

Zoonotic and Foodborne Transmission of Hepatitis E Virus

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Abstract

Hepatitis E is an important disease in many developing countries of Asia and Africa with large explosive outbreaks and is also endemic with sporadic or cluster cases of hepatitis in many industrialized countries. The causative agent, hepatitis E virus (HEV), is currently classified in the family *Hepeviridae*. Thus far, four putative genera of HEV representing mammalian, avian, and fish species have been identified and characterized worldwide. Within the mammalian HEV that infects humans, genotypes 1 and 2 are associated with epidemics and restricted to humans, whereas genotypes 3 and 4 are zoonotic and associated with sporadic and cluster cases of hepatitis E. As a fecal–orally transmitted disease, waterborne transmission is still an important route of HEV transmission especially for large outbreaks associated with genotypes 1 and 2. However, genetic identification of numerous animal strains of HEV and the demonstrated ability of cross-species infection by these animal strains have significantly broadened the host range and diversity of HEV and raised public health concerns for zoonosis and food safety associated with genotypes 3 and 4 HEV infection. Pigs and likely other animal species serve as reservoirs for HEV. Direct contact with infected pigs and other animals and consumption of contaminated animal meat and meat products pose risks for HEV infection. In this article, the current understanding of the zoonotic and foodborne transmissions of HEV as well as strategies to prevent zoonosis and ensure food safety is discussed.

Keywords

- ▶ hepatitis E virus
- ▶ HEV
- ▶ zoonosis
- ▶ foodborne transmission
- ▶ zoonotic transmission
- ▶ animal reservoirs

Hepatitis E, an important human disease, is characterized by explosive outbreaks of acute hepatitis in developing countries, and sporadic and cluster cases of hepatitis E in industrialized countries.^{1,2} The causative agent, hepatitis E virus (HEV), has been genetically identified from humans and several other animal species including pig, chicken, deer, mongoose, rabbit, rat, ferret, and fish.^{3–5} The host range and diversity of HEV have been significantly expanded in recent years. Hepatitis E is now a recognized zoonotic disease, and pigs and likely other animal species are reservoirs for HEV (▶ Fig. 1).⁵ Direct contact with infected animals and consumption of contaminated animal meat and meat products have been linked to sporadic and cluster cases of acute hepatitis E, thus raising concerns over zoonosis and food safety.³ Recently, genotype 3 HEV-associat-

ed persistent infection has become a significant clinical problem in immunocompromised individuals,^{6,7} which further underscores the clinical importance of these zoonotic genotypes 3 and 4 HEV strains. Here the natural history and emerging zoonotic risks of HEV are reviewed with emphases on the zoonotic and foodborne transmissions of the virus and potential strategies to prevent zoonosis and ensure food safety.

Hepatitis E Virus Nomenclature

HEV belongs to the family *Hepeviridae*, and according to the 9th Report of the International Committee on the Taxonomy of Viruses (ICTV),⁸ currently there is a single genus *Hepevirus* within the family along with a floating species of avian HEV.

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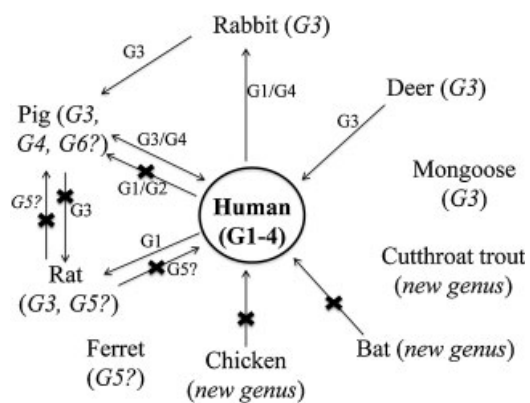


Fig. 1 Animal reservoirs and cross-species infection of hepatitis E virus (HEV). The animal species from which strains of HEV have been genetically identified are indicated. The known (G1-G4) and putative (G5-6?) genotypes as well as the proposed new genus are included in parenthesis of each animal species. The demonstrated ability of cross-species infection by strains of HEV between two animal species is indicated by arrows and the infecting genotypes (next to the arrows). The symbol X on an arrow indicates the inability to infect across species as reported in the literature.

The viruses within the genus *Hepevirus* all infect mammals and have been genetically identified from humans, pig, mongoose, deer, rat, rabbit, and ferret (► **Fig. 1**). However, the recent identification of genetically and phylogenetically distinct strains of HEV from several other animal species such as fish and bat^{9,10} warrant reclassification of HEV in the near future.

The genus *Hepevirus* includes four recognized genotypes and at least two putative new genotypes.⁸ Genotype 1 HEV consists of Asian strains of human HEV that are responsible for large outbreaks in humans. Genotype 2 HEV consists of a single Mexican strain and some African strains of human HEV and is also associated with epidemics in humans. Genotype 3

HEV contains strains from sporadic, cluster, and chronic cases of hepatitis E in humans and from several animal species including pig, deer, rat, mongoose, and rabbit. Genotype 4 HEV includes strains from sporadic and cluster cases of hepatitis E in humans and animal HEV strains from pigs and possibly cattle and sheep.³ The two putative new genotypes of mammalian *hepeviruses* include strains of HEV from rat and ferret,¹¹⁻¹³ and a novel strain of HEV from wild boars in Japan.^{14,15} A tentative genus *Orthohepevirus* is proposed here to include all these mammalian strains of HEV (► **Table 1**).

