pathogens

MDPI

Editorial

Hepatitis E Virus (HEV) Infection among Humans and Animals: Epidemiology, Clinical Characteristics, Treatment, and Prevention

Jelena Prpić [1,*] and Magdalena Baymakova [2,*]

[1] Croatian Veterinary Institute, Savska Cesta 143, 10000 Zagreb, Croatia
[2] Department of Infectious Diseases, Military Medical Academy, 1606 Sofia, Bulgaria
* Correspondence: balatinec@veinst.hr (J.P.); dr.baymakova@gmail.com (M.B.)

The public health significance of hepatitis E is very important. According to the World Health Organization (WHO), there are an estimated 20 million hepatitis E virus (HEV) infections worldwide every year, leading to an estimated 3.3 million symptomatic cases of hepatitis E [1]. The WHO estimates that HEV infection caused approximately 44,000 deaths in 2015, which represents 3.3% of mortality rates due to viral hepatitis [1]. The HEV was identified in 1983 by a Soviet (Russian) scientific group with team leader Mikhail S. Balayan [2]. For years, the HEV was believed to be endemic in places with poor biosecurity and hygiene measures, and was therefore considered to be travel-related. Nowadays, the HEV represents an emerging zoonotic infection in many European countries [1]. It is estimated that 5–15% of all acute viral hepatitis infections of unknown origin in Europe are caused by the HEV [1].

The HEV is a single-stranded positive-sense RNA virus [3]. According to the last classification released in 2022 on the International Committee on Taxonomy of Viruses (ICTV), the HEV is classified in the *Hepeviridae* family (divided in two subfamilies: *Orthohepevirinae* and *Parahepevirinae*) [3,4]. The *Orthohepevirinae* subfamily includes four genera: *Avihepevirus* genus (member species: *Avihepevirus egretti* and *Avihepevirus magniiecur*), *Chirohepevirus* genus (member species: *Chirohepevirus desmodi*, *Chirohepevirus eptesici*, and *Chirohepevirus rhinolophi*), *Paslahepevirus* genus (member species: *Paslahepevirus alci* and *Paslahepevirus balayani*), and *Rocahepevirus* genus (member species: *Rocahepevirus eothenomi* and *Rocahepevirus ratti*) [3]. The *Parahepevirinae* subfamily includes only one genus—*Piscihepevirus heenan* species (cut-throat trout virus) [5]. *Avihepevirus magniiecur* species (avian HEV) was detected only in birds and its strains have been divided into four genotypes: genotype 1 (gt 1) is restricted to Australia; gt 2 and gt 3 have been detected in Asia, Europe, and the USA; and gt 4 has been found in Asia and Hungary [6–12]. The *Chirohepevirus* genus (bat HEV) was found only in bats with no scientific evidence of transmission to humans [13]. The *Paslahepevirus* genus has a different host range (humans, domestic, and wild mammals) [14]. *Paslahepevirus balayani* species have been assigned to eight genotypes: HEV gt 1 (humans; Southern Asia), HEV gt 2 (humans; Africa and Mexico), HEV gt 3 and HEV gt 4 (bottlenose dolphins, cattle, deer, goats, humans, pigs, rabbits, rats, sheep, etc.; America, Asia, and Europe), HEV gt 5 and HEV gt 6 (wild boars; Japan), HEV gt 7 (*Camelus dromedarius*, human; United Arab Emirates), and HEV gt 8 (*Camelus bactrianus*; China) [14–25]. The *Rocahepevirus* genus (rat HEV/ferret HEV/vole HEV) was found in rodents, shrews, and carnivores [3]. *Rocahepevirus ratti* species (gt C1) were detected in eulipotyphlids (musk shrew, *Suncus murinus*), humans, and rodents (*Bandicota indica*, *Rattus* sp.) [26–33]. *Rocahepevirus ratti* species (gt C2) were found among mustelids (ferret, mink, etc.) [34,35].

