "One Health" concept (Tables 1-3).

Table 1 Prevalence of hepatitis E in different population groups

Country	Population	Sample size	Method	anti-HEV	HEV RNA (%) / genotype (subtype)	Ref.
Albania	Refugees in Greece (pregnant women)	500	EIA	2% ¹	NT	Malamitsi-Puchner <i>et al</i> ^[16]
	Refugees in Greece (adult population)	350	EIA/IB	4.85% ¹	NT	Dalekos <i>et al</i> ^[17]
	General population	ND	ND	IgG 9.7%	NT	Adhami <i>et al</i> ^[18]
	Thalassemic children	ND	ND	IgG 0%	NT	
	Patients with chronic liver disease	109	EIA	36.6% ¹	NT	Kondili <i>et al</i> ^[19]
	Patients with no apparent liver disease	190	EIA	12.1% ¹	NT	
Bulgaria	Patients with symptoms of acute hepatitis	806	EIA	IgM/IgG 2.48%	NT	Baymakova <i>et al</i> ^[23]
	Hospitalized patients with clinical symptoms of hepatitis and outpatients with laboratory data of liver dysfunction	325	EIA	IgM 13.2% IgG 20.9%	NT NT	Stoykova <i>et al</i> ^[25]
	Patients with acute hepatitis E (IgM positive)	105	RT-PCR	NT	G3 98% (3e 62%; 3f 24%; 3c 13%); G1 2%	Bruni <i>et al</i> ^[26]
	Patients conducting ambulatory examination due to various reasons	741	EIA	IgM/IgG 1.48% IgG 9.04%		Teoharov <i>et al</i> ^[27]
Croatia	Patients with clinical symptoms of hepatitis negative for HAV/HBV/HCV	504	EIA/IB/RT-PCR	IgM/IgG 10.7%	IgM positive 35.7%	Đaković Rode <i>et al</i> ^[31]
	HIV-infected patients	88	EIA/IB	IgG 1.1%	NT	
	Liver transplant recipients	242	EIA	IgG 24.5%	NT	Mrzljak <i>et al</i> ^[32]
	Alcohol abusers	56	EIA/IB	IgG 8.9%	NT	Vilibic-Cavlek <i>et al</i> ^[33]
	Patients with PTSD	35	EIA/IB	IgG 8.1%	NT	
	Injecting drug users	49	EIA/IB	IgG 6.1%	NT	
	Persons with risk sexual behaviour	37	EIA/IB	IgG 0%	NT	
	Forest workers	37	EIA/IB	IgG 8.1%	NT	Jeličić <i>et al</i> ^[34]
	Healthcare workers	50	EIA/IB	IgG 2.0%	NT	Jeličić <i>et al</i> ^[34]
	Pregnant women	68	EIA/IB	IgG 2.9%	NT	Jeličić <i>et al</i> ^[35]
	Hunters	25	EIA/IB	IgG 4.0%	NT	Jeličić <i>et al</i> ^[35]
	General population	87	EIA/IB	IgG 3.4%	NT	Jeličić <i>et al</i> ^[34]
	Blood donors	1036	EIA/IB EIA	IgM 1.7% IgG 20.3%	NT	Miletic Lovric <i>et al</i> ^[36]
Greece	Transplant patients	76	RT-PCR	NT	1 positive/1.3% G3	Sinakos <i>et al</i> ^[45]
	Transfusion dependent thalassaemia	96	EIA	IgG 0%	0%	Klonizakis <i>et al</i> ^[44]
	Blood donors	1 200	EIA	IgG 2.9%	NT	Zervou <i>et al</i> ^[49]
	HIV patients	243	EIA	IgG 7.3%	NT	Politou <i>et al</i> ^[48]
	Blood donors (South Greece)	265	EIA	IgG 9.43	NT	Pittaras <i>et al</i> ^[47]
	Patients after open-heart surgery	204	EIA	IgG 5.4%	NT	Zervou <i>et al</i> ^[43]

