Review
J Vet Sci 2016, 17(1), 1-11 · http://dx.doi.org/10.4142/jvs.2016.17.1.1

Hepatitis E virus as an emerging zoonotic pathogen

Woo-Jung Park[1], Byung-Joo Park[1], Hee-Seop Ahn[1], Joong-Bok Lee[1], Seung-Yong Park[1], Chang-Seon Song[1], Sang-Won Lee[1], Han-Sang Yoo[2], In-Soo Choi[1,*]

[1]*Department of Infectious Diseases, College of Veterinary Medicine, Konkuk University, Seoul 05029, Korea*
[2]*Department of Infectious Diseases, College of Veterinary Medicine, Seoul National University, Seoul 08826, Korea*

Hepatitis E outbreaks are a serious public health concern in developing countries. The disease causes acute infections, primarily in young adults. The mortality rate is approximately 2%; however, it can exceed 20% in pregnant women in some regions in India. The causative agent, hepatitis E virus (HEV), has been isolated from several animal species, including pigs. HEV genotypes 3 and 4 have been isolated from both humans and animals, and are recognized as zoonotic pathogens. Seroprevalence studies in animals and humans indirectly suggest that HEV infections occur worldwide. The virus is primarily transmitted to humans via undercooked animal meats in developed countries. Moreover, transfusion- and transplantation-mediated HEV infections have recently been reported. This review summarizes the general characteristics of hepatitis E, HEV infection status in animals and humans, the zoonotic transmission modes of HEV, and HEV vaccine development status.

Keywords: hepatitis E, hepatitis E virus, pig, transmission, zoonotic pathogen

Virological characteristics of hepatitis E virus

Hepatitis E virus (HEV) has been isolated from humans and several animal hosts, including pigs. A taxonomic scheme of the viral family was recently proposed to create a consensus classification based on the complete genome sequences of HEV isolates [102]. The family *Hepeviridae* comprises two genera: *Orthohepevirus* and *Piscihepevirus*. *Orthohepevirus* contains four species: *Orthohepevirus* A–D. *Orthohepevirus* A includes four major genotypes (HEV-1 to HEV-4) that infect humans, with HEV-1 and HEV-2 occurring only in humans. HEV-3 has been isolated from humans and several animal species including pigs. HEV-4 has been isolated from humans and pigs. It is proposed that additional genotypes including HEV-5 and HEV-6, which were recently identified in wild boars, and HEV-7, which was identified in camels, belong to *Orthohepevirus* A. HEV has a positive-sense single-stranded RNA genome with a cap and poly-(A) tail at its 5′ and 3′ ends, respectively. The HEV genome contains three open reading frames (ORFs) designated ORF1, ORF2, and ORF3 that encode nonstructural proteins including RNA-dependent RNA polymerase, a capsid protein, and a small protein, respectively [107].

Humans are generally infected with HEV via the oral route, and patients excrete many viruses in their feces. Hepatitis E outbreaks in human populations are usually associated with the consumption of feces-contaminated water, heavy rainfall, and flooding in developing countries [2]. Classical hepatitis E virus induces acute infection, but not the chronic infection observed in hepatitis B and C. Clinical signs of acute hepatitis E appear after two to six weeks of incubation. The major symptoms of hepatitis E are fever, nausea, abdominal pain, loss of appetite, vomiting, hepatomegaly, jaundice, itching, pale stools, and darkened urine [83]. Epidemiological studies indicate that most cases of hepatitis E occur in young adults (15–45 years old) [64]. The overall mortality rate of hepatitis E is approximately 2%, but can be more than 20% among pregnant women in some regions because of fulminant hepatic failure [64].

HEV infection in animal species

HEV genomic sequences were initially detected in 6% of the serum and fecal samples of pigs (3/47) in Nepal in 1995 [15]. That study also demonstrated HEV-specific antibodies in 33% of pigs (18/55), indicating HEV infections occur in pigs. Two years later, Meng *et al*. [81] proposed the term “swine HEV” and demonstrated a human HEV-like but distinct virus in pigs reared in the USA. Pigs naturally infected with swine HEV did not present any of the clinical signs observed in human patients.

Received 20 Jan. 2015, Revised 27 Jul. 2015, Accepted 22 Aug. 2015
*Corresponding author: Tel: +82-2049-6055; Fax: +82-3436-5880; E-mail: ischoi@konkuk.ac.kr
pISSN 1229-845X
eISSN 1976-555X

However, the infectivity of swine HEV was verified in pigs that developed viremia, replication intermediate (negative-sense antigenomic) RNA, seroconversion, and mild hepatitis. Only microscopic hepatitis characterized by mild multifocal lymphoplasmacytic hepatitis was observed in the liver tissues of HEV-infected pigs. That study also demonstrated the cross-reactivity of sera obtained from infected pigs with the capsid protein of human HEV strain, very high seroprevalence (80−100%) in pigs older than 3 months, and a high genetic homology between swine and human HEV strains. A subsequent study determined the seroprevalence of HEV in pig populations in two HEV-endemic countries (China and Thailand) and two HEV−non-endemic countries (Korea and Canada) [79]. The results showed that considerable proportions of pigs (20−90%) older than 3 to 4 months in all countries had anti-HEV IgG antibodies. Thus, the aforementioned studies indicate most HEV infections begin in 2 to 3-month-old pigs after weaning at about one month. Despite the small number of countries included in those studies, the results suggest hepatitis E is enzootic in pig populations in both endemic and non-endemic countries.

The cross-species infectivity of swine HEV was verified by experimental infection of non-human primates [80]. Two rhesus monkeys and a chimpanzee inoculated with swine HEV (genotype 3) exhibited evidence of viral replication, such as viremia, seroconversion, fecal viral shedding, and mild hepatitis with elevated serum alanine aminotransferase (ALT). Therefore, the possibility of human infection with swine HEV was proposed. Pregnant gilts were experimentally infected with swine HEV to reproduce fulminant hepatitis, which was observed in pregnant women living in some geographic regions of developing countries [58]. However, this failed to reproduce fulminant hepatitis and abortion.

The identification of swine HEV prompted the serological surveillance of HEV infections in several animal species. Animals evaluated in the United States showed the following seroprevalence rates: bison, 4.6%; cattle, 15%; dogs, 0.9%; Norway rats, 0.6%; farmed swine, 41.2%; and wild swine, 2.9% [23]. In contrast, cattle and dogs did not have anti-HEV antibodies, but 8.1% of cats harbored antibodies against HEV in Korea [103]. A recent seroprevalence study in China reported that 21.12% and 6.28% of dogs and cats have anti-HEV antibodies, respectively [71]. In India, 4.4 to 6.9% of cattle, 54.6 to 74.4% of pigs, 22.7% of dogs, and 2.1 to 21.5% of rodents have anti-HEV antibodies in their sera [5]. Although those authors did not detect antibodies against HEV in goat sera, a recent study reported serological evidence of infection of HEV-like agents in a goat population in the United States [97]. In addition to this indirect serological evidence of HEV infection, the identities of HEV or the HEV genome have been demonstrated in several animal species, including rabbits, chickens, deer, wild boars, mongooses, rats, bats, ferrets, camels, and trout [102].