The HEV often presents undetectable viral pathology in infected organisms (among humans and/or animals). Usually, the viral load remains low, and viral shedding is shorter (acute HEV infection) or longer (chronic HEV infection) [36]. In immunocompetent persons under the age of 50 years, acute HEV infection is asymptomatic and takes a mild clinical form or moderate clinical form in comparison with individuals over 50 years of

Citation: Prpić, J.; Baymakova, M. Hepatitis E Virus (HEV) Infection among Humans and Animals: Epidemiology, Clinical Characteristics, Treatment, and Prevention. *Pathogens* **2023**, *12*, 931. https://doi.org/10.3390/pathogens12070931

Received: 6 July 2023
Accepted: 11 July 2023
Published: 12 July 2023

age; the severe clinical form is more often observed in them [36]. Chronic HEV infection is rare and is most commonly reported in immunosuppressed and immunocompromised persons (patients with solid organ transplantation; hematologic malignancy patients; HIV-positive individuals; inflammatory bowel disease patients; persons with rheumatic diseases; etc.) [36]. Numerous monitoring studies have been performed in Europe in the past in order to determine HEV circulation in the animal population. Domestic pigs and wild boars are considered the main reservoirs of the virus and a potential source of zoonotic transmissions based on serological and molecular results [37–42]. HEV infection is mainly transmitted through the consumption of contaminated food or water [43]. Direct contact transmission has been demonstrated in domestic pigs [44,45]. There are reports available that associate HEV infection with the consumption of raw or undercooked food products of pigs, wild boar, deer, or contaminated shellfish [46–49]. In comparison with the general population, a statistically higher seroprevalence is found in pig farmeers and veterinarians [50]. This suggests that contact exposure to domestic pigs may also be a risk factor.