	Patients on haemodialysis	351	EIA	IgG 4.8%	NT	Stefanidis <i>et al</i> ^[46]
	Non-A,-B hepatitis patients	198	EIA/RT-PCR	IgG 7.6% IgM 1%	1 positive	Psichogiou <i>et al</i> ^[42]
Epirus region	Healthy controls	316	EIA/RT-PCR	IgM 0%/IgG 2.2%	NT	
	Healthy blood donors	2636	EIA/IB	IgG 0.23%	NT	Dalekos <i>et al</i> ^[17]
	Refugees from southern Albania	350	EIA/IB	IgG 4.85%	NT	
	Children	165	EIA/IB	IgG 0%	NT	
	Injecting drug users	65	EIA/IB	IgG 0%	NT	
	Multiply transfused patients	62	EIA/IB	IgG 0%	NT	
	Patients with chronic viral hepatitis	75	EIA/IB	IgG 5.30%	NT	
	Chronic haemodialysis patients	149	EIA/IB	IgG 1.34%	NT	
Agrinion area	Healthy blood donors	380	EIA/IB	IgG 0.53%	NT	
	Chronic hemodialysis patients	62	EIA/IB	IgG 9.7%	NT	
Kosovo	Kosovar refugees	104	EIA/RT-PCR	IgM 7.7%	0%	Rey <i>et al</i> ^[56]
Montenegro	Patients with acute viral hepatitis	400	EIA	IgM 6%	NT	Terzić <i>et al</i> ^[57]
Romania	Patients with hepatitis B or C	25	EIA	IgG 12%	NT	Anita <i>et al</i> ^[59]
	Students	40	EIA	IgG 12.5%	NT	Voiculescu <i>et al</i> ^[60]
	Doctors and nurses	93	EIA	IgG 13.98%	NT	Voiculescu <i>et al</i> ^[60]
	Persons undergoing routine hematological tests	148	EIA	IgG 14.86%	NT	Anita <i>et al</i> ^[61]
	General population	67	EIA	IgG 5.9%	NT	Savuta G <i>et al</i> ^[62]
Serbia	Blood donors	200	EIA RT-PCR	IgG 15%	0%	Petrović <i>et al</i> ^[66]
Slovenia	Acute/recent hepatitis E (IgM antibodies)	10	RT-PCR	NT	3/10 (G3e and G1)	Steyer <i>et al</i> ^[74]

¹Total anti-hepatitis E virus antibodies. HEV: Hepatitis E virus; EIA: Enzyme immunoassay; IB: Immunoblot; RT-PCR: Reverse-transcriptase polymerase chain reaction; NT: Not tested; ND: No data.

Search strategy and selection criteria

A literature search was conducted in the following electronic databases: PubMed, Web of Science, Medline and Scopus along with hand-searching references of key articles and a ResearchGate and Google search with no limitations placed on year of publication and language restriction. The search included articles in peer-reviewed journals and grey literature. Books, dissertations, review articles and unpublished reports were excluded. In addition, non-relevant studies by the review of the abstracts were also excluded. Keywords searched were: Hepatitis E virus, epidemiology, human, animals, pigs, wild boars, environment, waste water, vegetables, seroprevalence, risk factors, HEV RNA, genotype. Once a comprehensive list of abstracts has been retrieved and reviewed, any studies appearing to meet inclusion criteria were reviewed in full.

Out of 11 south-eastern European countries, data for Albania, Bulgaria, Croatia, Greece, Kosovo, Montenegro, Romania, Serbia and Slovenia are available and presented in this review (Figure 1). So far, there have been no data published on HEV for Bosnia and Herzegovina and the Republic of North Macedonia.

ALBANIA

There are few studies on hepatitis E in Albania published in 1990s and 2000s. In the