Rabbit HEV was recently identified in China [121]. The full-length nucleotide sequences of two rabbit HEV isolates shared 74%, 73%, 78 to79%, 74 to75%, and 46 to 47% identity with genotypes 1, 2, 3, and 4, and avian HEV, respectively. That study reported the HEV seroprevalence in rabbits in China to be 57% (191/335). Additional analysis of full genome sequences of rabbit HEV isolates show that they have unique several characteristics, including an insertion of 31 amino acids in ORF1 (amino acids 927−957), which is never found in any isolate of HEV genotypes 1 to 4 [28]. Surprisingly, research rabbits including specific pathogen-free rabbits exhibited 40 to 50% of HEV seroprevalence in the United States [8]. These findings indicate rabbit HEV is widespread in rabbit farms and research facilities. Therefore, the effects of co-infection of rabbits with HEV and other pathogens need to be evaluated. Complete genome sequence analysis indicates rabbit HEV is closely related to HEV genotype 3 [19]. Rabbit HEV strains isolated from Mongolia share 80 to 97% identities with other rabbit HEV strains isolated from China, the USA, and France [47]. Hence, like other human and swine HEV isolates, variants of rabbit HEV appear to emerge in different geographic regions.

Rabbits infected with rabbit HEV do not show any clinical signs of hepatitis. However, they present with serologic and microscopic evidence of hepatitis with elevated serum ALT levels and local hepatocellular necrosis in the liver tissues [75]. In addition, specific pathogen free rabbits infected with rabbit HEV showed persistent fecal viral shedding for a long period, as well as chronic hepatitis and some degree of fibrosis [32]. The development of chronic hepatitis and fibrosis was never reported in other animals naturally or experimentally infected with HEV. Very interestingly, a recent study provided evidence of abortion, vertical transmission of HEV, and high rates of mortality in pregnant rabbits experimentally infected with rabbit HEV [116]. As mentioned above, pregnant pigs infected with swine HEV did not exhibit high mortality rates or reproductive failure. Therefore, these results indicate rabbits are a better animal model for studying HEV than pigs because they reproduce outcomes similar to those in HEV-infected patients.

Rabbit HEVs isolated in Mongolia efficiently replicated in a human lung cancer cell line (A549) and a hepatocarcinoma cell line (PLC/PRF/5) [47]. Rabbit HEV isolated in China also successfully infected cynomolgus macaques, which subsequently developed hepatitis [73]. They presented with elevated ALT, viremia, fecal viral shedding, and seroconversion. HEV amplification was identified in the kidneys, small intestine, spleen, and stomach of infected animals, indicating extrahepatic replication of rabbit HEV. Those experimental infections in human cell lines and non-human primates suggest rabbit HEV is another candidate zoonotic agent that can be transmitted to humans.

A novel HEV designated avian HEV was isolated from bile

Table 1. Nationwide HEV seroprevalence of human population

Population (n)	Year of report or study	Evaluation method (manufacturer)	Prevalence (%)	Reference
Korea (2,450)	2007–2009	ELISA (Wantai, China)	5.9	118
Japan (12,600)	2010	ELISA (In-house and Cosmic, Japan)	3.4	104
China (15,862)	2005–2006	ELISA (MP Biomedical, Singapore)	23.5	43
Hong Kong (450)	2008–2009	ELISA (Biotec Lab., UK)	28.7	13
USA (7,885)	2009–2010	ELISA (Diagnostic System, Italy)	6.0	21
Germany (1,019)	2014	ELISA (*recom*Well, Germany)	6.8	47
England (2,731)	1991, 2004	ELISA (Fortress Diagnostics, Northern Ireland)	13.0	40
Austria (997)	2009	ELISA (Fortress Diagnostics, Northern Ireland)	14.3	64

ELISA, enzyme-linked immunosorbent assay.

samples of chickens with hepatitis-splenomegaly syndrome in the United States [33]. The nucleotide sequence of the capsid protein of avian HEV shared 57 to 60% identity with those of other HEV strains. In a subsequent study, approximately 71% of chicken flocks and 30% of chickens in California, Colorado, Connecticut, Virginia, and Wisconsin in the United States were positive for HEV antibodies [38]. In that study, 11 additional avian HEVs were isolated from chickens exhibiting hepatitis-splenomegaly syndrome. Their nucleotide sequences were 78 to 100% homologous with each other and 56 to 61% with other strains of human and swine HEV. The seroprevalence rates of avian HEV in Korea were comparable to those in the United States [65]. In Korea, 57% of chicken flocks and 28% of chickens were found to be positive for antibodies against avian HEV. These studies imply avian HEV infections are prevalent in chicken flocks, at least in these two countries. Phylogenetic analysis classified avian HEV isolates into genotype 1 (Australia), genotype 2 (USA), and genotype 3 (Europe) [7]. Rhesus monkeys as a human surrogates were experimentally inoculated with avian HEV to identify the cross-species infectivity [39], but no evidence of virus infection was observed; *i.e.*, they did not show viremia, seroconversion, fecal viral shedding, or increased serum liver enzyme. Therefore, unlike swine and rabbit HEV, avian HEV does not appear to be transmissible to humans.

HEV infection in humans

Hepatitis E has historically been referred to as enterically transmitted non-A, non-B hepatitis. The disease frequently causes endemics and outbreaks in developing countries in Asia and Africa [2]. HEV infection status in human populations has primarily been assessed in Asia, America, and Europe. HEV seroprevalence in China, Korea, and Japan is approximately 20 to 30%, 12 to 20%, and 6.0%, respectively [3,13,14,22,109]. Analysis of seroprevalence revealed several characteristics of hepatitis E, including a tendency toward increased seroprevalence with age. The detection rate of anti-HEV antibodies in children younger than 10 years is approximately 8%, whereas that in individuals above 60 years old is 21 to 56% in Hong Kong and eastern China [13,22]. The HEV seroprevalence in England and Germany is approximately 13 to 17%, with the highest prevalence occurring in individuals aged above 50 to 60 years [24,42]. Similarly, more than 16% of American blood donors harbor anti-HEV antibodies, and this amount increases with age [118].

However, a recent re-evaluation of HEV seroprevalence in large populations in both developing and developed countries revealed they have decreased dramatically in most countries when compared to previous studies (Table 1). There are several possible reasons for the higher seroprevalence in previous studies, including relatively small sample sizes, limited study areas, different detection kits, and different analytic methods [21]. Nevertheless, those studies commonly report an age-dependent increase of HEV seroprevalence in most countries [13,21,42,45,49,106,120]. Therefore, the higher HEV seroprevalence in elderly than younger people implies subclinical HEV infections might increase with age.

Interestingly, very high mortality rates (up to 66%) are identified in HEV-infected pregnant women in certain regions of India [46,63,86]. Most of these women suffer from fulminant hepatic failure and have significantly higher viral load than non-pregnant women [57]. In contrast, the mortality rate of HEV-infected pregnant women in Egypt does not differ significantly from that of non-pregnant women, despite their very high anti-HEV prevalence rate [104]. Several plausible factors may explain these discrepancies, such as less-virulent HEV strains circulating in that region and long-lasting immunity acquired by HEV exposure at an early age. However, more data are required to draw conclusions about these intriguing consequences of HEV infections in pregnant women.

Risk factors for HEV infection

Hepatitis E was previously thought to be an endemic disease

in developing countries without a clean water supply system. Sporadic cases of HEV infection in developed countries were mainly attributed to travel to HEV-endemic developing countries [1,11]. Such individuals were assumed to be infected by drinking contaminated water during travel. However, autochthonous HEV infections are increasingly being reported in industrialized countries [90]. The precise sources of infection for the autochthonous cases are currently unknown, but several risk factors associated with those HEV infections have recently been suggested [12].