The surveillance and control of HEV infection are very important around the world in order to decrease the knowledge gap in terms of its transmission and reservoirs, based on its zoonotic potential. In recent years, the One Health approach has high popularity and importance for specialists working on the topic of the HEV. Human and veterinary scientists (physicians) increasingly recognize the importance of working together on important zoonoses such as HEV infection. Professionals from all fields of science are responsible for controlling and dealing with this infection. Of course, it is recommended that the efforts of scientists be supported by adequate and timely policies and programs led by international and national health authorities and organizations.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. World Health Organization (WHO). Hepatitis E. Available online: https://www.who.int/news-room/fact-sheets/detail/hepatitis-e (accessed on 5 July 2023).
2. Balayan, M.S.; Andjaparidze, A.G.; Savin skaya, S.S.; Ketiladze, E.S.; Braginsky, D.M.; Suavinov, A.P.; Poleschuk, V.F. Evidence for a virus in non-A, non-B hepatitis transmitted via the fecal-oral route. *Intervirology* **1983**, *20*, 23–31. [CrossRef]
3. International Committee on Taxonomy of Viruses (ICTV). Family: Hepeviridae. Available online: https://ictv.global/ (accessed on 5 July 2023).
4. Purdy, M.A.; Drexler, J.F.; Meng, X.-J.; Norder, H.; Okamoto, H.; Van der Poel, W.H.M.; Reuter, G.; de Souza, W.M.; Ulrich, R.G.; Smith, D.B. ICTV virus taxonomy profile: *Hepeviridae* 2022. *J. Gen. Virol.* **2022**, *103*, 001778. [CrossRef]
5. Batts, W.; Yun, S.; Hedrick, R.; Winton, J. A novel member of the family *Hepeviridae* from cutthroat trout (*Oncorhynchus clarkii*). *Virus Res.* **2011**, *158*, 116–123. [CrossRef] [PubMed]
6. Payne, C.J.; Ellis, T.M.; Plant, S.L.; Gregory, A.R.; Wilcox, G.E. Sequence data suggests big liver and spleen disease virus (BLSV) is genetically related to hepatitis E virus. *Vet. Microbiol.* **1999**, *68*, 119–125. [CrossRef]
7. Haqshenas, G.; Shivaprasad, H.L.; Woolcock, P.R.; Read, D.H.; Meng, X.J. Genetic identification and characterization of a novel virus related to human hepatitis E virus from chickens with hepatitis–splenomegaly syndrome in the United States. *J. Gen. Virol.* **2001**, *82*, 2449–2462. [CrossRef]
8. Haqshenas, G.; Huang, F.F.; Fenaux, M.; Guenette, D.K.; Pierson, F.W.; Larsen, C.T.; Shivaprasad, H.L.; Toth, T.E.; Meng, X.J. The putative capsid protein of the newly identified avian hepatitis E virus shares antigenic epitopes with that of swine and human hepatitis E viruses and chicken big liver and spleen disease virus. *J. Gen. Virol.* **2002**, *83*, 2201–2209. [CrossRef]
9. Huang, F.F.; Haqshenas, G.; Shivaprasad, H.L.; Guenette, D.K.; Woolcock, P.R.; Larsen, C.T.; Pierson, F.W.; Elvinger, F.; Toth, T.E.; Meng, X.J. Heterogeneity and seroprevalence of a newly identified avian hepatitis E virus from chickens in the United States. *J. Clin. Microbiol.* **2002**, *40*, 4197–4202. [CrossRef]
10. Bilic, I.; Jaskulska, B.; Basic, A.; Morrow, C.J.; Hess, M. Sequence analysis and comparison of avian hepatitis E viruses from Australia and Europe indicate the existence of different genotypes. *J. Gen. Virol.* **2009**, *90*, 863–873. [CrossRef] [PubMed]
11. Bányai, K.; Tóth, A.G.; Ivanics, E.; Glávits, R.; Szentpáli-Gavallér, K.; Dán, A. Putative novel genotype of avian hepatitis E virus, Hungary, 2010. *Emerg. Infect. Dis.* **2012**, *18*, 1365–1368. [CrossRef] [PubMed]
12. Zhang, X.; Bilic, I.; Troxler, S.; Hess, M. Evidence of genotypes 1 and 3 of avian hepatitis E virus in wild birds. *Virus Res.* **2017**, *228*, 75–78. [CrossRef] [PubMed]
13. Drexler, J.F.; Seelen, A.; Corman, V.M.; Fumie Tateno, A.; Cottontail, V.; Melim Zerbinati, R.; Gloza-Rausch, F.; Klose, S.M.; Adu-Sarkodie, Y.; Oppong, S.K.; et al. Bats worldwide carry hepatitis E virus-related viruses that form a putative novel genus within the family *Hepeviridae*. *J. Virol.* **2012**, *86*, 9134–9147. [CrossRef]