Table 2 Prevalence of hepatitis E in different animal species

Country	Population	Sample size	Method	anti-HEV	HEV RNA (%)/genotype (subtype)	Ref.		
Bulgaria	Piglets	44	EIA	IgG 50%	NT	Pishmisheva <i>et al</i> ^[28]		
	Fattening pigs	41	EIA	IgG 29.2%	NT			
Croatia	Domestic pigs	848	RT-PCR	NT	24.5% (G3)	Prpić <i>et al</i> ^[40]		
	Wild boars	536	RT-PCR	NT	12.3% (G3)			
	Molluscs (mussels, oysters)	538	RT-PCR	NA	0%			
	Cattle	32	RT-PCR	NT	0%			
	Red fox	50	RT-PCR	NT	0%			
	Deer	320	RT-PCR	NT	0%			
	Mufkons	12	RT-PCR	NT	0%			
	Ferrets	8	RT-PCR	NT	0%			
	Martens	10	RT-PCR	NT	0%			
	Pigs (serum samples)	60	EIA/RT-PCR	IgG 91.7%	13.3% 8.1%		Lipej <i>et al</i> ^[39]	
	Pigs (bile samples)	60	RT-PCR	NA	8.1%			
	Croatia	Pigs, domestic	1424	EIA/RT-PCR	IgG 32.94%		0%	Jemersić <i>et al</i> ^[41]
Wild boars		1000	EIA/RT-PCR	IgG 31.10%	11.33%			
Mussels		51	RT-PCR	NT	0%			
Greece	Black rats/Norway rats	20	RT-PCR	NT	10%	Diez-Valcarce <i>et al</i> ^[55]		
Romania	Farm pigs	50	EIA/IB	IgG 50%	NT	Savuta <i>et al</i> ^[62]		
	Backyard pigs	95	EIA/IB	IgG 38.94%				
	Backyard pigs	112	EIA	IgG 49.27%	NT		Savuta <i>et al</i> ^[58]	
	Pigs (2-4 mo) stool samples	19	RT-PCR	NT	31.58% (G3)		Anita <i>et al</i> ^[61]	
	Wild boars	52	EIA	9.61% ¹	NT		Porea <i>et al</i> ^[63]	
	Wild boars	68	EIA	IgG 10.29%	NT		Porea <i>et al</i> ^[63]	
	Wild boars	50	RT-PCR	NT	18% (G3)		Porea <i>et al</i> ^[65]	
	Farm pigs (pooled stool samples)	30	RT-PCR	NT	30%		Petrovic <i>et al</i> ^[67]	
	Farm pigs (pooled tissue samples)	20	RT-PCR	NT	45%			
	Serbia	Backyard pigs (pooled tissue samples)	15	RT-PCR	NT		0%	Lupulovic <i>et al</i> ^[68]
Wild boars (pooled stool samples)		10	RT-PCR	NT	0%			
Backyard pigs		315	EIA	IgG 34.6%	NT			
Pigs (liver samples)		50	NT	NT	26%	Savic <i>et al</i> ^[69]		
Fattening pigs		95	NT	NT	7.37%	Petrović <i>et al</i> ^[71]		
Piglets (8 wk)		50	NT	NT	64%			
Pigs (blood samples)		55	EIA	IgG 54.54%	NT	Lupulovic <i>et al</i> ^[70]		
Pigs (meat juice samples)		55	EIA	IgG 20%	NT			
Slovenia		Black rats/Norway rats	17/1	RT-PCR	NT	0%	Ryll <i>et al</i> ^[50]	
		Domestic pigs	85	RT-PCR	NT	20.3%		
	Suckling pigs (0-3 wk)	38	RT-PCR	NT	5.3%			
	Weanling pigs (3-10 wk)	21	RT-PCR	NT	28.6%			
	Fattening pigs (> 10 wk)	26	RT-PCR	NT	26.9%			
	Wild boars	288	EIA/RT-PCR	30.21% ¹	0.35%	Žele <i>et al</i> ^[75]		
	Pigs (stool samples)	811	RT-PCR	NT	5.4%	Raspor Lainšček <i>et al</i> ^[76]		
	Pigs (bile samples)	811	RT-PCR	NT	4.9%			
	Pigs (liver samples)	811	RT-PCR	NT	5.3% (G3a, 3b, 3c, 3e)			

¹Total anti-hepatitis E virus antibodies. HEV: Hepatitis E virus; EIA: Enzyme immunoassay; IB: Immunoblot; RT-PCR: Reverse-transcriptase polymerase chain reaction; NT: Not tested; NA: Not applicable.

studies conducted among Albanian refugees in Greece, the anti-HEV prevalence was 2% among pregnant women^[16] and 4.85% in the adult population from southern Albania^[17]. In 2000s, acute HEV in Albania made up 2.4% of all acute viral hepatitis cases. HEV infections occurred more frequently in women (female to male ratio 2:1),

Table 3 Prevalence of hepatitis E virus RNA in different environmental samples

Country	Sample	Sample size	HEV RNA (%)/ genotype (subtype)	Ref.
Greece	Vegetable leafy greens	Pooled samples	4.76% ¹ 3.2% ¹	Kokkinos <i>et al</i> ^[51]
	Sewage	48	0%	Kokkinos <i>et al</i> ^[54]
	Sewage	5	0%	Clemente-Casares <i>et al</i> ^[53]
Serbia	Vegetable leafy greens	Pooled samples	4.76% ¹ 3.2% ¹	Kokkinos <i>et al</i> ^[51]
	Berry fruits	Pooled samples	2.5% ¹	Maunula <i>et al</i> ^[15]
	Surface waters	60	16.67%	Lazić <i>et al</i> ^[73]
	Urban sewage	6	0%	
Slovenia	Waste water treatment plant	12	0%	Steyer <i>et al</i> ^[77]
	Swabs from the different site on the slaughter line	62	3.2% (G3)	Raspor Lainšček <i>et al</i> ^[76]
	Minced meat	22	0%	
	Bratwurst	30	0%	
	Surface water	60	3.3% (G3)	Steyer <i>et al</i> ^[74]

¹Pooled samples. HEV: Hepatitis E virus; EIA: Enzyme immunoassay; IB: Immunoblot; NT: Not tested.

as well as in adults over 35 years (73.3%). In the general population, the prevalence of anti-HEV antibodies was 9.7% and increased progressively with age, from 1.2% in children less than 9 years to 17.7% in persons older than 60 years. There was no difference in the prevalence between the general population and patients with chronic liver disease (10.5%). The prevalence of anti-HEV antibodies in pregnant women was lower than in the general population (1.1%). No positive cases were found among children with thalassemia receiving multiple transfusions^[18]. In contrast, in the other Albanian case-control study, HEV antibodies were found in 36.6% patients with chronic liver disease compared to 12.1% in patients with no apparent liver disease. In the univariate analysis, anti-HEV prevalence was found to be associated with the age (> 50 years), lower education status (≤ 8 years of formal education) and positivity for hepatitis B surface antigen (HBsAg), while no association was observed in people who lived in villages and/or those who were occupationally involved with handling animals. In the multivariate analysis, significant associations remained for age and HBsAg positivity^[19].