The prevalence of anti-HEV antibodies was evaluated to assess the relationship between HEV infection risk and occupation. Accordingly, farmers have a significantly higher HEV seroprevalence than other occupations in China (34.4%) [45]. The seroprevalence of HEV is approximately 1.5 times higher in veterinarians working on swine than in normal blood donors in the United States [82]. In addition, the risk of HEV infection of swine farmers is reported to be 3.5-fold higher than that in the general population in rural Taiwan [68]. Moreover, the seroprevalence of HEV-reactive antibodies is higher in swine-exposed humans such as those working in slaughterhouses, meat inspectors, swine farmers, and veterinarians than in control blood donors in Germany and Spain [26,62]. Of note, individuals working in slaughterhouses are reported to have the highest seroprevalence (41.7%). These results indicate individuals who work with pigs or in close contact with animals have a higher risk of HEV infection than those who do not.

In contrast, some authors recently argued that the HEV seroprevalence rates of people exposed to pigs are not significantly higher than those of people not exposed to pigs in Northern Thailand and Austria [37,66]. More interestingly, women working on swine farms have lower HEV infection rates than the general population in Guangdong province in China [72]. These studies suggest occupations involving pigs and coming into contact with animals are not the main risk factors for HEV infection. Accordingly, more studies are required to resolve this controversy regarding the occupation-related risk factors for HEV infection.

The following evidence provides important clues about the cause of autochthonous HEV infection. HEV sequences isolated from patients with hepatitis E are almost identical to or closely related to sequences of swine HEV strains [9,10,25,113]. Furthermore, swine HEV sequences have been detected in sera obtained from indigenous patients in the Netherlands who had never traveled to HEV-endemic countries [35]. Similarly, indigenous cases of acute hepatitis E infection due to the consumption of pork meat and entrails have occurred in Japan [84]. These autochthonous infections predominantly occurred in middle-aged or elderly men who usually consumed pork [20,87]. A few cases of HEV infection acquired by eating undercooked or uncooked pork have been reported in other countries. Therefore, pigs are now recognized as the main risk factor for HEV infections in people in developed countries.

In addition, pork liver sausage and wild boar are acknowledged as important risk factors for HEV infection in European countries [67]. Pork liver sausage appears to contribute significantly to HEV infection in France [17]. HEV present in pork liver sausage infected a human hepatocarcinoma cell line, suggesting the possibility of HEV infection via consumption of these sausages [6]. A case of acute hepatitis E infection was reported in an individual who consumed raw bile juice from a wild boar in Korea [59]. The causative agent isolated from the wild boar was HEV-4. HEV transmission to humans may also occur through the consumption of meat from other animals. HEV-3 isolates are commonly detected in humans and animals including swine, deer, and wild boars in Hungary [92]. Interestingly, the same HEV sequences were identified in both humans and roe deer. HEV isolated from wild boars in Japan have almost the same nucleotide sequence as HEV isolated from deer and hepatitis E patients who ate raw deer meat [105]. These data indicate interspecies transmission of HEV is possible, and that wild boars and deer play an important role in the transmission of HEV to humans.

HEV genomes and infectious HEV particles have been reported in wastewater samples [48,76,88], and this wastewater probably contaminates seawater and shellfish. Indeed, an HEV-3 strain was isolated from seawater in Japan, and its sequence was very similar to that of human strains [43]. An estimated 4 million people annually are infected with hepatitis A and E viruses as a result of the consumption of raw or lightly steamed shellfish harvested from polluted seawater [101]. Approximately 18% of shellfish samples collected from a coastal area of China were contaminated with 16 strains of HEV-4, which were closely related to swine and human strains [27]. In addition, 8.7% of oysters collected from coastal regions in Korea were contaminated with HEV and their nucleotide sequences were very similar to those of swine HEV [103]. Several cases in developed countries confirm that eating raw shellfish is a major cause of HEV infections in humans [60,67,91]. Collectively, these findings suggest that most HEV transmissions are mediated by the consumption of animal meats, meat products, and seafood, particularly in developed countries.

Traditional HEV transmission is well known to occur via the fecal-oral route. However, it has also been suggested that blood transfusion plays an important role in HEV transmission in HEV-endemic countries [4]. This suggestion was based on evidence of the appearance of HEV-specific antibodies and increased levels of ALT in some HEV-negative recipients after blood transfusion. Transfusion-associated hepatitis E infections have been confirmed in rhesus monkeys that developed acute hepatitis after plasma transfusion from hepatitis E-viremic donors [117]. Autochthonous HEV infections have recently been reported in developed countries where HEV is not

endemic. These infections may be due to blood transfusion-mediated transmission. Indeed, some blood recipients have actually been infected with HEV via blood transfusion [34,36,77]. Most HEV infections occur primarily in young adults aged 15 to 45 years in HEV-endemic regions [16]. However, a few studies suggest that children can be infected with HEV via blood transfusion [18,41]. Therefore, blood transfusion is now recognized as a new risk factor for HEV transmission.

Chronic hepatitis E

Immunosuppressed patients exhibit a tendency to develop chronic or persistent HEV infection [53]. Persistent HEV infection has also been reported in a patient with T-cell lymphoma who did not produce antibodies against HEV because of lymphoma and chemotherapy [108]. Accordingly, the absence of HEV-specific antibodies is one possible reason for the long-term HEV infection in this patient. Furthermore, chronic HEV infection was observed in a patient concurrently infected with human immunodeficiency virus (HIV) [44,50]. Other authors have proposed that solid organ transplantations can enhance the development of chronic hepatitis E and cirrhosis [52,93]. The incidence of chronic hepatitis E is higher in liver transplant recipients than normal control groups [29,31,89]. Similarly, many chronic hepatitis E patients are kidney or heart transplant recipients [61,85]. The factors associated with the development of chronic hepatitis E in solid organ recipients were analyzed from relatively large numbers of clinic records [53]. The treatment of solid organ recipients with the immunosuppressive drug tacrolimus but not cyclosporine A was strongly associated with the induction of chronic hepatitis E [53]. The effects of immunosuppressive drugs including steroids, tacrolimus, cyclosporine A, and mycophenolic acid (MPA) on HEV replication were further evaluated *in vitro* with the human hepatoma cell line Huh7 [111]. A high dose of tacrolimus, a T-cell–specific immunosuppressant, enhanced HEV infection, whereas steroids did not influence HEV infection in liver cells. These findings suggest that suppression of the T-cell–mediated immune response is an important reason that increases the development of chronic hepatitis E in solid organ recipients.

HEV treatment

Reduction of immunosuppressive therapy is clinically recommended to resolve chronic HEV infection [53,61,85]. However, some chronic hepatitis E patients are unresponsive to such reductions and require applicable antiviral drugs. Pegylated interferon-α-2a (Peg-IFN-α-2a) and Peg-IFN-α-2b have been successfully used to treat chronic HEV infection in liver transplantation patients [30,55]. Peg-IFN-α-2a has also been administered to chronic hepatitis E patients who developed the disease after kidney transplantation [51]. As a result, Peg-IFN therapy inhibited HEV replication in the majority of these chronic hepatitis patients. Ribavirin is another antiviral drug that may cure chronic hepatitis E [56]. The effects of ribavirin monotherapy were evaluated in 59 solid-organ transplant recipients who developed chronic HEV infections [54]. This treatment resulted in HEV clearance in 95% of the patients' sera. HEV RNA could not be detected in 78% of the patients at least 6 months after stopping ribavirin therapy. A recent study demonstrated that MPA, an inhibitor of inosine monophosphate dehydrogenase, inhibits HEV replication in Huh7 cells [111]. That study also demonstrates that combined therapy with MPA and ribavirin more effectively suppresses HEV replication than MPA or ribavirin alone. Therefore, these therapeutic drugs may be administered to hepatitis E patients.

