

# Insights into hepatitis E virus epidemiology in Croatia

---

Jeličić, Pavle; Ferenc, Thomas; Mrzljak, Anna; Jemeršić, Lorena; Janev-Holcer, Nataša; Milošević, Milan; Bogdanić, Maja; Barbić, Ljubo; Kolarić, Branko; Stevanović, Vladimir; ...

Source / Izvornik: **World Journal of Gastroenterology, 2022, 28, 5494 - 5505**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.3748/wjg.v28.i37.5494>

Permanent link / Trajna poveznica: <https://urn.nsk.hr/urn:nbn:hr:105:773153>

Rights / Prava: [Attribution-NonCommercial 4.0 International/Imenovanje-Nekomercijalno 4.0 međunarodna](#)

Download date / Datum preuzimanja: **2024-07-17**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine Digital Repository](#)



## Observational Study

## Insights into hepatitis E virus epidemiology in Croatia

Pavle Jelacic, Thomas Ferenc, Anna Mrzljak, Lorena Jemersic, Natasa Janev-Holcer, Milan Milosevic, Maja Bogdanic, Ljubo Barbic, Branko Kolaric, Vladimir Stevanovic, Mateja Vujica, Zeljka Jurekovic, Jadranka Pavicic Saric, Maja Vilibic, Tatjana Vilibic-Cavlek

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:**

Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): 0  
Grade C (Good): C, C  
Grade D (Fair): 0  
Grade E (Poor): 0

**P-Reviewer:** Jackson K, Australia; Zhou C, China

**Received:** July 16, 2022

**Peer-review started:** July 16, 2022

**First decision:** August 6, 2022

**Revised:** August 15, 2022

**Accepted:** September 16, 2022

**Article in press:** September 16, 2022

**Published online:** October 7, 2022



**Pavle Jelacic, Natasa Janev-Holcer**, Department of Environmental Health, Croatian Institute of Public Health, Zagreb 10000, Croatia

**Thomas Ferenc**, Department of Radiology, Merkur University Hospital, Zagreb 10000, Croatia

**Anna Mrzljak**, Department of Gastroenterology and Hepatology, University Hospital Center Zagreb, Zagreb 10000, Croatia

**Anna Mrzljak, Tatjana Vilibic-Cavlek**, School of Medicine, University of Zagreb, Zagreb 10000, Croatia

**Lorena Jemersic**, Department of Virology, Croatian Veterinary Institute, Zagreb 10000, Croatia

**Natasa Janev-Holcer**, Department of Social Medicine and Epidemiology, Faculty of Medicine University of Rijeka, Rijeka 51000, Croatia

**Milan Milosevic**, Department of Occupational and Environmental Health, Andrija Stampar School of Public Health, Zagreb 10000, Croatia

**Maja Bogdanic, Tatjana Vilibic-Cavlek**, Department of Virology, Croatian Institute of Public Health, Zagreb 10000, Croatia

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

**Branko Kolaric**, Department of Gerontology and Social Medicine, Andrija Stampar Teaching Institute of Public Health, Zagreb 10000, Croatia

**Mateja Vujica**, Institute of Emergency Medicine of Krapina-Zagorje County, Krapina 49000, Croatia

**Zeljka Jurekovic**, Department of Nephrology, Merkur University Hospital, Zagreb 10000, Croatia

**Jadranka Pavicic Saric**, Department of Anesthesiology, University Hospital Merkur, Zagreb 10000, Croatia

**Maja Vilibic**, Department for Social Psychiatry, Psychotherapy and Psychodiagnostics, University Clinical Hospital Center "Sestre Milosrdnice", Zagreb 10000, Croatia

**Corresponding author:** Anna Mrzljak, FEBG, PhD, Adjunct Professor, Associate Professor, Department of Gastroenterology and Hepatology, University Hospital Center Zagreb, Kispaticeva 12, Zagreb 10000, Croatia. [anna.mrzljak@gmail.com](mailto:anna.mrzljak@gmail.com)

## Abstract

### BACKGROUND

Hepatitis E virus (HEV) is an emerging virus of global health concern. The seroprevalence rates differ greatly according to geographic region and population group.

### AIM

To analyze the seroprevalence of HEV in exposed (animal-related professions) and nonexposed populations, as well as solid organ and hematopoietic stem cell transplant patients.

### METHODS

Forestry workers ( $n = 93$ ), hunters ( $n = 74$ ), and veterinarians ( $n = 151$ ) represented the exposed population. The general population ( $n = 126$ ) and pregnant women ( $n = 118$ ) constituted the control group. Transplant patients included liver transplant recipients (LTRs) ( $n = 83$ ), kidney transplant recipients (KTRs) ( $n = 43$ ), and hematopoietic stem cell transplant recipients (HSCRs) ( $n = 39$ ). HEV immunoglobulin G antibodies were detected using the enzyme-linked immunosorbent assay and confirmed by the immunoblot test.

### RESULTS

The HEV seroprevalence significantly differed between groups: Veterinarians 15.2%, hunters 14.9%, forestry workers 6.5%, general population 7.1%, and pregnant women 1.7%. In transplant patients, the seropositivity was highest in LTRs (19.3%), while in KTRs and HSCRs, the seroprevalence was similar to the general population (6.9% and 5.1%, respectively). A significant increase in seropositivity with age was observed from 2.9% in individuals less than 30 years to 23.5% in those older than 60 years. Sociodemographic characteristics (sex, educational level, area of residence, and number of household members), eating habits (game meat, offal, and pork products consumption), and environmental and housing conditions (drinking water supply, type of water drainage/sewer, waste disposal, domestic animals) were not associated with HEV seropositivity. However, individuals who reported a pet ownership were more often seropositive compared to those who did not have pet animals (12.5% *vs* 7.0%).

### CONCLUSION

The results of this study showed that individuals in professional contact with animals and LTRs are at higher risk for HEV infection. In addition, age is a significant risk factor for HEV seropositivity.

**Key Words:** Hepatitis E virus; Seroprevalence; Veterinarians; Hunters; Forestry workers; Transplant patients; Croatia

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** Hepatitis E virus (HEV) is an emerging viral pathogen of public health concern. We analyzed the epidemiological characteristics of HEV infection in different groups in Croatia. The highest seroprevalence was reported in professionally exposed individuals such as veterinarians, hunters, and liver transplant recipients. Seropositivity was similar in the general population, forestry workers, kidney transplant patients, and hematopoietic stem cell transplant patients. The lowest seroprevalence was recorded in pregnant women. A significant increase in seroprevalence with age was observed. Pet ownership was also associated with HEV seropositivity. Sex, environmental and housing conditions, and eating habits were not associated with HEV seroprevalence.