14. Smith, D.B.; Izopet, J.; Nicot, F.; Simmonds, P.; Jameel, S.; Meng, X.-J.; Norder, H.; Okamoto, H.; van der Poel, W.H.M.; Reuter, G.; et al. Update: Proposed reference sequences for subtypes of hepatitis E virus (*species Orthohepevirus A*). *J. Gen. Virol.* **2020**, *101*, 692–698. [CrossRef] [PubMed]
15. Zhao, C.; Ma, Z.; Harrison, T.J.; Feng, R.; Zhang, C.; Qiao, Z.; Fan, J.; Ma, H.; Li, M.; Song, A.; et al. A novel genotype of hepatitis E virus prevalent among farmed rabbits in China. *J. Med. Virol.* **2009**, *81*, 1371–1379. [CrossRef]
16. Lack, J.B.; Volk, K.; Van Den Bussche, R.A. Hepatitis E virus genotype 3 in wild rats, United States. *Emerg. Infect. Dis.* **2012**, *18*, 1268–1273. [CrossRef]
17. Izopet, J.; Dubois, M.; Bertagnoli, S.; Lhomme, S.; Marchandeau, S.; Boucher, S.; Kamar, N.; Abravanel, F.; Guérin, J.-L. Hepatitis E virus strains in rabbits and evidence of a closely related strain in humans, France. *Emerg. Infect. Dis.* **2012**, *18*, 1274–1281. [CrossRef] [PubMed]
18. Takahashi, M.; Nishizawa, T.; Nagashima, S.; Jirintai, S.; Kawakami, M.; Sonoda, Y.; Suzuki, T.; Yamamoto, S.; Shigemoto, K.; Ashida, K.; et al. Molecular characterization of a novel hepatitis E virus (HEV) strain obtained from a wild boar in Japan that is highly divergent from the previously recognized HEV strains. *Virus Res.* **2014**, *180*, 59–69. [CrossRef] [PubMed]
19. Woo, P.C.; Lau, S.K.; Teng, J.L.; Tsang, A.K.L.; Joseph, M.; Wong, E.Y.; Tang, Y.; Sivakumar, S.; Xie, J.; Bai, R.; et al. New hepatitis E virus genotype in camels, the Middle East. *Emerg. Infect. Dis.* **2014**, *20*, 1044–1048. [CrossRef]
20. Wu, J.; Si, F.; Jiang, C.; Li, T.; Jin, M. Molecular detection of hepatitis E virus in sheep from Southern Xinjiang, China. *Virus Genes* **2015**, *50*, 410–417. [CrossRef] [PubMed]
21. Lee, G.-H.; Tan, B.-H.; Teo, E.C.; Lim, S.-G.; Dan, Y.-Y.; Wee, A.; Aw, P.P.K.; Zhu, Y.; Hibberd, M.L.; Tan, C.-K.; et al. Chronic infection with camelid hepatitis E virus in a liver transplant recipient who regularly consumes camel meat and milk. *Gastroenterology* **2016**, *150*, 355–357.e3. [CrossRef] [PubMed]
22. Huang, F.; Li, Y.; Yu, W.; Jing, S.; Wang, J.; Long, F.; He, Z.; Yang, C.; Bi, Y.; Cao, W.; et al. Excretion of infectious hepatitis E virus into milk in cows imposes high risks of zoonosis. *Hepatology* **2016**, *64*, 350–359. [CrossRef]
23. Di Martino, B.; Di Profio, F.; Melegari, I.; Sarchese, V.; Robetto, S.; Marsilio, F.; Martella, V. Detection of hepatitis E virus (HEV) in goats. *Virus Res.* **2016**, *225*, 69–72. [CrossRef]
24. Woo, P.C.; Lau, S.K.P.; Teng, J.L.; Cao, K.-Y.; Wernery, U.; Schountz, T.; Chiu, T.H.; Tsang, A.K.; Wong, P.-C.; Wong, E.Y.; et al. New hepatitis e virus genotype in Bactrian camels, Xinjiang, China, 2013. *Emerg. Infect. Dis.* **2016**, *22*, 2219–2221. [CrossRef] [PubMed]
25. Montalvo Villalba, M.C.; Cruz Martínez, D.; Ahmad, I.; Rodriguez Lay, L.A.; Bello Corredor, M.; Guevara March, C.; Martínez, L.S.; Martínez-Campo, L.S.; Jameel, S. Hepatitis E virus in bottlenose dolphins *Tursiops truncatus*. *Dis. Aquat. Org.* **2017**, *123*, 13–18. [CrossRef]