HEV vaccine

The HEV capsid protein encoded by ORF2 plays an important role in protection against HEV infection and interaction with host cells [40]. It was suggested that several neutralizing antibody epitopes might be present in the capsid protein [78,99]. Subsequent studies indicate that most neutralizing antibody epitopes are concentrated in the E2s domain, which is a protruding domain in the HEV capsid protein [69,119]. Although several experimental HEV vaccines have been developed, only one was recently approved after a successful phase III clinical trial in China [114]. This vaccine was generated in *Escherichia coli* as a virus-like particle (VLP) comprising the E2 domain of HEV-1 capsid protein [70]. Its efficacy was 100% after the administration of three doses in the general population. The same degree of efficacy without any side effects was achieved in pregnant women [115,122]. Furthermore, the vaccine's efficacy was demonstrated in non-human primates by protection against the heterologous HEV-4 as well as the homologous HEV-1 [70]. The vaccine was recently demonstrated to contain neutralizing antibody epitopes on the VLP surface that may be involved in the VLP's high prophylactic efficacy [112].

Another HEV vaccine has been developed, and its safety and efficacy were evaluated in a phase II clinical trial in Nepal [100]. The vaccine was generated from insect cells infected with recombinant baculovirus expressing a truncated capsid protein of HEV-1 Pakistani strain [94]. The recombinant protein vaccine was demonstrated to be effective in non-human primates and humans in pre-clinical studies [95,110]. In the phase II clinical trial, the efficacy of the recombinant capsid protein vaccine was 95.5% after the administration of three doses [100]. Serologically, 100% of subjects developed at least 20 Walter Reed antibody units of anti-HEV antibodies per milliliter of sera. It was speculated that this high antibody

response could protect subjects from HEV infections.

Because HEV infections are widespread among animal species, the only possible means to interrupt the transmission of HEV from animals to humans is effective animal HEV vaccines. A vaccine made up of a single genotype would provide cross-protection efficacy against different genotypes of HEV. Indeed, pigs infected with genotype 3 swine HEV were protected from subsequent infections with genotype 3 human and swine HEV, and genotype 4 human HEV 12 weeks later [96]. However, pigs immunized with N-truncated capsid proteins originating from swine, rat, and avian HEV were not completely protected from challenge with human HEV-3 [98]. These findings suggest that capsid protein alone cannot provide complete cross-protection of pigs from challenge by different genotypes. However, rabbits immunized with HEV 239 vaccine developed with the capsid protein of HEV-1 were completely protected from swine HEV-4 and rabbit HEV with high titers of anti-HEV antibodies [74]. Therefore, a human HEV 239 vaccine is an alternative measure for the prevention of HEV infections in rabbits. However, the development of HEV vaccines that provide complete cross-species protection to pigs requires further research.

Conclusion

Hepatitis E is now recognized as an emerging zoonosis. The seroprevalence and isolation of HEV indicate that HEV infections may be highly prevalent in both humans and animals. Most HEV infections in humans are mediated by the consumption of contaminated water and undercooked animal meats. Meanwhile, the blood transfusion-mediated transmission of HEV and the development of chronic hepatitis E in patients who receive solid organ transplantation are emerging issues. A prophylactic HEV vaccine for humans has been licensed and used in China. The development of more efficient HEV vaccines for uses in both humans and animals can be expected. Application of HEV vaccines to animals will contribute to suppression of HEV transmission from animals to humans.

Acknowledgments

This study was supported by Konkuk University in 2014.

Conflicts of Interest

There is no conflict of interest.

References

1. **Abid M, O'Brien SJ, Boxall EH, Skidmore SJ.** Hepatitis and travel abroad: a case report. J Travel Med 1997, **4**, 187-188.
2. **Aggarwal R.** Hepatitis E: epidemiology and natural history. J Clin Exp Hepatol 2013, **3**, 125-133.
3. **Ahn JM, Kang SG, Lee DY, Shin SJ, Yoo HS.** Identification of novel human hepatitis E virus (HEV) isolates and determination of the seroprevalence of HEV in Korea. J Clin Microbiol 2005, **43**, 3042-3048.
4. **Arankalle VA, Chobe LP.** Retrospective analysis of blood transfusion recipients: evidence for post-transfusion hepatitis E. Vox Sang 2000, **79**, 72-74.
5. **Arankalle VA, Joshi MV, Kulkarni AM, Gandhe SS, Chobe LP, Rautmare SS, Mishra AC, Padbidri VS.** Prevalence of anti-hepatitis E virus antibodies in different Indian animal species. J Viral Hepat 2001, **8**, 223-237.
6. **Berto A, Grierson S, Hakze-van der Honing R, Martelli F, Johne R, Reetz J, Ulrich RG, Pavio N, Van der Poel WHM, Banks M.** Hepatitis E virus in pork liver sausage, France. Emerg Infect Dis 2013, **19**, 264-266.
7. **Bilic I, Jaskulska B, Basic A, Morrow CJ, 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.
8. **Birke L, Cormier SA, You D, Stout RW, Clement C, Johnson M, Thompson H.** Hepatitis E antibodies in laboratory rabbits from 2 US vendors. Emerg Infect Dis 2014, **20**, 693-696.
9. **Borgen K, Herremans T, Duizer E, Vennema H, Rutjes S, Bosman A, de Roda Husman AM, Koopmans M.** Non-travel related hepatitis E virus genotype 3 infections in the Netherlands; a case series 2004-2006. BMC Infect Dis 2008, **8**, 61.
10. **Brost S, Wenzel JJ, Ganten TM, Filser M, Flechtenmacher C, Boehm S, Astani A, Jilg W, Zeier M, Schnitzler P.** Sporadic cases of acute autochthonous hepatitis E virus infection in Southwest Germany. J Clin Virol 2010, **47**, 89-92.
11. **Centers for Disease Control and Prevention (US).** Hepatitis E among U.S. travelers, 1989-1992. MMWR Morb Mortal Wkly Rep 1993, **42**, 1-4.
12. **Chaussade H, Rigaud E, Allix A, Carpentier A, Touzé A, Delzescaux D, Choutet P, Garcia-Bonnet N, Coursaget P.** Hepatitis E virus seroprevalence and risk factors for individuals in working contact with animals. J Clin Virol 2013, **58**, 504-508.
13. **Chiu DMY, Chan MCW, Yeung ACM, Ngai KLK, Chan PKS.** Seroprevalence of hepatitis E virus in Hong Kong, 2008-2009. J Med Virol 2013, **85**, 459-461.
14. **Choi IS, Kwon HJ, Shin NR, Yoo HS.** Identification of swine hepatitis E virus (HEV) and prevalence of anti-HEV antibodies in swine and human populations in Korea. J Clin Microbiol 2003, **41**, 3602-3608.
15. **Clayson ET, Innis BL, Myint KSA, Narupiti S, Vaughn DW, Giri S, Ranabhat P, Shrestha MP.** Detection of hepatitis E virus infections among domestic swine in the Kathmandu Valley of Nepal. Am J Trop Med Hyg 1995, **53**, 228-232.
16. **Clayson ET, Shrestha MP, Vaughn DW, Snitbhan R, Shrestha KB, Longer CF, Innis BL.** Rates of hepatitis E virus infection and disease among adolescents and adults in Kathmandu, Nepal. J Infect Dis 1997, **176**, 763-766.