**Citation:** Jelicic P, Ferenc T, Mrzljak A, Jemersic L, Janev-Holcer N, Milosevic M, Bogdanic M, Barbic L, Kolaric B, Stevanovic V, Vujica M, Jurekovic Z, Pavicic Saric J, Vilibic M, Vilibic-Cavlek T. Insights into hepatitis E virus epidemiology in Croatia. *World J Gastroenterol* 2022; 28(37): 5494-5505

**URL:** <https://www.wjgnet.com/1007-9327/full/v28/i37/5494.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v28.i37.5494>

## INTRODUCTION

Hepatitis E virus (HEV) is an emerging viral pathogen of global health concern. It is a nonenveloped RNA virus, a member of the *Hepeviridae* family, genus *Orthohepevirus*[1]. Along with hepatitis B and hepatitis C virus (1.5 million new infections per year for each virus)[2,3], HEV is a major cause of viral hepatitis worldwide with approximately 20 million documented infections annually, over three million symptomatic cases, and 60-70000 fatal outcomes[4]. East and South Asia account for more than 60% of all reported cases[5]. There are eight known HEV genotypes. HEV-1 and HEV-2 are confined to humans and mainly cause infections in developing countries of tropical and subtropical regions[4-6]. HEV-3 and HEV-4 have been isolated from humans and different animal species (pigs, wild boars, deer, rabbits, goats, cows), primarily causing sporadic, autochthonous human infections in the developed world[5,7]. HEV-5 and HEV-6 have been restricted to wild boars only, while genotypes 7 and 8 have been isolated in dromedary and Bactrian camels[7,8]. In low-income countries, the main mode of HEV transmission is the fecal-oral route (contaminated drinking water, poor hygiene), whereas in more industrialized countries people are getting infected through zoonotic transmission (uncooked or undercooked animal products, mainly infected meat, and milk)[6,7]. Pigs are the main HEV animal reservoir. Almost 13% of domestic pigs and 9.5% of wild boars are actively infected by HEV with 10% of commercial pork products being HEV-RNA-positive[9]. Several other foods have also been proposed as a potential source of HEV infection in humans, *e.g.*, shellfish, mussels, and oysters[6]. One study found that HEV maintains infectivity for up to 21 d at 37 °C and up to 28 d at usual room temperature[8]. The virus can also be transmitted through blood transfusion, intravenous drug use, solid organ transplantation (SOT), hemodialysis, or maternal-fetal interaction[5,7]. In most cases, HEV presents as a self-limiting acute illness with low mortality rates (1%-2%) in immunocompetent individuals. However, genotypes 3, 4, and 7 may induce chronic infection and subsequent cirrhosis in immunocompromised patients, especially in SOT recipients, and human immunodeficiency virus-positive individuals[4]. Pregnant women are more susceptible to rapid disease progression such as fulminant hepatic and extrahepatic manifestations and obstetric complications leading to high mortality rates (15%-25%) compared to the non-pregnant population[4,5]. Professionally exposed individuals (*e.g.*, forestry workers, veterinarians, hunters, farmers) are also at increased risk of getting infected by HEV. Detected HEV seroprevalence rates in professionally exposed workers differ greatly between countries: Forestry workers (2.2%-31.0%) [10-13], hunters (3.81%-22.2%)[13-15], and veterinarians (10.2%-43.7%)[16,17]. In the transplant population, HEV seroprevalence rates were reportedly between 6.0% and 29.6%[18].

The seroepidemiological studies have shown that HEV is widespread in Croatia with seroprevalence rates ranging from 2.7% in healthcare professionals to 24.4% in liver transplant patients and up to 43.5% in hemodialysis patients[19,20]. However, only preliminary data are available on the HEV seroprevalence in animal-related professions. The aim of this study was to analyze the HEV epidemiology in different professionally exposed (animal-related) and nonexposed population groups in Croatia.

## MATERIALS AND METHODS

### Study participants

From October 2016 to September 2017, serum samples collected from Croatian residents were tested for the presence of HEV immunoglobulin G (IgG) antibodies. Samples were obtained from different exposed and nonexposed population groups. Forestry workers, hunters, and veterinarians represented the exposed population. The general population and pregnant women constituted the control group. In addition, from January 2021 to December 2021, a total of 165 serum samples were collected from SOT recipients [liver transplant recipients (LTRs) and kidney transplant recipients (KTRs)] and hematopoietic stem cell transplant recipients (HSCRs). None of the participants showed symptoms of acute hepatitis or reported a recent febrile disease. The distribution of study participants according to the population group is presented in [Table 1](#).

### Methods

HEV IgG antibodies were detected using a commercial enzyme-linked immunosorbent assay (ELISA) based on recombinant antigens of HEV genotypes 1 and 3 (anti-hepatitis E virus IgG ELISA; Euroimmun, Lübeck, Germany). Reactive samples were tested for the presence of HEV IgM antibodies (anti-hepatitis E virus IgM ELISA; Euroimmun). Additionally, ELISA IgG-positive samples were confirmed by a commercial immunoblot (IB) assay using highly purified recombinant HEV antigens: O2N genotype 1/3, O2C genotype 1/3, O2M genotype 1, O3 genotype 1/3 (HEV Recomline; Mikrogen, Neuried, Germany). IB-positive samples were further retested using a second assay (Euroline anti-hepatitis E virus IgG, Euroimmun, Lübeck, Germany) based on the recombinant HEV genotypes 1-4 antigens (ORF2). For the IB, the manufacturer states a diagnostic sensitivity of 96.6% and specificity of 97.1% (Mikrogen) and 100% (Euroimmun).

**Table 1 Exposed and nonexposed population groups included in the study**

| Population                         | <i>n</i> | Median age, yr | IQR, yr |
|------------------------------------|----------|----------------|---------|
| <b>Exposed group</b>               |          |                |         |
| Hunters                            | 74       | 55             | 41-60   |
| Veterinarians                      | 151      | 46             | 36-55.5 |
| Forestry workers                   | 93       | 43             | 31-51   |
| <b>Non-exposed group</b>           |          |                |         |
| General population                 | 126      | 48             | 33-62   |
| Pregnant women                     | 118      | 31.5           | 29-35   |
| <b>Transplant patients</b>         |          |                |         |
| Liver transplant recipients        | 83       | 60             | 49-65.5 |
| Kidney transplant recipients       | 43       | 52.5           | 42-62   |
| Hematopoietic stem cell recipients | 39       | 55             | 51-64   |

IQR: Interquartile range.