Avian HEV from chicken¹⁶ is currently classified as a floating species within the family *Hepeviridae*.⁸ However, avian HEV is genetically and phylogenetically distinct from the mammalian *hepeviruses* sharing only ~50% nucleotide sequence identity.¹⁷⁻¹⁹ Therefore, avian HEV should be classified as a separate genus,^{4,20} and the tentative genus *Avihepevirus* is proposed here to include all three genotypes of avian HEV worldwide: genotype 1 from chickens in Australia and Korea, genotype 2 from chickens in the United States, and genotype 3 from chickens in Europe and China.^{19,21,22}

The novel strain of HEV, cutthroat trout virus (CTV)¹⁰ isolated from spawning adult trout in the United States, belongs to a new genus as well, and the tentative genus *Piscihepevirus* is proposed here for CTV. The novel strain of HEV recently identified from bats⁹ is also phylogenetically distinct from the known HEV strains, and thus is proposed to form a tentative genus *Chiropteranhepevirus* (► **Table 1**).

The Ever-Expanding Host Range of HEV

Genetic identification of HEV strains from various animal hosts and the demonstration of cross-species infection by some animal strains of HEV have broadened the host range and genetic diversity of virus (► **Table 1**).^{3,5}

Table 1 Proposed nomenclature of the hepatitis E virus (HEV)

Proposed genera	Natural hosts
<i>Orthohepevirus</i>	
Genotype 1	Man
Genotype 2	Man
Genotype 3	Man, domestic and wild pig, deer, mongoose, rabbit, rat
Genotype 4	Man, domestic and wild pig, cattle, sheep
Putative genotype 5	Rat, ferret
Putative genotype 6	Wild pig
<i>Avihepevirus</i>	
Genotype 1	Chicken (Australia, Korea)
Genotype 2	Chicken (USA, Canada)
Genotype 3	Chicken (Europe, China)
<i>Piscihepevirus</i>	
Cutthroat trout virus	Brown, Apache, and Gila trouts
<i>Chiropteranhepevirus</i>	
Bat HEV	Bat

Domestic Pig

The first animal strain of HEV, swine hepatitis E virus (swine HEV), was identified and characterized in 1997 from domestic pigs in the United States.²³ Thus far, two genotypes of HEV, genotypes 3 and 4, have been identified from pigs worldwide. HEV infection is widespread in swine farms and generally infects pigs of 2 to 4 months of age. The infected pigs are subclinical and generally have a transient viremia lasting for 1 to 2 weeks, and fecal virus shedding lasting for approximately 3 to 7 weeks. Gross pathological lesions were absent in the liver, although microscopic lesions of hepatitis characterized by multifocal lymphoplasmacytic hepatitis and focal hepatocellular necrosis were observed.²⁴ The transmission route for HEV in pigs is fecal-oral and virus-containing feces are the main source of virus for transmission. However, under experimental conditions, infection of pigs with HEV via the oral route of inoculation has been difficult, even though pigs can be readily infected via the intravenous route of inoculation.^{25,26} How HEV maintains in swine herds remains unknown; both genotypes 3 and 4 HEV from pigs are zoonotic and infect humans.

Wild Boar

Free-living wild boars (*Sus scrofa*) that are indigenous in many countries are known to harbor HEV.²⁷ Human habitation changes from rural to suburban areas, increased agricultural use of lands, deforestation, recreational hunting, and consumption of wild boar meats have increased the chances of contact exposure of wild boars to humans.²⁷ The HEV strains identified in wild boars worldwide are mostly genotype 3, although strains belonging to genotype 4 as well as a putative new genotype have also been detected in wild boars.^{14,15} Like domestic pigs, the genotypes 3 and 4 HEV from wild boars infect humans.

Chicken

Avian hepatitis E virus (avian HEV) was genetically identified from chickens with hepatitis-splenomegaly syndrome (HSS) in the United States.¹⁶ Avian HEV shares approximately 80% nucleotide sequence identity with the big liver and spleen disease virus (BLSV) from chickens in Australia,^{18,28} suggesting that BLS in Australia and HSS in the United States are caused by variant strains of the same virus. Avian HEV shares 50 to 60% nucleotide sequence identities and common antigenic epitopes in the capsid protein with human HEVs.¹⁸ At least three genotypes of avian HEV have been identified from chickens worldwide.^{19,21} In the United States, HEV infection in chickens is enzootic, and approximately 71% of chicken flocks and 30% of chickens were seropositive for avian HEV antibodies.^{17,29} The morbidity and mortality of HSS or BLS associated with avian HEV infection are low, and avian HEV infection in chickens is mostly subclinical. Gross lesions including subcapsular hemorrhages and enlarged livers were present in some but not all infected chickens, and microscopic hepatitis lesions are characterized by lymphocytic periphlebitis and phlebitis in the livers.^{30,31} Evidence of avian HEV infection in humans is currently lacking.³²

Rat

Strains of HEV have now been genetically identified from various species of rats.^{11,12,33} The rat HEV shared only approximately 60% and 50% sequence identity with other mammalian HEV and avian HEV, respectively, and thus belongs to a putative new genotype within the proposed *Orthohepevirus* genus. It remains to be determined if this putative new genotype of rat HEV can infect humans. Most recently, strains of HEV belonging to the genotype 3 have also been identified from rats in the United States,³⁴ suggesting that some strains of rat HEV are likely zoonotic and may infect humans.