Since there are no recent data on HEV infection in Albania, the burden of diseases caused by HEV is not known. Moreover, no data on the role of animals in the epidemiology of HEV infections in Albania is currently available. Therefore, more research should be done to evaluate a local HEV epidemiology in Albania.

BULGARIA

In Bulgaria, the first human cases of hepatitis E were reported in 1995^[20]. Several studies reported cases and hospitalized patients with acute hepatitis E^[21,22]. A retrospective study of acute viral hepatitis performed in Sofia (2004-2012) found anti-HEV IgM/IgG antibodies in 2.48% patients^[23]. HEV infection more frequently affected males (61%-69%), with the highest incidence in persons over 50 years of age^[23,24]. Another study in the North-Eastern Bulgaria (2012-2016) analyzed the prevalence of HEV infection in hospitalized patients with clinical symptoms of acute hepatitis and outpatients with laboratory data of liver dysfunction. Acute infection was documented in 13.2% patients, while 20.9% patients showed only IgG antibodies indicating past HEV infection^[25]. A study conducted from 2013 to 2015 analyzed HEV genotypes in patients with acute hepatitis E. Phylogenetic analysis showed HEV-3 in 98% and HEV-1 in 2% of cases. Subtyping of HEV-3 sequences showed 3e (62%), 3f (24%) and 3c (13%) subtypes. There were differences in the geographical distribution of genotypes. Subtypes 3f and 3c were scattered throughout the country, while 3e subtype was restricted to the South-West area^[26]. A seroepidemiological study conducted in the general Bulgarian population from Plovdiv region during 2012-2013 found anti-HEV IgG seroprevalence of 9.04%, while 1.48% participants showed both IgM and IgG antibodies. Seropositivity did not differ significantly between males (9.87%) and females (8.47%), but increased with the age from 3.53% in the age group 1-9 years to 19.23% in the group over 60 years^[27].

In 2016, serum samples from clinically healthy pigs from five industrial farms in two districts in South Bulgaria were collected and tested for the presence of anti-HEV

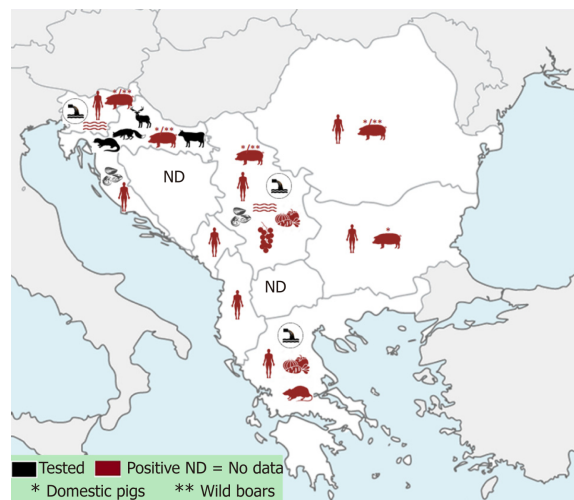


Figure 1 Data on hepatitis E prevalence in South-East Europe in humans, animals and environmental samples ("One health" concept).

antibodies. The overall HEV seroprevalence was 40.0% with 50.0% seropositive piglets and 29.2% fattening pigs. Seropositivity differed significantly among regions from 0% (Peshtera) to 100% (Nova Zagora)^[28]. In a recently published study, genetic diversity and the phylogenetic relationships among different strains of human HEV genotype 3 were analyzed to estimate the date of origin and the demographic history of HEV epidemic in Bulgaria. The root of the Bayesian tree showed at least two different epidemic entrances for HEV genotype 3e strains^[29].

Seroprevalence data and the high prevalence of clinical cases registered indicate that HEV infection in Bulgaria is endemic. Phylogenetic analysis showed that human HEV isolates in 98% of cases belonged to HEV 3 genotype.

CROATIA

In Croatia, the first autochthonous human case of hepatitis E was reported in 2012^[30]. A study conducted from 2011 to 2013 in patients with clinical symptoms of hepatitis and elevated liver enzymes who tested negative for hepatitis A-C, detected HEV IgM/IgG antibodies in 10.7% patients. Among IgM positive patients, 35.7% were positive for HEV RNA^[31].