17. **Colson P, Borentain P, Queyriaux B, Kaba M, Moal V, Gallian P, Heyries L, Raoult D, Gerolami R.** Pig liver sausage as a source of hepatitis E virus transmission to humans. J Infect Dis 2010, **202**, 825-834.
18. **Colson P, Coze C, Gallian P, Henry M, De Micco P, Tamalet C.** Transfusion-associated hepatitis E, France. Emerg Infect Dis 2007, **13**, 648-649.
19. **Cossaboom CM, Córdoba L, Cao D, Ni YY, Meng XJ.** Complete genome sequence of hepatitis E virus from rabbits in the United States. J Virol 2012, **86**, 13124-13125.
20. **Dalton HR, Thurairajah PH, Fellows HJ, Hussaini HS, Mitchell J, Bendall R, Banks M, Ijaz S, Teo CG, Levine DF.** Autochthonous hepatitis E in southwest England. J Viral Hepat 2007, **14**, 304-309.
21. **Ditah I, Ditah F, Devaki P, Ditah C, Kamath PS, Charlton M.** Current epidemiology of hepatitis E virus infection in the United States: low seroprevalence in the National Health and Nutrition Evaluation Survey. Hepatology 2014, **60**, 815-822.
22. **Dong C, Dai X, Shao JS, Hu K, Meng JH.** Identification of genetic diversity of hepatitis E virus (HEV) and determination of the seroprevalence of HEV in eastern China. Arch Virol 2007, **152**, 739-746.
23. **Dong C, Meng J, Dai X, Liang JH, Feagins AR, Meng XJ, Belfiore NM, Bradford C, Corn JL, Cray C, Glass GE, Gordon ML, Hesse RA, Montgomery DL, Nicholson WL, Pilny AA, Ramamoorthy S, Shaver DD, Drobeniuc J, Purdy MA, Fields HA, Kamili S, Teo CG.** Restricted enzooticity of hepatitis E virus genotypes 1 to 4 in the United States. J Clin Microbiol 2011, **49**, 4164-4172.
24. **Faber MS, Wenzel JJ, Jilg W, Thamm M, Höhle M, Stark K.** Hepatitis E virus seroprevalence among adults, Germany. Emerg Infect Dis 2012, **18**, 1654-1657.
25. **Fogeda M, Avellón A, Cilla CG, Echevarría JM.** Imported and autochthonous hepatitis E virus strains in Spain. J Med Virol 2009, **81**, 1743-1749.
26. **Galiana C, Fernández-Barredo S, García A, Gómez MT, Pérez-Gracia MT.** Occupational exposure to hepatitis E virus (HEV) in swine workers. Am J Trop Med Hyg 2008, **78**, 1012-1015.
27. **Gao S, Li D, Zha E, Zhou T, Wang S, Yue X.** Surveillance of hepatitis E virus contamination in shellfish in China. Int J Environ Res Public Health 2015, **12**, 2026-2036.
28. **Geng J, Fu H, Wang L, Bu Q, Liu P, Wang M, Sui Y, Wang X, Zhu Y, Zhuang H.** Phylogenetic analysis of the full genome of rabbit hepatitis E virus (rbHEV) and molecular biologic study on the possibility of cross species transmission of rbHEV. Infect Genet Evol 2011, **11**, 2020-2025.
29. **Haagsma EB, Niesters HGM, van den Berg AP, Riezebos-Brilman A, Porte RJ, Vennema H, Reimerink JHJ, Koopmans MPG.** Prevalence of hepatitis E virus infection in liver transplant recipients. Liver Transpl 2009, **15**, 1225-1228.
30. **Haagsma EB, Riezebos-Brilman A, van den Berg AP, Porte RJ, Niesters HGM.** Treatment of chronic hepatitis E in liver transplant recipients with pegylated interferon alpha-2b. Liver Transpl 2010, **16**, 474-477.
31. **Halac U, Béland K, Lapierre P, Patey N, Ward P, Brassard J, Houde A, Alvarez F.** Chronic hepatitis E infection in children with liver transplantation. Gut 2012, **61**, 597-603.
32. **Han J, Lei Y, Liu L, Liu P, Xia J, Zhang Y, Zeng H, Wang L, Wang L, Zhuang H.** SPF rabbits infected with rabbit hepatitis E virus isolate experimentally showing the chronicity of hepatitis. PLoS One 2014, **9**, e99861.
33. **Haqshenas G, Shivaprasad HL, Woolcock PR, Read DH, Meng XJ.** 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.
34. **Hauser L, Roque-Afonso AM, Beylouné A, Simonet M, Deau Fischer B, Burin des Roziers N, Mallet V, Tiberghien P, Bierling P.** Hepatitis E transmission by transfusion of intercept blood system-treated plasma. Blood 2014, **123**, 796-797.
35. **Herremans M, Vennema H, Bakker J, van der Veer B, Duizer E, Benne CA, Waar K, Hendrixks B, Schneeberger P, Blaauw G, Kooiman M, Koopmans MP.** Swine-like hepatitis E viruses are a cause of unexplained hepatitis in the Netherlands. J Viral Hepat 2007, **14**, 140-146.
36. **Hewitt PE, Ijaz S, Brailsford SR, Brett R, Dicks S, Haywood B, Kennedy ITR, Kitchen A, Patel P, Poh J, Russell K, Tettmar KI, Tossell J, Ushiro-Lumb I, Tedder RS.** Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. Lancet 2014, **384**, 1766-1773.
37. **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.
38. **Huang FF, Haqshenas G, Shivaprasad HL, Guenette DK, Woolcock PR, Larsen CT, Pierson FW, Elvinger F, Toth TE, Meng XJ.** Heterogeneity and seroprevalence of a newly identified avian hepatitis E virus from chickens in the United States. J Clin Microbiol 2002, **40**, 4197-4202.
39. **Huang FF, Sun ZF, Emerson SU, Purcell RH, Shivaprasad HL, Pierson FW, Toth TE, Meng XJ.** Determination and analysis of the complete genomic sequence of avian hepatitis E virus (avian HEV) and attempts to infect rhesus monkeys with avian HEV. J Gen Virol 2004, **85**, 1609-1618.
40. **Huang WJ, Zhang HY, Harrison TJ, Lan HY, Huang GY, Wang YC.** Immunogenicity and protective efficacy in rhesus monkeys of a recombinant ORF2 protein from hepatitis E virus genotype 4. Arch Virol 2009, **154**, 481-488.
41. **Huzly D, Umhau M, Bettinger D, Cathomen T, Emmerich F, Hasselblatt P, Hengel H, Herzog R, Kappert O, Maassen S, Schorb E, Schulz-Huotari C, Thimme R, Unmüssig R, Wenzel JJ, Panning M.** Transfusion-transmitted hepatitis E in Germany, 2013. Euro Surveill 2014, **19**, 20812.
42. **Ijaz S, Vyse AJ, Morgan D, Pebody RG, Tedder RS, Brown D.** Indigenous hepatitis E virus infection in England: more common than it seems. J Clin Virol 2009, **44**, 272-276.
43. **Ishida S, Yoshizumi S, Ikeda T, Miyoshi M, Goto A, Matsubayashi K, Ikeda H.** Detection and molecular characterization of hepatitis E virus in clinical, environmental