**Table 2 Hepatitis E virus immunoglobulin G prevalence in exposed and nonexposed populations**

| Population group                   | Tested, <i>n</i> (%) | HEV IgG, <i>n</i> (%) | 95%CI     | <i>P</i> value |
|------------------------------------|----------------------|-----------------------|-----------|----------------|
| Hunters                            | 74                   | 11 (14.9)             | 8.2-14.2  | 0.003          |
| Veterinarians                      | 151                  | 23 (15.2)             | 10.2-21.6 |                |
| Forestry workers                   | 93                   | 6 (6.5)               | 2.7-12.8  |                |
| General population                 | 126                  | 9 (7.1)               | 3.3-13.1  |                |
| Pregnant women                     | 118                  | 2 (1.7)               | 0.2-5.9   |                |
| Liver transplant recipients        | 83                   | 16 (19.3)             | 11.4-29.4 |                |
| Kidney transplant recipients       | 43                   | 3 (6.9)               | 1.5-19.1  |                |
| Hematopoietic stem cell recipients | 39                   | 2 (5.1)               | 0.6-7.3   |                |

CI: Confidence interval; HEV: Hepatitis E virus; IgG: Immunoglobulin G.

To identify potential risk factors that may be associated with HEV infection, for animal-related professions (exposed group) and nonexposed group, data on demographic characteristics and potential risk factors (eating habits, environmental and housing conditions, traveling history, and blood transfusion) were collected using a questionnaire. The modified Health-Environment-Life Style questionnaire created by the Andrija Stampar School of Public Health, School of Medicine, University of Zagreb was used in the study.

### Statistical analysis

The HEV IgG prevalence is presented as a percentage with 95% confidence intervals (CIs). Differences in categorical variables between HEV seropositive and seronegative participants were tested using the Fisher's exact or Fisher-Freeman-Halton test. Odds ratio (OR) and relative risk (RR) were also calculated. Variables with statistical significance in a bivariate analysis were analyzed in multivariate regression analysis (binary logistic regression).  $P < 0.05$  was considered statistically significant. Statistical analysis was performed using MedCalc® Statistical Software version 20.022 (MedCalc Software Ltd., Ostend, Belgium; <https://www.medcalc.org>; 2021).

## RESULTS

HEV IgG antibodies were detected in 72/727 (9.9%; 95%CI: 7.8-12.3) participants: 40/278 (12.6%; 95%CI: 9.3-16.6) in the exposed group, 11/244 (4.3%; 95%CI: 2.3-7.3) in the nonexposed group, and 12/165

**Table 3** Hepatitis E virus immunoglobulin G prevalence according to sociodemographic characteristics

| Characteristic              | Subjects <sup>1</sup> , n | HEV IgG, n (%) | 95%CI     | P value |
|-----------------------------|---------------------------|----------------|-----------|---------|
| Sex                         |                           |                |           | 0.065   |
| Male                        | 238                       | 29 (10.9)      | 7.6-15.0  |         |
| Female                      | 282                       | 22 (7.2)       | 4.7-10.6  |         |
| Age group in yr             |                           |                |           | < 0.001 |
| < 30                        | 99                        | 3 (2.9)        | 0.8-7.6   |         |
| 30-39                       | 147                       | 11 (7.0)       | 3.8-11.7  |         |
| 40-49                       | 94                        | 5 (5.1)        | 2.0-10.7  |         |
| 50-59                       | 90                        | 11 (10.9)      | 5.9-18.1  |         |
| 60 +                        | 62                        | 19 (23.5)      | 15.3-33.5 |         |
| Area of residence           |                           |                |           | 0.144   |
| Rural                       | 151                       | 16 (9.6)       | 5.8-14.7  |         |
| Suburban                    | 54                        | 11 (16.9)      | 9.3-27.4  |         |
| Urban                       | 255                       | 24 (8.6)       | 5.7-12.3  |         |
| Number of household members |                           |                |           | 0.301   |
| ≤ 3                         | 258                       | 22 (7.9)       | 5.1-11.4  |         |
| > 3                         | 177                       | 21 (10.6)      | 6.9-15.5  |         |
| Educational level           |                           |                |           | 0.467   |
| Primary school              | 58                        | 5 (7.9)        | 3.1-16.5  |         |
| High school                 | 254                       | 25 (9.0)       | 6.0-12.7  |         |

<sup>1</sup>Subjects who filled a questionnaire.

CI: Confidence interval; HEV: Hepatitis E virus; IgG: Immunoglobulin G.

(12.7%; 95% CI: 8.1-18.8) in transplant patients. None of the participants were HEV IgM-positive. There were significant differences in the IgG seroprevalence rates among population groups (Table 2). In animal-related professions, the seropositivity was higher (14.9% in hunters and 15.2% in veterinarians) than in pregnant women (1.7%) and the general population (7.1%). Seroprevalence in transplant populations was highest in LTR (19.3%), followed by KTR (6.9%) and HSCR (5.1%).

A significant increase in seroprevalence was observed according to age. Participants in the age group 60 + years and 50-59 years showed higher seropositivity rates (23.5% and 10.9%, respectively) compared to younger age groups (2.9%-7.0%). There was no difference in HEV seroprevalence according to sex, area of residence, number of household members, and educational level (Table 3). HEV seropositivity did not differ regarding to the frequency of game meat, offal, and pork products consumption. However, there was a difference in the seroprevalence rates according to the frequency of shellfish consumption (Table 4).

Analyzing the environmental and housing conditions of the study participants and HEV seropositivity (Table 5), no significant difference was found according to drinking water supply, type of water drainage/sewer, and waste disposal. However, participants who reported having pet animals had a higher seroprevalence rate compared to those who did not have pet animals (12.5% vs 7.0%). Travel history as well as previous blood transfusion, surgical procedure, and tattoo/piercing were not associated with HEV seroprevalence (Table 6).

Risk analysis showed that animal-related professions and liver transplant patients were more likely to be HEV seropositive than other tested groups: Hunters OR = 3.873, 95% CI: 1.605-9.341; RR = 3.445, 95% CI: 1.556-7.628; veterinarians OR = 3.985, 95% CI: 1.883-8.435; RR = 3.531, 95% CI: 1.771-7.038; LTRs OR = 5.058, 95% CI: 2.240-11.420; RR = 4.276, 95% CI: 2.068-8.839 (Table 7).