Several studies analyzed the seroprevalence of HEV infection in different population groups in Croatia. HEV IgG antibodies were detected in 24.5% liver transplant recipients^[32], 8.9% alcohol abusers^[33], 8.6% patients with war-related posttraumatic stress disorder^[33], 8.1% forest workers^[34], 6.1% injecting drug users^[33], 4.0% hunters^[35], 3.4% general population^[34], 2.9% pregnant women^[35], 2.0% healthcare workers^[34] and 1.1% HIV-infected patients^[31]. No person with high-risk sexual behavior was HEV seropositive^[33]. One study conducted among blood donors in 2016 showed a high IgG seroprevalence rate of 20.3% with 1.7% IgM positive. None of IgM positive samples was positive for HEV RNA^[36]. HEV IgG positivity increased significantly with the age^[33,37]. In addition, seroprevalence rates were higher in residents of suburban and rural areas compared with residents of urban areas, subjects living in families with more household members, persons who use wells as a source of drinking water^[33] and those who use a sewage system connected to a septic tank^[37]. Gender, marital status, educational level, history of blood transfusions, surgical procedures, tattooing and traveling were not associated with HEV seropositivity^[33]. In 2018, the first documented case of HEV induced acute-on-chronic liver failure was reported with severe clinical course considered for liver transplantation. The patient was treated with ribavirin and subsequently recovered^[38].

Several studies addressed the HEV distribution in domestic animals and wildlife in Croatia^[39,40]. During 2009-2010, a comprehensive survey was carried out based on HEV RNA detection in blood, spleen and liver samples originating from different domestic and wild animals from all Croatian counties. Furthermore, digestive gland samples from molluscs were also analyzed. A high HEV RNA prevalence was found in domestic pigs (24.5%) and wild boars (12.3%), whereas cattle, molluscs, ruminant and carnivore wildlife samples tested negative. Molecular characterization confirmed the phylogenetic clustering of the obtained sequences into HEV genotype 3^[40]. In 2012, the

epidemiology of naturally occurring hepatitis E was investigated in swine herds from three large pig farms in continental Croatia. Nearly all animals (91.7%) tested seropositive for HEV. In addition, active infection was detected in all age groups by detection of HEV RNA in 13.3% serum samples and 8.1% bile samples^[39]. In 2016, the overall HEV seroprevalence was shown to be 32.94% (range 8.33%-60.00%) in domestic pigs from 11 counties and 31.10% (range 7.70%-50.60%) in wild boars from six Croatian counties. While no positive HEV RNA samples were detected in domestic pigs, 11.33% seropositive wild boars were found to be HEV RNA positive indicating that wild boars may have a key role in HEV epidemiology^[41].

Data on genetic characterization of HEV are available only for animal species, confirming genotype 3 in pigs and wild boars. It is important to note a relatively small sample size of some tested population groups in humans. Therefore, studies on larger samples as well as species comparison studies on HEV genotypes are needed to obtain better insight into HEV epidemiology/molecular epidemiology in Croatia.

GREECE

In 1995, autochthonous hepatitis E virus was documented in Greece. Several studies investigated HEV infection in various population groups in different regions in Greece. A study conducted among patients with clinical signs of hepatitis showed a significantly higher anti-HEV IgG seroprevalence among acute non-A, non-B hepatitis patients (7.6%) compared to healthy controls (2.2%). Acute HEV infection (IgM antibodies) was confirmed in 1.0% of acute non-A, non-B hepatitis patients, while one patient was HEV RNA positive. None of anti-HEV IgM positive patients reported any possible risk factors^[42].

In the north-western Greece (Epirus and Agrinion region), a very low anti-HEV IgG prevalence was reported in various populations. In Epirus region, none of different population groups such as children, injecting drug users or multiply transfused patients tested positive for HEV antibodies. Seroprevalence in healthy blood donors was only 0.23%. In contrast, higher anti-HEV prevalence was found among patients with chronic viral hepatitis (5.3%) and patients on hemodialysis (HD) (1.34%). Even higher anti-HEV prevalence was found among HD patients in the Agrinion region (9.7%). No association between the seroprevalence and duration of hemodialysis, seropositivity for hepatitis B or C, history of hepatitis, increased alanine aminotransferase, renal transplantation, history of transfusion or number of units transfused was detected^[17]. Another study from the Epirus region (Ioannina) analyzed the risk of blood borne HEV transmission among patients after open-heart surgery who had received more than three blood units perioperatively. Past HEV infections were documented in 5.2% of surgical patients and 0% of healthy controls^[43].

Another study from northern Greece analyzed the presence of antibodies and HEV RNA in transfusion dependent thalassaemia patients. The study confirmed no past or acute HEV infection in this multi-transfused population^[44].

The most recent data from northern Greece (Thessaloniki) found that 1.3% of liver transplant patients were positive for HEV RNA. Phylogenetic analysis showed that the sequences clustered into the HEV genotype 3 clade. The only patient that tested RNA positive experienced acute hepatitis flare without progression into chronic form. The HEV RNA prevalence in the Greek transplant population (1.3%) corresponds with previously reported data in immunocompromised patients from other European countries^[45].

Study from the semi-rural region of central Greece (Thessalia region) on HD patients in three different HD units found a total seroprevalence rate of 4.8% (varying from 1.8%-9.8% according to the unit). The highest anti-HEV prevalence was found in Karditsa unit (9.8%), which finding the authors assume to have been a result of a local infection in the past. Risk factors for HEV seropositivity (age, sex, duration of HD, hepatitis B or C virus infection markers, previously elevated aminotransferase levels or history of transfusion) were not identified^[46].