and putative animal sources. Arch Virol 2012, **157**, 2363-2368.
44. **Jardi R, Crespo M, Homs M, van den Eynde E, Girones R, Rodriguez-Manzano J, Caballero A, Buti M, Esteban R, Rodriguez-Frias F.** HIV, HEV and cirrhosis: evidence of a possible link from eastern Spain. HIV Med 2012, **13**, 379-383.
45. **Jia Z, Yi Y, Liu J, Cao J, Zhang Y, Tian R, Yu T, Wang H, Wang X, Su Q, Zhou W, Cui F, Liang X, Bi S.** Epidemiology of hepatitis E virus in China: results from the Third National Viral Hepatitis Prevalence Survey, 2005-2006. PLoS One 2014, **9**, e110837.
46. **Jilani N, Das BC, Husain SA, Baweja UK, Chattopadhya D, Gupta RK, Sardana S, Kar P.** Hepatitis E virus infection and fulminant hepatic failure during pregnancy. J Gastroenterol Hepatol 2007, **22**, 676-682.
47. **Jirintai S, Jinshan, Tanggis, Manglai D, Mulyanto, Takahashi M, Nagashima S, Kobayashi T, Nishizawa T, Okamoto H.** Molecular analysis of hepatitis E virus from farm rabbits in Inner Mongolia, China and its successful propagation in A549 and PLC/PRF/5 cells. Virus Res 2012, **170**, 126-137.
48. **Jothikumar N, Aparna K, Kamatchiammal S, Paulmurugan R, Saravanadevi S, Khanna P.** Detection of hepatitis E virus in raw and treated wastewater with the polymerase chain reaction. Appl Environ Microbiol 1993, **59**, 2558-2562.
49. **Juhl D, Baylis SA, Blümel J, Görg S, Hennig H.** Seroprevalence and incidence of hepatitis E virus infection in German blood donors. Transfusion 2014, **54**, 49-56.
50. **Kaba M, Richet H, Ravaux I, Moreau J, Poizot-Martin I, Motte A, Nicolino-Brunet C, Dignat-George F, Ménard A, Dhiver C, Brouqui P, Colson P.** Hepatitis E virus infection in patients infected with the human immunodeficiency virus. J Med Virol 2011, **83**, 1704-1716.
51. **Kamar N, Abravanel F, Garrouste C, Cardeau-Desangles I, Mansuy JM, Weclawiak H, Izopet J, Rostaing L.** Three-month pegylated interferon-alpha-2a therapy for chronic hepatitis E virus infection in a haemodialysis patient. Nephrol Dial Transplant 2010, **25**, 2792-2795.
52. **Kamar N, Abravanel F, Selves J, Garrouste C, Esposito L, Lavayssière L, Cointault O, Ribes D, Cardeau I, Nogier MB, Mansuy JM, Muscari F, Peron JM, Izopet J, Rostaing L.** Influence of immunosuppressive therapy on the natural history of genotype 3 hepatitis-E virus infection after organ transplantation. Transplantation 2010, **89**, 353-360.
53. **Kamar N, Garrouste C, Haagsma EB, Garrigue V, Pischke S, Chauvet C, Dumortier J, Cannesson A, Cassuto-Viguier 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.
54. **Kamar N, Izopet J, Tripon S, Bismuth M, Hillaire S, Dumortier J, Radenne S, Coilly A, Garrigue V, D'Alteroche L, Buchler M, Couzi L, Lebray P, Dharancy S, Minello A, Hourmant M, Roque-Afonso AM, Abravanel F, Pol S, Rostaing L, Mallet V.** Ribavirin for chronic hepatitis E virus infection in transplant recipients. N Engl J Med 2014, **370**, 1111-1120.
55. **Kamar N, Rostaing L, Abravanel F, Garrouste C, Esposito L, Cardeau-Desangles I, Mansuy JM, Selves J, Peron JM, Otal P, Muscari F, Izopet J.** Pegylated interferon-alpha for treating chronic hepatitis E virus infection after liver transplantation. Clin Infect Dis 2010, **50**, e30-33.
56. **Kamar N, Rostaing L, Abravanel F, Garrouste C, Lhomme S, Esposito L, Basse G, Cointault O, Ribes D, Nogier MB, Alric L, Peron JM, Izopet J.** Ribavirin therapy inhibits viral replication on patients with chronic hepatitis e virus infection. Gastroenterology 2010, **139**, 1612-1618.
57. **Kar P, Jilani N, Husain SA, Pasha ST, Anand R, Rai A, Das BC.** Does hepatitis E viral load and genotypes influence the final outcome of acute liver failure during pregnancy? Am J Gastroenterol 2008, **103**, 2495-2501.
58. **Kasorndorkbua C, Thacker BJ, Halbur PG, Guenette DK, Buitenwerf RM, Royer RL, Meng XJ.** Experimental infection of pregnant gilts with swine hepatitis E virus. Can J Vet Res 2003, **67**, 303-306.
59. **Kim YM, Jeong SH, Kim JY, Song JC, Lee JH, Kim JW, Yun H, Kim JS.** The first case of genotype 4 hepatitis E related to wild boar in South Korea. J Clin Virol 2011, **50**, 253-256.
60. **Koizumi Y, Isoda N, Sato Y, Iwaki T, Ono K, Ido K, Sugano K, Takahashi M, Nishizawa T, Okamoto H.** Infection of a Japanese patient by genotype 4 hepatitis E virus while traveling in Vietnam. J Clin Microbiol 2004, **42**, 3883-3885.
61. **Koning L, Pas SD, de Man RA, Balk AHMM, de Knegt RJ, ten Kate FJ, Osterhaus ADME, van der Eijk AA.** Clinical implications of chronic hepatitis E virus infection in heart transplant recipients. J Heart Lung Transplant 2013, **32**, 78-85.
62. **Krumbholz A, Mohn U, Lange J, Motz M, Wenzel JJ, 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.
63. **Kumar A, Beniwal M, Kar P, Sharma JB, Murthy NS.** Hepatitis E in pregnancy. Int J Gynaecol Obstet 2004, **85**, 240-244.
64. **Kumar S, Subhadra S, Singh B, Panda BK.** Hepatitis E virus: the current scenario. Int J Infect Dis 2013, **17**, e228-233.
65. **Kwon HM, Sung HW, Meng XJ.** Serological prevalence, genetic identification, and characterization of the first strains of avian hepatitis E virus from chickens in Korea. Virus Genes 2012, **45**, 237-245.
66. **Lagler H, Poeppl W, Winkler H, Herkner H, Faas A, Mooseder G, Burgmann H.** Hepatitis E virus seroprevalence in Austrian adults: a nationwide cross-sectional study among civilians and military professionals. PLoS One 2014, **9**, e87669.
67. **La Rosa G, Muscillo M, Vennarucci VS, Garbuglia AR, La Scala P, Capobianchi MR.** Hepatitis E virus in Italy: molecular analysis of travel-related and autochthonous cases. J Gen Virol 2011, **92**, 1617-1626.
68. **Lee JT, Shao PL, Chang LY, Xia NS, Chen PJ, Lu CY, Huang LM.** Seroprevalence of hepatitis E virus infection among swine farmers and the general population in rural