## DISCUSSION

The zoonotic risk of HEV transmission is well established, while exact transmission routes remain to be determined. The HEV seroprevalence rates vary greatly according to geographical region and study



Table 4 Hepatitis E virus immunoglobulin G prevalence according to eating habits

| Eating habits             | Subjects <sup>1</sup> , n | HEV IgG, n (%) | 95%CI               | P value |
|---------------------------|---------------------------|----------------|---------------------|---------|
| Shellfish consumption     |                           |                |                     | 0.004   |
| Never                     | 60                        | 15 (25.0)      | 14.4-37.0           |         |
| Rarely                    | 374                       | 32 (8.6)       | 6.0-11.7            |         |
| Once a month              | 16                        | 2 (12.5)       | 2.7-34.4            |         |
| Every week                | 2                         | 0 (0)          | 0-84.1 <sup>2</sup> |         |
| Game meat consumption     |                           |                |                     | 0.104   |
| Never                     | 20                        | 1 (5.0)        | 0.5-21.1            |         |
| Rarely                    | 324                       | 30 (9.3)       | 6.5-12.8            |         |
| Once a month              | 89                        | 14 (15.7)      | 9.3-24.3            |         |
| Every week                | 19                        | 4 (21.1)       | 7.6-42.6            |         |
| Offal consumption (liver) |                           |                |                     | 0.070   |
| Never                     | 25                        | 0 (0)          | 0-13.7 <sup>2</sup> |         |
| Rarely                    | 296                       | 29 (9.8)       | 6.8-13.6            |         |
| Once a month              | 120                       | 18 (15.0)      | 9.5-22.2            |         |
| Every week                | 11                        | 2 (18.2)       | 4-46.7              |         |
| Pork products consumption |                           |                |                     | 0.216   |
| No                        | 204                       | 18 (8.8)       | 5.5-13.3            |         |
| Yes                       | 249                       | 31 (12.4)      | 8.8-17.0            |         |

<sup>1</sup>Subjects who filled a questionnaire.

<sup>2</sup>One-sided 97.5% confidence interval.

CI: Confidence interval; HEV: Hepatitis E virus; IgG: Immunoglobulin G.

cohorts. The proposed transmission routes linked to professional exposures include frequent contact with the zoonotic HEV reservoirs, such as pigs and other wildlife species (mainly wild boar)[12]. Forestry workers, hunters, and veterinarians represented risk populations in this study. The HEV seroprevalence was significantly higher in the exposed population (12.6%) compared to the nonexposed population (4.3%). In the exposed group, seroprevalence was similar in the veterinarians (15.2%) and hunters (14.9%), while it was lower in the forestry workers (6.5%).

HEV seropositivity in forestry workers included in this study was similar to the seroprevalence in the Croatian general population (7.1%). Seroepidemiological studies conducted among forestry workers in Europe showed seropositivity of 31% in France (2002-2003)[11] and 18% in Germany (Brandenburg, 2008)[21]. In more recent studies, HEV antibodies were detected in 2.2% of forest rangers from western Poland (Poznan, 2014)[10], 5% of forestry workers from eastern Poland (Lubelskie Voivodship, 2014-2015)[13], and 14% of forestry workers in Italy (Trentino-Alto Adige Region, 2014-2015)[12]. Although forestry workers have been identified as being at risk of HEV infection in several studies, the French study revealed for the first time that woodcutters are at a particularly high risk of infection. Among woodcutters, 37.2% were found to be seropositive compared to game and fishing keepers/rangers and silviculturists (20.0% and 24.8% seropositive, respectively)[11]. Close contact with wild boar stools in the forest environment could be an additional source of HEV infection in this risk population.

HEV seropositivity in the Croatian hunters included (14.9%) was two times higher than that in the general population. Two studies conducted among Polish hunters from 2010 to 2012 showed a HEV seropositivity of 25%[22] and 22.2%, respectively[14]. A similar seroprevalence rate (25%) was detected in Italian hunters from the Latium Region tested during the hunting season[23] and German hunters (21%) from Central Germany tested in 2013[15]. By contrast, only 4.2% of hunters from nine Estonian counties were seropositive to HEV in 2013[24] as well as 3.81% of Polish hunters from the Lubelskie Voivodship (eastern Poland) tested from 2014 to 2015[13].

In 2009, serum samples were collected from participants of the National Veterinary Congress in Helsinki. Finnish veterinarians commonly have HEV antibodies with a seroprevalence of 10.2%. The highest seroprevalence rate of 17.8% was unexpectedly detected in small animal practitioners[17]. A study from Norway in 2013 found IgG seroprevalence of 14%. When stratifying by work experience, HEV seroprevalence in Norwegian veterinarians working with swine was more than two times higher

**Table 5** Hepatitis E virus immunoglobulin G prevalence according to environmental and housing conditions

| Characteristics                | Subjects <sup>1</sup> , n (%) | HEV IgG, n (%) | 95%CI               | P value |
|--------------------------------|-------------------------------|----------------|---------------------|---------|
| Drinking water supply          |                               |                |                     | 0.694   |
| Public water supply            | 431                           | 43 (10.0)      | 7.4-13.1            |         |
| Private water well             | 70                            | 7 (10.0)       | 4.6-18.6            |         |
| Bottled water                  | 4                             | 0 (0)          | 0-60.2 <sup>2</sup> |         |
| Others                         | 4                             | 1 (25.0)       | 2.8-71.6            |         |
| Type of water drainage/sewer   |                               |                |                     | 0.781   |
| Public sewer                   | 320                           | 33 (10.3)      | 7.3-14              |         |
| Septic tank                    | 185                           | 18 (9.7)       | 6.1-14.6            |         |
| Others                         | 4                             | 0 (0)          | 0-60.2 <sup>2</sup> |         |
| Waste disposal                 |                               |                |                     | 1.000   |
| Public                         | 501                           | 51 (10.2)      | 7.8-13.1            |         |
| Burning                        | 5                             | 0 (0)          | 0-52.2 <sup>2</sup> |         |
| Slurry                         | 2                             | 0 (0)          | 0-84.1 <sup>2</sup> |         |
| Having pet animals             |                               |                |                     | 0.039   |
| Yes                            | 265                           | 33 (12.5)      | 8.9-16.8            |         |
| No                             | 243                           | 17 (7.0)       | 4.3-10.7            |         |
| Having domestic animals        |                               |                |                     | 0.629   |
| Yes                            | 140                           | 16 (11.4)      | 7.0-17.5            |         |
| No                             | 348                           | 35 (10.1)      | 7.2-13.5            |         |
| Rodent control in the basement |                               |                |                     | 0.670   |
| Yes                            | 264                           | 28 (10.6)      | 7.3-14.7            |         |
| No                             | 243                           | 23 (9.5)       | 6.3-13.6            |         |
| Storing food in the basement   |                               |                |                     | 0.346   |
| Yes                            | 122                           | 15 (12.3)      | 7.4-19.0            |         |
| No                             | 385                           | 36 (9.4)       | 6.7-12.6            |         |

<sup>1</sup>Subjects who filled a questionnaire.