26. Johne, R.; Plenge-Bönig, A.; Hess, M.; Ulrich, R.G.; Reetz, J.; Schielke, A. Detection of a novel hepatitis E-like virus in faeces of wild rats using a nested broad-spectrum RT-PCR. *J. Gen. Virol.* **2010**, *91*, 750–758. [CrossRef]
27. Purcell, R.H.; Engle, R.E.; Rood, M.P.; Kabrane-Lazizi, Y.; Nguyen, H.T.; Govindarajan, S.; St Claire, M.; Emerson, S.U. Hepatitis E virus in rats, Los Angeles, California, USA. *Emerg. Infect. Dis.* **2011**, *17*, 2216–2222. [CrossRef] [PubMed]
28. Johne, R.; Dremsek, P.; Kindler, E.; Schielke, A.; Plenge-Bönig, A.; Gregersen, H.; Wessels, U.; Schmidt, K.; Rietschel, W.; Groschup, M.H.; et al. Rat hepatitis E virus: Geographical clustering within Germany and serological detection in wild Norway rats (*Rattus norvegicus*). *Infect. Genet. Evol.* **2012**, *12*, 947–956. [CrossRef]
29. Sridhar, S.; Yip, C.C.Y.; Wu, S.; Cai, J.; Zhang, A.J.; Leung, K.-H.; Chung, T.W.H.; Chan, J.F.W.; Chan, W.-M.; Teng, J.L.L.; et al. Rat hepatitis E virus as cause of persistent hepatitis after liver transplant. *Emerg. Infect. Dis.* **2018**, *24*, 2241–2250. [CrossRef] [PubMed]
30. Andonov, A.; Robbins, M.; Borlang, J.; Cao, J.; Hatchette, T.; Stueck, A.; Deschaumbault, Y.; Murnaghan, K.; Varga, J.; Johnston, B. Rat hepatitis e virus linked to severe acute hepatitis in an immunocompetent patient. *J. Infect. Dis.* **2019**, *220*, 951–955. [CrossRef] [PubMed]
31. Reuter, G.; Boros, A.; Pankovics, P. Review of hepatitis e virus in rats: Evident risk of species *Orthohepevirus C* to human zoonotic infection and disease. *Viruses* **2020**, *12*, 1148. [CrossRef] [PubMed]
32. Sridhar, S.; Yip, C.C.; Wu, S.; Chew, N.F.; Leung, K.H.; Chan, J.F.; Zhao, P.S.; Chan, W.M.; Poon, R.W.; Tsoi, H.W.; et al. Transmission of rat hepatitis E virus infection to humans in Hong Kong: A clinical and epidemiological analysis. *Hepatology* **2021**, *73*, 10–22. [CrossRef] [PubMed]
33. Rivero-Juarez, A.; Frias, M.; Perez, A.B.; Pineda, J.A.; Reina, G.; Fuentes-Lopez, A.; Freyre-Carrillo, C.; Ramirez-Arellano, E.; Alados, J.C.; Rivero, A. Orthohepevirus C infection as an emerging cause of acute hepatitis in Spain: First report in Europe. *J. Hepatol.* **2022**, *77*, 326–331. [CrossRef] [PubMed]
34. Raj, V.S.; Smits, S.L.; Pas, S.D.; Provacia, L.B.; Moorman-Roest, H.; Osterhaus, A.D.; Haagmans, B.L. Novel hepatitis E virus in ferrets, the Netherlands. *Emerg. Infect. Dis.* **2012**, *18*, 1369–1370. [CrossRef] [PubMed]
35. Krog, J.S.; Breum, S.O.; Jensen, T.H.; Larsen, L.E. Hepatitis E virus variant in farmed mink, Denmark. *Emerg. Infect. Dis.* **2013**, *19*, 2028–2030. [CrossRef]
36. European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines on hepatitis E virus infection. *J. Hepatol.* **2018**, *68*, 1256–1271. [CrossRef]
37. Jemeršić, L.; Prpić, J.; Brnić, D.; Keros, T.; Pandak, N.; Dakovic Rode, O. Genetic diversity of hepatitis E virus (HEV) strains derived from humans, swine and wild boars in Croatia from 2010 to 2017. *BMC Infect. Dis.* **2019**, *19*, 269. [CrossRef] [PubMed]
38. Prpić, J.; Černi, S.; Škorić, D.; Keros, T.; Brnić, D.; Cvetnić, Z.; Jemeršić, L. Distribution and molecular characterization of hepatitis E virus in domestic animals and wildlife in Croatia. *Food Environ. Virol.* **2015**, *7*, 195–205. [CrossRef] [PubMed]