Data from southern Greece showed even higher seroprevalence rates. In 2014, a study among blood donors from urban population of Athens demonstrated a seroprevalence of 9.43%^[47]. Furthermore, a study on HIV patients in Athens indicated 7.3% anti-HEV IgG seroprevalence^[48].

A recent study from 11 Blood Services throughout Greece revealed 2.9% and 3.6% of anti-HEV IgG seroprevalence among blood donors and multi-transfused patients, respectively. The highest seroprevalence rate (13.3%) had male blood donors from Heraklion, Crete. The seroprevalence was higher in persons older than 50 years (5.9%) compared to younger group (1.8%)^[49].

There is only one study on HEV infection among animals in Greece. The animals

tested included Norway rats (*Rattus norvegicus*) and Black rats (*R. rattus*) from northern Greece, with the total prevalence of 10% in both species^[50].

HEV was reported in a leafy green vegetable supply chain in Greece, showing that HEV RNA was found in 4.76% and 3.2% samples from the primary production and point-of-sale phases, respectively^[51]. Later, the same authors investigated the presence of HEV in irrigation water samples used for the leafy green vegetables production and showed that one out of 20 samples tested positive^[52]. The sample which was found HEV positive was a groundwater sample collected from the depth of 100 m, indicating well contamination unlikely^[51].

Further two studies tested sewage samples from Patras (western Greece) for the presence of HEV. HEV RNA was not found in any of the samples^[53,54]. Likewise, commercial mussels tested at the retail in Greece showed no samples positive for HEV RNA^[55].

In conclusion, higher seroprevalence rates were detected in southern parts of Greece, the highest so far being in Crete, in contrary to the seroprevalence rates in the northern regions. Moreover, the prevalence of anti-HEV in risk populations (transplant, HIV, HD patients) was higher than in healthy blood donors. Phylogenetic analysis of human HEV isolates in Greece showed that the sequences clustered into the HEV genotype 3 clade. Further researches are needed, especially in animals and environmental samples in individual regions in Greece to gain a better insight in local HEV epidemiology.

KOSOVO

An outbreak of acute hepatitis E occurred among the Kosovar refugees in July 1999, after the return to their country. Several field surveys were undertaken as well as a serological study in patients with symptoms of hepatitis to assess the possible risk factors for HEV infection. A higher incidence of HEV infection was found among well-water consumers compared to those drinking network waters. An acute HEV infection (anti-HEV IgM positive) was found in 7.7% of refugees that had been tested. Only four persons had clinical symptoms, while the others were asymptomatic. There are no other published data on HEV prevalence/seroprevalence in Kosovo^[56].

MONTENEGRO

The first available investigation about HEV infection in Montenegro was published in 2009. Data included hospitalized and out-patients with acute viral hepatitis collected from 2000 to 2007, showing that 6% of patients had acute hepatitis E. Although a higher seropositivity was found in males (62.5%) than in females (37.5%), the difference was not statistically significant. Epidemiological data showed that the majority of patients had never travelled out of the country, indicating an autochthonous HEV infection in Montenegro. An asymptomatic form of the disease was serologically confirmed in 7/24 patients, whereas the mild or short course of subclinical disease in 5/7 patients. No one patient had severe, fulminant or chronic course of disease^[57].

ROMANIA

There are several studies on HEV infection in humans in Romania. The earliest human studies analyzed anti-HEV IgG prevalence in eastern Romania. The seroprevalence rate of 5.9% was found in the general population^[58] and of 12% among patients with hepatitis B or C^[59].

A study from 2010 analyzed the prevalence rates in low risk population groups in South and South-Eastern Romania. The seroprevalence of anti-HEV IgG among students (mean age: 22.91 ± 0.56 years) was 12.5%, whereas among doctors and nurses (mean age: 36.71 ± 8.88 years) was 13.98%^[60].

A following study from the North-Eastern Romania among persons undergoing routine haematological tests with no signs of hepatitis showed anti-HEV IgG seroprevalence of 17.1% and 12.82% in 2011 and 2012, respectively. In 2011, the youngest age group (9-20 years) tested negative, whereas as older age groups (> 20 and > 40 years) had seroprevalence of 28.6% and 12.9%, respectively. In 2012, the youngest age group (18-45 years) had seroprevalence of 6.25%, whereas the older groups had the seroprevalence up to 28%. These results indicate that HEV infections in this region mainly affect middle-aged adults. Moreover, anti-HEV IgG was more

prevalent in women (15.78%) than in men (10%)^[61].

One of the earliest animal studies investigated swine population for the presence of anti-HEV IgG in farm and backyard pigs. The immunoblot results for the backyard pigs showed seroprevalence rates of 50%^[58,62] and for the farm pigs of 38.94%^[62].