<sup>2</sup>One-sided 97.5% confidence interval.

CI: Confidence interval; HEV: Hepatitis E virus; IgG: Immunoglobulin G.

compared to those who did not work with swine (22% *vs* 9%)[25]. Chinese studies conducted from 2003 to 2017 demonstrated high IgG seropositivity in veterinarians ranging from 26.7%[16] to 43.7%[26]. In addition, a high seroprevalence rate of 23% was notified in swine veterinarians in the United States[27].

By contrast, a Thai study found no association between HEV seroprevalence and frequent direct occupational pig contact[28]. A very low HEV seropositivity (2.6%) was found in Estonian veterinarians. All antibody-positive veterinarians worked in small animal clinics and some of them were cat or dog owners[29]. The majority of veterinarians included in this study are small animal practitioners and showed seropositivity to HEV of 15.2%. In some countries, significant regional differences in the HEV seroprevalence were observed. In Polish hunters, seroprevalence varied from 10% to 42.4%[14].

A recent meta-analysis of 14626 transplant recipients showed that anti-HEV seroprevalence ranges from 6%-29.6%[18]. This wide HEV seroprevalence range reflects the differences in viral circulation within different geographical regions and the impact of assays used in the particular study. In our transplant cohort, LTRs showed the highest seroprevalence rate of 19.3%, and in the risk analysis for HEV IgG seropositivity exhibited the highest OR of 5.058 among tested groups. This supports the hypothesis that HEV in combination with other factors may promote chronic inflammation and even be a cofactor in hepatocellular carcinoma occurrence leading to liver transplant candidacy[30]. Chronicity of HEV infection is of emerging relevance in transplant recipients; however, there are still conflicting viewpoints on the overall anti-HEV seroprevalence and rate of chronic HEV infection in immunocompromised patients[31].



**Table 6** Hepatitis E virus immunoglobulin G prevalence according to other potential risk factors

| Characteristics     | Subjects <sup>1</sup> , n | HEV IgG, n (%) | 95%CI    | P value |
|---------------------|---------------------------|----------------|----------|---------|
| Traveling abroad    |                           |                |          | 0.621   |
| Yes                 | 119                       | 11 (9.2)       | 5-15.4   |         |
| No                  | 369                       | 40 (10.8)      | 8-14.3   |         |
| Blood transfusion   |                           |                |          | 0.120   |
| Yes                 | 44                        | 8 (18.2)       | 9-31.4   |         |
| No                  | 410                       | 41 (10)        | 7.4-13.2 |         |
| Surgical procedure  |                           |                |          | 0.570   |
| Yes                 | 230                       | 23 (10)        | 6.6-14.4 |         |
| No                  | 223                       | 26 (11.7)      | 7.9-16.4 |         |
| Tattoo and piercing |                           |                |          | 0.540   |
| Yes                 | 72                        | 6 (8.3)        | 3.6-16.4 |         |
| No                  | 378                       | 43 (11.4)      | 8.5-14.9 |         |

<sup>1</sup>Subjects who filled a questionnaire.

CI: Confidence interval; HEV: Hepatitis E virus; IgG: Immunoglobulin G.

**Table 7** Risk analysis for hepatitis E virus immunoglobulin G seropositivity

| Population group                   | OR    | 95%CI        | P value | RR    | 95%CI       | P value |
|------------------------------------|-------|--------------|---------|-------|-------------|---------|
| General population                 | Ref   |              |         | Ref   |             |         |
| Hunters                            | 3.873 | 1.605-9.341  | 0.002   | 3.445 | 1.556-7.628 | 0.002   |
| Veterinarians                      | 3.985 | 1.883-8.435  | < 0.001 | 3.531 | 1.771-7.038 | < 0.001 |
| Forestry workers                   | 1.529 | 0.549-4.261  | 0.416   | 1.495 | 0.569-3.929 | 0.414   |
| Liver transplant recipients        | 5.058 | 2.240-11.420 | < 0.001 | 4.276 | 2.068-8.839 | < 0.001 |
| Kidney transplant recipients       | 1.588 | 0.424-5.946  | 0.491   | 1.547 | 0.450-5.320 | 0.488   |
| Hematopoietic stem cell recipients | 1.145 | 0.244-5.373  | 0.863   | 1.137 | 0.262-4.938 | 0.863   |

CI: Confidence interval; OR: Odds ratio; RR: Relative risk.

Several studies have found sex variations in HEV seropositivity, with males having higher seropositivity compared to women[14,32]. This study found no significant difference in the seropositivity between men (10.9%) and women (7.2%). Similarly, a German study found no sex differences in the HEV seropositivity[15]. An increase in HEV seroprevalence with age, which is likely to reflect cumulative exposure to HEV over time was observed in many studies[11,12,14,27]. In this study, the highest seropositivity (23.5%) was observed in the age group 60 + years compared to 2.9%-10.9% in other age groups. By contrast, one German study conducted in forestry workers did not find a statistically significant association between seropositivity and age[21]. Similarly, no association of HEV seroprevalence with age was observed in Norwegian veterinarians[25].

Working with a septic tank was identified as a strong risk factor for HEV infection in the Netherlands [33]. Additionally, using a stream or well as a source of water has been identified as a risk factor for HEV infection in some countries[34]. Similar to a previous Croatian study[35], in this study, we found no difference in the HEV seroprevalence regarding the type of drainage/sewer, type of water supply, and waste disposal.