39. Jemeršić, L.; Keros, T.; Maltar, L.; Barbić, L.; Čavlek, T.V.; Jeličić, P.; Dakovic-Rode, O.; Prpić, J. Differences in hepatitis E virus (HEV) presence in naturally infected seropositive domestic pigs and wild boars—An indication of wild boars having an important role in HEV epidemiology. *Vet. Arhi* **2017**, *87*, 651–663. [CrossRef]
40. Tsachev, I.; Baymakova, M.; Dimitrov, K.K.; Gospodinova, K.; Marutsov, P.; Pepovich, R.; Kundurzhiev, T.; Ciccozzi, M.; Dalton, H.R. Serological evidence of hepatitis E virus infection in pigs from Northern Bulgaria. *Vet. Ital.* **2021**, *57*, 155–159. [CrossRef]
41. Tsachev, I.; Baymakova, M.; Marutsov, P.; Gospodinova, K.; Kundurzhiev, T.; Petrov, V.; Pepovich, R. Seroprevalence of hepatitis E virus infection among wild boars in Western Bulgaria. *Vector-Borne Zoonotic Dis.* **2021**, *21*, 441–445. [CrossRef]
42. Tsachev, I.; Baymakova, M.; Pepovich, R.; Palova, N.; Marutsov, P.; Gospodinova, K.; Kundurzhiev, T.; Ciccozzi, M. High seroprevalence of hepatitis E virus infection among East Balkan swine (*Sus scrofa*) in Bulgaria: Preliminary Results. *Pathogens* **2020**, *9*, 911. [CrossRef] [PubMed]
43. Yugo, D.M.; Meng, X.-J. Hepatitis E virus: Foodborne, waterborne and zoonotic transmission. *Int. J. Environ. Res. Public Health* **2013**, *10*, 4507–4533. [CrossRef] [PubMed]
44. Andraud, M.; Dumarest, M.; Cariolet, R.; Aylaj, B.; Barnaud, E.; Eono, F.; Pavio, N.; Rose, N. Direct contact and environmental contaminations are responsible for HEV transmission in pigs. *Veter-Res.* **2013**, *44*, 102. [CrossRef] [PubMed]
45. Kasorndorkbua, C.; Guenette, D.K.; Huang, F.F.; Thomas, P.J.; Meng, X.-J.; Halbur, P.G. Routes of transmission of swine hepatitis E virus in pigs. *J. Clin. Microbiol.* **2004**, *42*, 5047–5052. [CrossRef] [PubMed]
46. Said, B.; Ijaz, S.; Kafatos, G.; Booth, L.; Thomas, H.L.; Walsh, A.; Ramsay, M.; Morgan, D. Hepatitis E outbreak on cruise ship. *Emerg. Infect. Dis.* **2009**, *15*, 1738–1744. [CrossRef]
47. Tamada, Y.; Yano, K.; Yatsuhashi, H.; Inoue, O.; Mawatari, F.; Ishibashi, H. Consumption of wild boar linked to cases of hepatitis E. *J. Hepatol.* **2004**, *40*, 869–870. [CrossRef]
48. Tei, S.; Kitajima, N.; Takahashi, K.; Mishiro, S. Zoonotic transmission of hepatitis E virus from deer to human beings. *Lancet* **2003**, *362*, 371–373. [CrossRef]
49. Yazaki, Y.; Mizuo, H.; Takahashi, M.; Nishizawa, T.; Sasaki, N.; Gotanda, Y.; Okamoto, H. Sporadic acute or fulminant hepatitis E in Hokkaido, Japan, may be food-borne, as suggested by the presence of hepatitis E virus in pig liver as food. *J. Gen. Virol.* **2003**, *84*, 2351–2357. [CrossRef]
50. Krumbholz, A.; Mohn, U.; Lange, J.; Motz, M.; Wenzel, J.J.; Jilg, W.; Walther, M.; Straube, E.; Wutzler, P.; Zell, R. Prevalence of hepatitis E virus-specific antibodies in humans with occupational exposure to pigs. *Med. Microbiol. Immunol.* **2012**, *201*, 239–244. [CrossRef]