A more recent study tested fecal samples from five swine farms (pigs aged between 2 and 4 mo) for HEV RNA, and 6 out of 19 samples tested positive. Phylogenetic analysis showed that Romanian swine isolates grouped into genotype 3 and were closely related to the swine and human HEV isolates identified in other European countries^[61]. In 2015 and 2016, serological studies investigated HEV prevalence in wild boars from eastern Romania. The seroprevalence rates were 9.61% (5/52)^[63] and 10.29% (7/68), respectively^[64]. A recent study on molecular detection of HEV in liver and spleen samples from wild boars aged > 1 year from eastern Romania showed an overall prevalence of 18%. All isolates belonged to the genotype 3 subtypes 3a and 3h^[65].

Studies in humans are scarce and new data are needed to define the seroprevalence of HEV infection. Studies conducted in animal species show high seroprevalence rates. Phylogenetic analyses show that Romanian swine and wild boar isolates grouped into genotype 3.

SERBIA

There is only one published study on the HEV seroprevalence in humans in Serbia. The study was conducted among volunteer blood donors aged 19 to 65 years (average age 39.3 years), of whom 15% tested positive for anti-HEV IgG. No significant difference in anti-HEV IgG seropositivity was found between men and women (14.6% and 16.7%, respectively). HEV seroprevalence increased with age, as higher rates were recorded in subjects older than 51 years (21.5%) when compared with younger age groups (< 50 years or < 30 years)^[66].

Several studies on HEV prevalence were conducted in Serbia in different animal species. The first study on HEV in swine population in 2007, tested pooled swine stool and tissue samples (spleen, mesenteric lymph node and liver). Thirty percent of stool and 45% of tissue samples tested HEV positive. HEV RNA was detected in four out of five pig farms examined. Simultaneously, all samples from backyard pigs and wild boars were negative^[67]. Further studies also confirmed the high prevalence of HEV among pigs in Serbia. The first HEV serology testing in pigs was done on 315 serum samples collected from 3-4 mo old backyard pigs in 63 herds from 28 towns and villages of four different districts in northern Serbia (Vojvodina province), demonstrating seroprevalence rate of 34.6%. The prevalence of anti-HEV antibodies varied widely between municipalities (range 16.7%-75.0%) and herds (range 0-100%)^[68].

Furthermore, a study in 2010 analyzed liver tissue samples from 50 dead farm pigs aged 7 to 15 wk which died on pig farms from different regions in Serbia, and detected HEV RNA in 13 of samples (26%)^[69]. In 2013, a study on 55 serum samples and meat juice samples collected from three slaughterhouses were analyzed for the presence of anti-HEV IgG antibodies. The mean seroprevalence in the pig serum and meat juice samples was 54.54% and 20%, respectively^[70]. In addition, stool, liver, bile and meat samples from 145 animals (95 fatteners and 50 eight weeks piglets) collected on during slaughter were tested for HEV RNA. Among fatteners, HEV has been detected in 7.37% of the stool samples. In piglets, HEV RNA prevalence was high and detected in 54%, 26%, 16% and 10% samples of stool, bile, liver and meat, respectively^[71]. The presence of HEV IgG and HEV RNA was examined in 201 blood and 298 liver samples from wild boars culled during hunting season from January 2010 until February 2011. The samples were collected from 27 hunting grounds located on the territory of 7 counties of the country. The overall seroprevalence rate was 34.33%. HEV RNA prevalence was 9.40% with marked regional differences. A high proportion of adult wild sow and wild boars were found positive for HEV RNA^[72].

In addition to animal studies, there are few data regarding the environment reporting the contamination of vegetable supply chain in Serbia. Namely, HEV RNA was found in 4.76 % and 3.2% of samples of leafy green vegetable from the primary production and point-of-sale phases, respectively^[51]. Another report also documented the presence of HEV RNA in frozen raspberries (2.6%)^[15]. Lately, HEV RNA has also been detected in surface waters in northern Serbia (Vojvodina Province) where 16.67% of samples tested positive for HEV RNA, during summer sampling occasion, whereas none of the tested urban sewage systems tested positive^[73].

In Serbia, different population groups should be studied in future in order to reflect

local epidemiology, modes of transmission and risk factors for HEV infection. Animal and environmental studies on larger samples as well as studies on HEV genotyping are needed to obtain better insight into HEV epidemiology.

SLOVENIA

Human studies on HEV infection in Slovenia are scarce. Steyer *et al.*^[74] tested 10 serum samples of patients with the diagnosis of acute/recent hepatitis E based on detection of HEV IgM antibodies, and three samples tested HEV RNA positive. One sample was typed as genotype 3, clustered in the lineage "e" and the second was genotype 1 strain. Slovenian human HEV strains were not related to porcine HEV strains identified in this study^[74].