Eating habits were associated with HEV seropositivity in some studies. Eating internal pig organs more than twice a week was linked to a higher seroprevalence of anti-HEV IgG in a rural community in Thailand[28]. In France, the presence of anti-HEV IgG was associated with the consumption of pork meat, pork liver sausages, game meat, offal, and oysters[36]. The association between HEV seroprevalence and consumption of stewed offal was also confirmed among Polish hunters[12]. In Italy, many seropositive individuals reported consumption of raw or undercooked food, particularly shellfish (mussels) and unbottled drinking water[37]. This study found no association between offal consumption

and HEV seropositivity. Although participants who reported eating pork liver every week showed a higher seroprevalence rate (18.2%) compared to those who did not eat or ate pork liver rarely (0%-15.0%), this difference was not significant. In addition, there was no difference in the seropositivity regarding pork meat and game meat consumption. Similar to our results, a German study showed that wild boar meat consumption was not associated with HEV seroprevalence. However, HEV RNA was detected in muscle specimens from wild boar, suggesting this is a possible HEV transmission route[15]. Surprisingly, there was a significant difference in the seroprevalence regarding shellfish consumption in our study, with the highest seroprevalence in participants who reported to never eat shellfish. However, due to a very small number in the tested subgroups regarding the frequency of shellfish consumption, this limitation should be considered when interpreting the results.

In this study, a pet ownership was associated with HEV seroprevalence with a seropositivity rate of 12.5% in individuals who reported having a cat/dog compared to 7.0% in those who did not have pet animals. Animal ownership, including both domestic and pet animals, was not found to be a risk factor for HEV infection in a Jordanian study[38]. The use of a self-reported questionnaire in the study is a limitation that should be addressed. In addition, data on the risk factors in the transplant patients were not available.

---

## CONCLUSION

---

The results of this study showed that individuals in professional contact with animals are at higher risk for HEV infection. Identification of people at risk for HEV infection is essential to implement preventive measures and educate these groups about modes of HEV transmission and prevention. Since immunocompromised populations such as SOT are at risk of chronic hepatitis E, such individuals should be counseled regarding the risk of HEV before and after transplantation.

## ARTICLE HIGHLIGHTS

### **Research background**

Hepatitis E virus (HEV) seroprevalence rates differ greatly according to the geographic region and population group.

### **Research motivation**

Only preliminary data are available on the HEV seroprevalence in some population groups in Croatia.

### **Research objectives**

To determine the HEV seroprevalence in different populations (animal-related professions, transplant patients, general population).

### **Research methods**

HEV immunoglobulin G antibodies were detected using an enzyme-linked immunosorbent assay. Initially, reactive samples were confirmed by immunoblot test.

### **Research results**

Significant differences in HEV seropositivity were observed among the population groups: Veterinarians 15.2%, hunters 14.9%, forestry workers 6.5%, general population 7.1%, pregnant women 1.7%, liver transplant recipients 19.3%, kidney transplant recipients 6.9%, and hematopoietic stem cell recipients 5.1%. Older age was a significant risk factor for HEV seropositivity. In addition, pet ownership was associated with HEV seroprevalence. Sociodemographic characteristics, eating habits, and environmental and housing conditions were not associated with the HEV seropositivity.

### **Research conclusions**

Professional contact with animals and older age are significant risk factors for HEV infection.

### **Research perspectives**

Further studies on a large sample of exposed and nonexposed population are needed to determine the HEV RNA prevalence/seroprevalence and clinical significance of HEV infection in the Croatian population.

## FOOTNOTES

**Author contributions:** Jelicic P and Vilibic-Cavlek T conceived the study and wrote the original draft; Ferenc T, Mrzljak A, and Vilibic-Cavlek T wrote the original draft; Janev-Holcer N, Bogdanic M, Mrzljak A, Barbic L, Stevanovic V, Vujica M, Jurekovic Z, Pavicic Saric J, and Vilibic M were involved in the data collection and analysis; Milosevic M and Kolaric B performed the statistical analyses; Jemersic L and Vilibic-Cavlek T revised the manuscript critically; and all authors approved the final version of the manuscript.

**Supported by** the Croatian Science Foundation (Emerging and Neglected Hepatotropic Viruses after Solid Organ and Hematopoietic Stem Cell Transplantation to Mrzljak A), No. IP-2020-02-7407.

**Institutional review board statement:** The study was approved by the Ethic Committee of the Croatian Institute of Public Health (protocol code 80327/1-16, approved on 12 February 2016) and School of Medicine University of Zagreb (protocol code 641-01/20-02/01, approved on 22 October 2020).

**Informed consent statement:** Written informed consent was obtained from all participants included in the study.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** Data sharing available upon request.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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

**Country/Territory of origin:** Croatia

**ORCID number:** Pavle Jelicic 0000-0003-3200-1596; Thomas Ferenc 0000-0002-4917-9270; Anna Mrzljak 0000-0001-6270-2305; Lorena Jemersic 0000-0002-8379-4787; Natasa Janev-Holcer 0000-0002-2584-6681; Milan Milosevic 0000-0001-9008-7645; Maja Bogdanic 0000-0002-8236-3205; Ljubo Barbic 0000-0002-5170-947X; Branko Kolaric 0000-0002-0884-4043; Vladimir Stevanovic 0000-0002-9572-8760; Mateja Vujica 0000-0001-7766-5113; Zeljka Jurekovic 0000-0003-0690-2577; Jadranka Pavicic Saric 0000-0003-4124-8056; Maja Vilibic 0000-0002-5357-5890; Tatjana Vilibic-Cavlek 0000-0002-1877-5547.

**S-Editor:** Wang JJ

**L-Editor:** Filipodia

**P-Editor:** Wang JJ

## REFERENCES

- 1 **Webb GW**, Dalton HR. Hepatitis E: an underestimated emerging threat. *Ther Adv Infect Dis* 2019; **6**: 2049936119837162 [PMID: 30984394 DOI: 10.1177/2049936119837162]
- 2 **World Health Organization.** Hepatitis B. [cited 10 June 2022]. Available from: <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b>
- 3 **World Health Organization.** Hepatitis C. [cited 10 June 2022]. Available from: <https://www.who.int/news-room/fact-sheets/detail/hepatitis-c>
- 4 **Nimgaonkar I**, Ding Q, Schwartz RE, Ploss A. Hepatitis E virus: advances and challenges. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 96-110 [PMID: 29162935 DOI: 10.1038/nrgastro.2017.150]
- 5 **Raji YE**, Toung OP, Taib NM, Sekawi ZB. Hepatitis E Virus: An emerging enigmatic and underestimated pathogen. *Saudi J Biol Sci* 2022; **29**: 499-512 [PMID: 35002446 DOI: 10.1016/j.sjbs.2021.09.003]
- 6 **Doceul V**, Bagdassarian E, Demange A, Pavio N. Zoonotic Hepatitis E Virus: Classification, Animal Reservoirs and Transmission Routes. *Viruses* 2016; **8** [PMID: 27706110 DOI: 10.3390/v8100270]
- 7 **Primadharsini PP**, Nagashima S, Okamoto H. Mechanism of Cross-Species Transmission, Adaptive Evolution and Pathogenesis of Hepatitis E Virus. *Viruses* 2021; **13** [PMID: 34069006 DOI: 10.3390/v13050909]
- 8 **Ferri G**, Vergara A. Hepatitis E Virus in the Food of Animal Origin: A Review. *Foodborne Pathog Dis* 2021; **18**: 368-377 [PMID: 33784472 DOI: 10.1089/fpd.2020.2896]
- 9 **Li P**, Ji Y, Li Y, Ma Z, Pan Q. Estimating the global prevalence of hepatitis E virus in swine and pork products. *One Health* 2022; **14**: 100362 [PMID: 34977322 DOI: 10.1016/j.onehlt.2021.100362]
- 10 **Bura M**, Bukowska A, Michalak M, Bura A, Nawrocki MJ, Karczewski M, Mozer-Lisewska I. Exposure to hepatitis E virus, hepatitis A virus and *Borrelia* spp. infections in forest rangers from a single forest district in western Poland. *Adv Clin Exp Med* 2018; **27**: 351-355 [PMID: 29533542 DOI: 10.17219/acem/65787]