Taiwan. PLoS One 2013, **8**, e67180.
69. **Li S, Tang X, Seetharaman J, Yang C, Gu Y, Zhang J, Du H, Shih JW, Hew CL, Sivaraman J, Xia N.** Dimerization of hepatitis E virus capsid protein E2s domain is essential for virus-host interaction. PLoS Pathog 2009, **5**, e1000537.
70. **Li SW, Zhang J, Li YM, Ou SH, Huang GY, He ZQ, Ge SX, Xian YL, Pang SQ, Ng MH, Xia NS.** A bacterially expressed particulate hepatitis E vaccine: antigenicity, immunogenicity and protectivity on primates. Vaccine 2005, **23**, 2893-2901.
71. **Liang H, Chen J, Xie J, Sun L, Ji F, He S, Zheng Y, Liang C, Zhang G, Su S, Li S.** Hepatitis E virus serosurvey among pet dogs and cats in several developed cities in China. PLoS One 2014, **9**, e98068.
72. **Liang H, Su S, Deng S, Gu H, Ji F, Wang L, Liang C, Wang H, Zhang G.** The prevalence of hepatitis E virus infections among swine, swine farmers and the general population in Guangdong Province, China. PLoS One 2014, **9**, e88106.
73. **Liu P, Bu QN, Wang L, Han J, Du RJ, Lei YX, Ouyang YQ, Li J, Zhu YH, Lu FM, Zhuang H.** Transmission of hepatitis E virus from rabbits to cynomolgus macaques. Emerg Infect Dis 2013, **19**, 559-565.
74. **Liu P, Du R, Wang L, Han J, Liu L, Zhang Y, Xia J, Lu F, Zhuang H.** Management of hepatitis E virus (HEV) zoonotic transmission: protection of rabbits against HEV challenge following immunization with HEV 239 vaccine. PLoS One 2014, **9**, e87600.
75. **Ma H, Zheng L, Liu Y, Zhao C, Harrison TJ, Ma Y, Sun S, Zhang J, Wang Y.** Experimental infection of rabbits with rabbit and genotypes 1 and 4 hepatitis E viruses. PLoS One 2010, **5**, e9160.
76. **Masclaux FG, Hotz P, Friedli D, Savova-Bianchi D, Oppliger A.** High occurrence of hepatitis E virus in samples from wastewater treatment plants in Switzerland and comparison with other enteric viruses. Water Res 2013, **47**, 5101-5109.
77. **Matsubayashi K, Nagaoka Y, Sakata H, Sato S, Fukai K, Kato T, Takahashi K, Mishiro S, Imai M, Takeda N, Ikeda H.** Transfusion-transmitted hepatitis E caused by apparently indigenous hepatitis E virus strain in Hokkaido, Japan. Transfusion 2004, **44**, 934-940.
78. **Meng J, Dai X, Chang JC, Lopareva E, Pillot J, Fields HA, Khudyakov YE.** Identification and characterization of the neutralization epitope(s) of the hepatitis E virus. Virology 2001, **288**, 203-211.
79. **Meng XJ, Dea S, Engle RE, Friendship R, Lyoo YS, Sirinarumitr T, Urairong K, Wang D, Wong D, Yoo D, Zhang Y, Purcell RH, Emerson SU.** Prevalence of antibodies to the hepatitis E virus in pigs from countries where hepatitis E is common or is rare in the human population. J Med Virol 1999, **59**, 297-302.
80. **Meng XJ, Halbur PG, Shapiro MS, Govindarajan S, Bruna JD, Mushahwar IK, Purcell RH, Emerson SU.** Genetic and experimental evidence for cross-species infection by swine hepatitis E virus. J Virol 1998, **72**, 9714-9721.
81. **Meng XJ, Purcell RH, Halbur PG, Lehman JR, Webb DM, Tsareva TS, Haynes JS, Thacker BJ, Emerson SU.** A novel virus in swine is closely related to the human hepatitis E virus. Proc Natl Acad Sci U S A 1997, **94**, 9860-9865
82. **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.
83. **Mirazo S, Ramos N, Mainardi V, Gerona S, Arbiza J.** Transmission, diagnosis, and management of hepatitis E: an update. Hepat Med 2014, **6**, 45-59.
84. **Miyashita K, Kang JH, Saga A, Takahashi K, Shimamura T, Yasumoto A, Fukushima H, Sogabe S, Konishi K, Uchida T, Fujinaga A, Matsui T, Sakurai Y, Tsuji K, Maguchi H, Taniguchi M, Abe N, Fazle Akbar SM, Arai M, Mishiro S.** Three cases of acute or fulminant hepatitis E caused by ingestion of pork meat and entrails in Hokkaido, Japan: zoonotic food-borne transmission of hepatitis E virus and public health concerns. Hepatol Res 2012, **42**, 870-878.
85. **Moal V, Legris T, Burtey S, Morange S, Purgus R, Dussol B, Garcia S, Motte A, Gérolami R, Berland Y, Colson P.** Infection with hepatitis E virus in kidney transplant recipients in southeastern France. J Med Virol 2013, **85**, 462-471.
86. **Patra S, Kumar A, Trivedi SS, Puri M, Sarin SK.** Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. Ann Intern Med 2007, **147**, 28-33.
87. **Péron JM, Mansuy JM, Poirson H, Bureau C, Dupuis E, Alric L, Izopet J, Vinel JP.** Hepatitis E is an autochthonous disease in industrialized countries: analysis of 23 patients in South-West France over a 13-month period and comparison with hepatitis A. Gastroenterol Clin Biol 2006, **30**, 757-762.
88. **Pina S, Jofre J, Emerson SU, Purcell RH, Girones R.** Characterization of a strain of infectious hepatitis E virus isolated from sewage in an area where hepatitis E is not endemic. Appl Environ Microbiol 1998, **64**, 4485-4488.
89. **Pischke S, Suneetha PV, Baechlein C, Barg-Hock H, Heim A, Kamar N, Schlue J, Strassburg CP, Lehner F, Raupach R, Bremer B, Magerstedt P, Cornberg M, Seehusen F, Baumgaertner W, Klempnauer J, Izopet J, Manns MP, Grummer B, Wedemeyer H.** Hepatitis E virus infection as a cause of graft hepatitis in liver transplant recipients. Liver Transpl 2010, **16**, 74-82.
90. **Preiss JC, Plentz A, Engelmann E, Schneider T, Jilg W, Zeitz M, Duchmann R.** Autochthonous hepatitis E virus infection in Germany with sequence similarities to other European isolates. Infection 2006, **34**, 173-175.
91. **Renou C, Moreau X, Pariente A, Cadranel JF, Maringe E, Morin T, Causse X, Payen JL, Izopet J, Nicand E, Bourlière M, Penaranda G, Hardwigsen J, Gerolami R, Péron JM, Pavio N; ANGH, France.** A national survey of acute hepatitis E in France. Aliment Pharmacol Ther 2008, **27**, 1086-1093.
92. **Reuter G, Fodor D, Forgách P, Kátai A, Szucs G.** Characterization and zoonotic potential of endemic hepatitis E virus (HEV) strains in humans and animals in Hungary. J Clin Virol 2009, **44**, 277-281.
93. **Riveiro-Barciela M, Buti M, Homs M, Campos-Varela I, Cantarell C, Crespo M, Castells L, Tabernero D, Quer J, Esteban R, Rodriguez-Frías F.** Cirrhosis, liver transplantation and HIV infection are risk factors associated with hepatitis