There are several studies in different animal species in Slovenia. In 2011^[74], 20.3% stool samples of domestic pigs were positive for HEV RNA, of which 5.3%, 28.6% and 26.9% were from suckling, weanling and fattening pigs, respectively. All HEV strains were analyzed at 5' ORF1 and 5' ORF2 regions and both genome regions confirmed that Slovenian HEV strains represent a distinct genotype 3 lineage. All but one HEV strains detected in pigs in Slovenia represent a monophyletic branch in phylogenetic trees, with a high degree of sequence identity. One human HEV strain belonged to genotype 1 and two to genotype 3 but did not match the new genotype 3 lineage detected in Slovenian pig herds.

HEV RNA was tested in Norway rat and Black rats from one site close to Ljubljana and none of the rats tested HEV-RNA positive^[50]. The HEV presence in the wild boar population in Slovenia was first documented in 2016, showing HEV antibodies in 30.2% of animals tested, whereas HEV RNA was detected in only one sample (1/288)^[75].

Recently, the possibility of HEV entering into the food supply chain was investigated in a large study analyzing pigs entering a slaughterhouse. The study covered three different age groups and three different samples (feces, bile and liver), showing the overall HEV RNA (sample) prevalence of 5.4%, 4.9% and 5.3%, respectively^[76]. In the group of three months old pigs, 13.7% of feces, 13.0% of bile and 2.1% of liver samples were HEV RNA positive. The youngest group originating from Slovenia (none imported), was proven to be a group for highest risk for HEV infection. In the group of six months old pigs (imported from Austria), only one liver and one bile sample out of 400 tested positive. In the category of sows, no positive samples were found. The same study analyzed swabs collected at three different sites on the slaughter line (the hooks that were used to hang the liver and the lung, the containers in which livers were stored and the hooks for hanging carcasses in the cooling room). Of 62 swab samples, two were positive (a swab from the hook that carried liver and one from the liver container). However, all minced meat and bratwurst samples from these studies tested HEV RNA negative^[76]. The phylogenetic analysis revealed that detected strains were clustered into subtypes 3a, 3b, 3c and 3e.

Further environmental studies investigated surface water and waste water treatment plant. Out of 60 surface water samples tested throughout the country, only two (3.3%) were HEV RNA positive, one of them in the near vicinity of a pig farm. HEV sequences detected in the surface water belonged to genotype 3^[74]. In another study, the waste water treatment plant samples were collected from the effluent on a monthly basis from January to December 2012 and tested for HEV RNA. No HEV RNA was detected during the whole length of the study, neither before nor after the concentration step^[77].

There are several studies in different animal species showing high prevalence of HEV RNA in Slovenia, with the genotype 3 being the most common. On the other hand, studies in humans are lacking.

CONCLUSION

In the South-East Europe, anti-HEV seroprevalence as in other parts of Europe varies greatly, depending on the population studied, geographical area and assays used for the detection. Studies on HEV RNA detection and phylogenetic characterization in human samples showed that human HEV strains from the South-East European countries mainly belong to the genotype 3. Detection of the same genotype in animals as well as in the environment emphasizes the need of the multidisciplinary collaboration ("One Health" approach) in the surveillance and control of this emerging infection.

Although significant progress in HEV epidemiology has been made in the past

decade, many important questions remain^[9]. The origin of HEV is still largely unknown. Swine and wild boars were proven to be the primary natural HEV reservoir, but recent studies indicate that rabbits may serve as an additional reservoir of HEV^[78]. Some hepatitis E cases observed in immunocompromised patients clustered with rabbit HEV strains confirming their contribution to zoonotic HEV transmission^[79,80]. It is still unclear whether HEV strains present in other animals can cross the species barrier and infect humans. However, it is likely that the known host range of HEV has increased and novel strains continue to be identified. Transmission of HEV-3 from deer to humans has been described, although deer most probably undergoes spillover infections from wild boars, rather than being a natural HEV reservoir^[7]. It seems that recently described new HEV-7 has been widely distributed in dromedary camels from the Middle East^[3,81], but was also detected in an immunocompromised transplant patient who regularly consumed camel milk and meat^[4]. While HEV transmission by breast milk was confirmed in humans^[81], a recent study from China indicates that viral RNA of HEV-4 can be excreted by cow milk^[82]. Although cattle have been rarely described to be infected with HEV, these findings implicate possible HEV transmission through milk or milk products. Human contacts with other animals, especially pet animals should be investigated in future for better understanding of HEV epidemiology. Rabbits are commonly farmed in many countries for meat consumption and fur production but also as pet and possible transmission from pet house rabbits to humans should be considered as another possible transmission route^[83]. Infection of dogs and cats with HEV is confirmed serologically^[84], but their importance in HEV epidemiology need to be further investigated.

Although HEV infection is not an economically important pig disease, development of a vaccine against the zoonotic genotypes 3 and 4 and vaccination of swine should be considered as a possible public health measure. Such vaccine should also be useful for high-risk populations such as organ transplant recipients since the majority of the chronic hepatitis E are caused by the zoonotic HEV-3^[9].

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