- 11 **Carpentier A**, Chaussade H, Rigaud E, Rodriguez J, Berthault C, Boué F, Tognon M, Touzé A, Garcia-Bonnet N, Choutet P, Coursaget P. High hepatitis E virus seroprevalence in forestry workers and in wild boars in France. *J Clin Microbiol* 2012; **50**: 2888-2893 [PMID: [22718947](#) DOI: [10.1128/JCM.00989-12](#)]
- 12 **Monini M**, Ostanello F, Dominicis A, Tagliapietra V, Vaccari G, Rizzoli A, Trombetta CM, Montomoli E, Di Bartolo I. Seroprevalence of Hepatitis E Virus in Forestry Workers from Trentino-Alto Adige Region (Northern Italy). *Pathogens* 2020; **9** [PMID: [32674277](#) DOI: [10.3390/pathogens9070568](#)]
- 13 **Weiner M**, Tokarska-Rodak M, Plewik D, Pańczuk A, Szepeluk A, Krajewska M. The Serological Surveillance of Hepatitis E virus among Hunters and Foresters in Eastern Poland. *Pol J Microbiol* 2017; **66**: 277-279 [PMID: [28735306](#) DOI: [10.5604/01.3001.0010.7882](#)]
- 14 **Baumann-Popczyk A**, Popczyk B, Gołąb E, Rożej-Bielicka W, Sadkowska-Todys M. A cross-sectional study among Polish hunters: seroprevalence of hepatitis E and the analysis of factors contributing to HEV infections. *Med Microbiol Immunol* 2017; **206**: 367-378 [PMID: [28776194](#) DOI: [10.1007/s00430-017-0515-0](#)]
- 15 **Schielke A**, Ibrahim V, Czogiel I, Faber M, Schrader C, Dremsek P, Ulrich RG, John R. Hepatitis E virus antibody prevalence in hunters from a district in Central Germany, 2013: a cross-sectional study providing evidence for the benefit of protective gloves during disembowelling of wild boars. *BMC Infect Dis* 2015; **15**: 440 [PMID: [26493830](#) DOI: [10.1186/s12879-015-1199-y](#)]
- 16 **Kang YH**, Cong W, Zhang XY, Wang CF, Shan XF, Qian AD. Hepatitis E virus seroprevalence among farmers, veterinarians and control subjects in Jilin province, Shandong province and Inner Mongolia Autonomous Region, China. *J Med Virol* 2017; **89**: 872-877 [PMID: [27664799](#) DOI: [10.1002/jmv.24693](#)]
- 17 **Kantala T**, Kinnunen PM, Oristo S, Jokelainen P, Vapalahti O, Maunula L. Hepatitis E Virus Antibodies in Finnish Veterinarians. *Zoonoses Public Health* 2017; **64**: 232-238 [PMID: [27621202](#) DOI: [10.1111/zph.12312](#)]
- 18 **Buescher G**, Ozga AK, Lorenz E, Pischke S, May J, Addo MM, Horvatits T. Hepatitis E seroprevalence and viremia rate in immunocompromised patients: a systematic review and meta-analysis. *Liver Int* 2021; **41**: 449-455 [PMID: [33034121](#) DOI: [10.1111/liv.14695](#)]
- 19 **Mrzljak A**, Dinjar-Kujundzic P, Vilibic-Cavlek T, Jemersic L, Prpic J, Dakovic-Rode O, Kolaric B, Vince A. Hepatitis E seroprevalence and associated risk factors in Croatian liver transplant recipients. *Rev Soc Bras Med Trop* 2019; **52**: e20190302 [PMID: [31618309](#) DOI: [10.1590/0037-8682-0302-2019](#)]
- 20 **Mrzljak A**, Dinjar-Kujundzic P, Knotek M, Kudumija B, Ilic M, Gulin M, Zibar L, Hrstic I, Jurekovic Z, Kolaric B, Jemersic L, Prpic J, Tomljenovic M, Vilibic-Cavlek T. Seroprevalence of hepatitis E in patients on haemodialysis in Croatia. *Int Urol Nephrol* 2020; **52**: 371-378 [PMID: [31894559](#) DOI: [10.1007/s11255-019-02363-3](#)]
- 21 **Dremsek P**, Wenzel JJ, John R, Ziller M, Hofmann J, Groschup MH, Werdermann S, Mohn U, Dorn S, Motz M, Mertens M, Jilg W, Ulrich RG. Seroprevalence study in forestry workers from eastern Germany using novel genotype 3- and rat hepatitis E virus-specific immunoglobulin G ELISAs. *Med Microbiol Immunol* 2012; **201**: 189-200 [PMID: [22179131](#) DOI: [10.1007/s00430-011-0221-2](#)]
- 22 **Sadkowska-Todys M**, Baumann-Popczyk A, Wnukowska N, Popczyk B, Kucharczyk B, Gołąb E. Occurrence and prevalence of selected zoonotic agents: *Echinococcus multilocularis*, *Trichinella spiralis* and hepatitis E virus (HEV) in the population of Polish hunters--results of the study conducted in 2010-2012. *Przegl Epidemiol* 2015; **69**: 673-678, 823 [PMID: [27139343](#)]
- 23 **Montagnaro S**, De Martinis C, Sasso S, Ciarcia R, Damiano S, Auletta L, Iovane V, Zottola T, Pagnini U. Viral and Antibody Prevalence of Hepatitis E in European Wild Boars (*Sus scrofa*) and Hunters at Zoonotic Risk in the Latium Region. *J Comp Pathol* 2015; **153**: 1-8 [PMID: [26025105](#) DOI: [10.1016/j.jcpa.2015.04.006](#)]
- 24 **Ivanova A**, Tefanova V, Reshetnjak I, Kuznetsova T, Geller J, Lundkvist Å, Janson M, Neare K, Velström K, Jokelainen P, Lassen B, Hütt P, Saar T, Viltrop A, Golovljova I. Hepatitis E Virus in Domestic Pigs, Wild Boars, Pig Farm Workers, and Hunters in Estonia. *Food Environ Virol* 2015; **7**: 403-412 [PMID: [26141050](#) DOI: [10.1007/s12560-015-9210-8](#)]
- 25 **Lange H**, Øverbø J, Borgen K, Dudman S, Hoddevik G, Urdahl AM, Vold L, Sjurseth SK. Hepatitis E in Norway: seroprevalence in humans and swine. *Epidemiol Infect* 2017; **145**: 181-186 [PMID: [27671461](#) DOI: [10.1017/S0950268816002144](#)]
- 26 **Yue N**, Wang Q, Zheng M, Wang D, Duan C, Yu X, Zhang X, Bao C, Jin H. Prevalence of hepatitis E virus infection among people and swine in mainland China: A systematic review and meta-analysis. *Zoonoses Public Health* 2019; **66**: 265-275 [PMID: [30884147](#) DOI: [10.1111/zph.12555](#)]
- 27 **Meng XJ**, Wiseman B, Elvinger F, Guenette DK, Toth TE, Engle RE, Emerson SU, Purcell RH. Prevalence of antibodies to hepatitis E virus in veterinarians working with swine and in normal blood donors in the United States and other countries. *J Clin Microbiol* 2002; **40**: 117-122 [PMID: [11773103](#) DOI: [10.1128/JCM.40.1.117-122.2002](#)]
- 28 **Hinjoy S**, Nelson KE, Gibbons RV, Jarman RG, Mongkolsirichaikul D, Smithsuwan P, Fernandez S, Labrique AB, Patchanee P. A cross-sectional study of hepatitis E virus infection in healthy people directly exposed and unexposed to pigs in a rural community in northern Thailand. *Zoonoses Public Health* 2013; **60**: 555-562 [PMID: [23280251](#) DOI: [10.1111/zph.12030](#)]
- 29 **Lassen B**, Janson M, Neare K, Tallo T, Reshetnjak I, Kuznetsova T, Viltrop A, Golovljova I, Jokelainen P. Prevalence of Antibodies Against Hepatitis E Virus in Veterinarians in Estonia. *Vector Borne Zoonotic Dis* 2017; **17**: 773-776 [PMID: [28933680](#) DOI: [10.1089/vbz.2017.2122](#)]
- 30 **Colson P**, Borentain P, Gérolami R. Hepatitis E virus as an agent of hepatocellular carcinoma. *Int J Infect Dis* 2019; **80**: 62-63 [PMID: [30634042](#) DOI: [10.1016/j.ijid.2018.12.015](#)]
- 31 **Kamar N**, Garrouste C, Haagsma EB, Garrigue V, Pischke S, Chauvet C, Dumortier J, Cannesson A, Cassuto-Viguiet E, Thervet E, Conti F, Lebray P, Dalton HR, Santella R, Kanaan N, Essig M, Mousson C, Radenne S, Roque-Afonso AM, Izopet J, Rostaing L. Factors associated with chronic hepatitis in patients with hepatitis E virus infection who have received solid organ transplants. *Gastroenterology* 2011; **140**: 1481-1489 [PMID: [21354150](#) DOI: [10.1053/j.gastro.2011.02.050](#)]
- 32 **Joon A**, Rao P, Shenoy SM, Baliga S. Prevalence of Hepatitis A virus (HAV) and Hepatitis E virus (HEV) in the patients presenting with acute viral hepatitis. *Indian J Med Microbiol* 2015; **33** Suppl: 102-105 [PMID: [25657123](#) DOI: [10.4103/0255-0857.150908](#)]