E virus infection. PLoS One 2014, **9**, e103028.
94. **Robinson RA, Burgess WH, Emerson SU, Leibowitz RS, Sosnovtseva SA, Tsarev S, Purcell RH.** Structural characterization of recombinant hepatitis E virus ORF2 proteins in baculovirus-infected insect cells. Protein Expr Purif 1998, **12**, 75-84.
95. **Safary A.** Perspectives of vaccination against hepatitis E. Intervirology 2001, **44**, 162-166.
96. **Sanford BJ, Dryman BA, Huang YW, Feagins AR, Leroith T, Meng XJ.** Prior infection of pigs with a genotype 3 swine hepatitis E virus (HEV) protects against subsequent challenges with homologous and heterologous genotypes 3 and 4 human HEV. Virus Res 2011, **159**, 17-22.
97. **Sanford BJ, Emerson SU, Purcell RH, Engle RE, Dryman BA, Cecere TE, Buechner-Maxwell V, Sponenberg DP, Meng XJ.** Serological evidence for a hepatitis E virus-related agent in goats in the United States. Transbound Emerg Dis 2013, **60**, 538-545.
98. **Sanford BJ, Opriessnig T, Kenney SP, Dryman BA, Córdoba L, Meng XJ.** Assessment of the cross-protective capability of recombinant capsid proteins derived from pig, rat, and avian hepatitis E viruses (HEV) against challenge with a genotype 3 HEV in pigs. Vaccine 2012, **30**, 6249-6255.
99. **Schofield DJ, Glamann J, Emerson SU, Purcell RH.** Identification by phage display and characterization of two neutralizing chimpanzee monoclonal antibodies to the hepatitis E virus capsid protein. J Virol 2000, **74**, 5548-5555.
100. **Shrestha MP, Scott RM, Joshi DM, Mammen MP Jr, Thapa GB, Thapa N, Myint KS, Fourneau M, Kuschner RA, Shrestha SK, David MP, Seriwatana J, Vaughn DW, Safary A, Endy TP, Innis BL.** Safety and efficacy of a recombinant hepatitis E vaccine. N Engl J Med 2007, **356**, 895-903.
101. **Shuval H.** Estimating the global burden of thalassogenic diseases: human infectious diseases caused by wastewater pollution of the marine environment. J Water Health 2003, **1**, 53-64.
102. **Smith DB, Simmonds P; International Committee on Taxonomy of Viruses *Hepeviridae* Study Group, Jameel S, Emerson SU, Harrison TJ, Meng XJ, Okamoto H, Van der Poel WHM, Purdy MA.** Consensus proposals for classification of the family Hepeviridae. J Gen Virol 2014, **95**, 2223-2232.
103. **Song YJ, Jeong HJ, Kim YJ, Lee SW, Lee JB, Park SY, Song CS, Park HM, Choi IS.** Analysis of complete genome sequences of swine hepatitis E virus and possible risk factors for transmission of HEV to humans in Korea. J Med Virol 2010, **82**, 583-591.
104. **Stoszek SK, Abdel-Hamid M, Saleh DA, El Kafrawy S, Narooz S, Hawash Y, Shebl FM, El Daly M, Said A, Kassem E, Mikhail N, Engle RE, Sayed M, Sharaf S, Fix AD, Emerson SU, Purcell RH, Strickland GT.** High prevalence of hepatitis E antibodies in pregnant Egyptian women. Trans R Soc Trop Med Hyg 2006, **100**, 95-101.
105. **Takahashi K, Kitajima N, Abe N, Mishiro S.** Complete or near-complete nucleotide sequences of hepatitis E virus genome recovered from a wild boar, a deer, and four patients who ate the deer. Virology 2004, **330**, 501-505.
106. **Takeda H, Matsubayashi K, Sakata H, Sato S, Kato T, Hino S, Tadokoro K, Ikeda H.** A nationwide survey for prevalence of hepatitis E virus antibody in qualified blood donors in Japan. Vox Sang 2010, **99**, 307-313.
107. **Tam AW, Smith MM, Guerra ME, Huang CC, Bradley DW, Fry KE, Reyes GR.** Hepatitis E virus (HEV): molecular cloning and sequencing of the full-length viral genome. Virology 1991, **185**, 120-131.
108. **Tamura A, Shimizu YK, Tanaka T, Kuroda K, Arakawa Y, Takahashi K, Mishiro S, Shimizu K, Moriyama M.** Persistent infection of hepatitis E virus transmitted by blood transfusion in a patient with T-cell lymphoma. Hepatol Res 2007, **37**, 113-120.
109. **Taniguchi M, Kim SR, Mishiro S, Takahashi K, Shin MH, Yun H, Park MS, Li ZM, Kim MK, Fang J, Hayashi Y.** Epidemiology of hepatitis E in Northeastern China, South Korea and Japan. J Infect 2009, **58**, 232-237.
110. **Tsarev SA, Tsareva TS, Emerson SU, Govindarajan S, Shapiro M, Gerin JL, Purcell RH.** Recombinant vaccine against hepatitis E: dose response and protection against heterologous challenge. Vaccine 1997, **15**, 1834-1838.
111. **Wang Y, Zhou X, Debing Y, Chen K, Van Der Laan LJW, Neyts J, Janssen HLA, Metselaar HJ, Peppelenbosch MP, Pan Q.** Calcineurin inhibitors stimulate and mycophenolic acid inhibits replication of hepatitis E virus. Gastroenterology 2014, **146**, 1775-1783.
112. **Wei M, Zhang X, Yu H, Tang ZM, Wang K, Li Z, Zheng Z, Li S, Zhang J, Xia N, Zhao Q.** Bacteria expressed hepatitis E virus capsid proteins maintain virion-like epitopes. Vaccine 2014, **32**, 2859-2865.
113. **Widén F, Sundqvist L, Matyi-Toth A, Metreveli G, Belák S, Hallgren G, Norder H.** Molecular epidemiology of hepatitis E virus in humans, pigs and wild boars in Sweden. Epidemiol Infect 2011, **139**, 361-371.
114. **Wu T, Li SW, Zhang J, Ng MH, Xia NS, Zhao Q.** Hepatitis E vaccine development: a 14 year odyssey. Hum Vaccin Immunother 2012, **8**, 823-827.
115. **Wu T, Zhu FC, Huang SJ, Zhang XF, Wang ZZ, Zhang J, Xia NS.** Safety of the hepatitis E vaccine for pregnant women: a preliminary analysis. Hepatology 2012, **55**, 2038.
116. **Xia J, Liu L, Wang L, Zhang Y, Zeng H, Liu P, Zou Q, Wang L, Zhuang H.** Experimental infection of pregnant rabbits with hepatitis E virus demonstrating high mortality and vertical transmission. J Viral Hepat 2015, **22**, 850-857.
117. **Xia NS, Zhang J, Zheng YJ, Ge SX, Ye XZ, Ou SH.** Transfusion of plasma from a blood donor induced hepatitis E in rhesus monkey. Vox Sang 2004, **86**, 45-47.
118. **Xu C, Wang RY, Schechterly CA, Ge S, Shih JW, Xia NS, Luban NL, Alter HJ.** An assessment of hepatitis E virus (HEV) in US blood donors and recipients: no detectable HEV RNA in 1939 donors tested and no evidence for HEV transmission to 362 prospectively followed recipients. Transfusion 2013, **53**, 2505-2511.
119. **Yamashita T, Mori Y, Miyazaki N, Cheng RH, Yoshimura M, Unno H, Shima R, Moriishi K, Tsukihara T, Li TC, Takeda N, Miyamura T, Matsuura Y.** Biological and immunological characteristics of hepatitis E virus-like particles based on the crystal structure. Proc Natl Acad Sci U S A 2009, **106**, 12986-12991.
120. **Yoon Y, Jeong HS, Yun H, Lee H, Hwang YS, Park B, Lee CJ, Lee S, Hyeon JY.** Hepatitis E virus (HEV) seroprevalence in

the general population of the Republic of Korea in 2007-2009: a nationwide cross-sectional study. BMC Infect Dis 2014, **14**, 517.

121. **Zhao C, Ma Z, Harrison TJ, Feng R, Zhang C, Qiao Z, Fan J, Ma H, Li M, Song A, Wang Y.** A novel genotype of hepatitis E virus prevalent among farmed rabbits in China. J Med Virol 2009, **81**, 1371-1379.

122. **Zhu FC, Zhang J, Zhang XF, Zhou C, Wang ZZ, Huang SJ, Wang H, Yang CL, Jiang HM, Cai JP, Wang YJ, Ai X, Hu YM, Tang Q, Yao X, Yan Q, Xian YL, Wu T, Li YM, Miao J, Ng MH, Shih JW, Xia NS.** Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. Lancet 2010, **376**, 895-902.