- 33 **Tulen AD**, Vennema H, van Pelt W, Franz E, Hofhuis A. A case-control study into risk factors for acute hepatitis E in the Netherlands, 2015-2017. *J Infect* 2019; **78**: 373-381 [PMID: [30738918](#) DOI: [10.1016/j.jinf.2019.02.001](#)]
- 34 **Meng QF**, You HL, Wang WL, Zhou N, Dong W, Cong W. Seroprevalence and risk factors of hepatitis E virus infection among children in China. *J Med Virol* 2015; **87**: 1573-1577 [PMID: [25940435](#) DOI: [10.1002/jmv.24203](#)]
- 35 **Vilibic-Cavlek T**, Vilibic M, Kolaric B, Jemersic L, Kucinar J, Barbic L, Bagaric A, Stevanovic V, Tabain I, Sviben M, Jukic V, Mlinaric-Galinovic G. Seroepidemiology of Hepatitis E in Selected Population Groups in Croatia: A Prospective Pilot Study. *Zoonoses Public Health* 2016; **63**: 494-502 [PMID: [26776465](#) DOI: [10.1111/zph.12254](#)]
- 36 **Mansuy JM**, Gallian P, Dimeglio C, Saune K, Arnaud C, Pelletier B, Morel P, Legrand D, Tiberghien P, Izopet J. A nationwide survey of hepatitis E viral infection in French blood donors. *Hepatology* 2016; **63**: 1145-1154 [PMID: [27008201](#) DOI: [10.1002/hep.28436](#)]
- 37 **La Fauci V**, Facciola A, Riso R, Calimeri S, Lo Giudice D, Squeri R. Seroprevalence of hev antibodies in a sample of pregnant women in the city of Messina. *Ann Ig* 2017; **29**: 232-238 [PMID: [28383615](#) DOI: [10.7416/ai.2017.2151](#)]
- 38 **Obaidat MM**, Roess AA. Seroprevalence and risk factors of Hepatitis E infection in Jordan's population: First report. *Int J Infect Dis* 2018; **66**: 121-125 [PMID: [29146513](#) DOI: [10.1016/j.ijid.2017.11.015](#)]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-3991568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
**Help Desk:** <https://www.f6publishing.com/helpdesk>  
<https://www.wjgnet.com>