Rabbit

A genetically distinct strain of HEV that is related to genotype 3 was identified from rabbits in China,³⁵ the United States,³⁶ and France.³⁷ The rabbit HEV shares approximately 74%, 73%, 78 to 79%, 74 to 75%, and 46 to 47% nucleotide sequence identity with genotypes 1, 2, 3, 4 HEV, and avian HEV, respectively. The capsid protein of the rabbit HEV cross-reacted with antibodies raised against avian, rat, swine, and human HEV.³⁸ Since the rabbit HEV belongs to the zoonotic genotype 3, thus the rabbit HEV may infect humans. Under experimental conditions, the rabbit HEV was successfully transmitted to pigs,³⁸ further demonstrating the ability of cross-species infection by rabbit HEV.

Deer

Antibodies to HEV have been detected in sika deer, Yezo deer, and red deer.³⁹⁻⁴¹ Strains of genotype 3 HEV have been genetically identified from sika deer in Japan and roe deer in Hungary.^{42,43} HEV transmission from deer to humans via the consumption of contaminated deer meat has been documented.^{44,45}

Mongoose

Approximately 8 to 21% of the mongooses in Japan were seropositive for HEV antibodies.⁴⁶ Strains of genotype 3 HEV have been genetically identified from mongoose.⁴⁷ Whether the mongoose HEV infects humans remains unknown, although genotype 3 HEV is known to be zoonotic.

Bat

Drexler et al⁹ tested 3,869 bat samples from 85 different bat species worldwide for HEV RNA. Novel strains of HEV were identified from African, Central American, and European bats. The bat HEV forms a novel phylogenetic clade belonging to a separate genus within the family *Hepeviridae*. Evidence of HEV transmission from bats to humans was absent.

Ferret

A unique strain of HEV was genetically identified from ferrets in the Netherlands.¹³ The ferret HEV shared the highest nucleotide sequence identity (72.3%) with the putative new genotype of rat HEV. Phylogenetic analysis revealed that the ferret HEV was distinct from the known genotype 1-4 mammalian HEV in the proposed *Orthohepevirus* genus and

clustered with the putative new genotype of rat HEV (►Table 1).

Fish

The CTV isolated from spawning adult trout in the United States¹⁰ shares only approximately 13 to 27% amino acid sequence identity with the proposed genera *Orthohepevirus* and *Avihepevirus*, and therefore likely belongs to another new proposed genus *Piscihepevirus* (►Table 1). Unlike other strains of HEV, CTV can be efficiently propagated in the Chinook salmon embryo (CHSE-214) cell line.

Cattle

Antibodies to HEV have been detected in cattle from different countries. A 189-bp sequence of HEV was reportedly amplified from the fecal samples of eight cows in China, and the bovine HEV appears to be a genotype 4.⁴⁸

Sheep

Serological evidence of HEV infection in sheep has been reported in China and Spain. A short 189-bp sequence of HEV was amplified from six sheep fecal samples in China by the same laboratory that reported the sequence of bovine HEV,⁴⁹ and the sheep HEV also appears to be a genotype 4. The genotype 4 HEV-like sequences reportedly amplified from sheep and cattle require further independent confirmation.

Other Potential Animal Reservoirs

In addition to the animal species described above from which strains of HEV have been genetically identified, serological evidence of HEV infection has been reported in several other animal species such as dog, cat, goat, and nonhuman primates,^{50,51} suggesting that these animals have been exposed to HEV as well. Identification of the source of seropositivity from these animal species will likely discover new HEV strains and further expand the host range and animal reservoirs of HEV.

Zoonotic Transmission of HEV

Zoonotic transmission is responsible for the sporadic and cluster cases of human hepatitis E caused by genotypes 3 and 4.⁵ Cases of persistent hepatitis E in immunocompromised individuals are also linked to the zoonotic genotype 3 HEV infection.⁴

Cross-Species Infection by HEV

Genotypes 1 and 2 HEV have a limited host range and are restricted to humans: Attempts to experimentally infect pig, rat, and goat with genotypes 1 and 2 human HEV were unsuccessful.^{52,53} In contrast, genotypes 3 and 4 HEV have a much broader host range and can infect across species barriers: genotypes 3 and 4 swine HEV infected nonhuman primates,^{54,55} and conversely genotypes 3 and 4 human HEV infected pigs.^{24,54,56,57} Cross-species HEV infection has also been reported in other animal species (►Fig. 1). Lambs and Wistar rats were reportedly infected by human HEV isolates of presumably genotype 1 origin,^{58,59} although others failed

to infect goats or rat with genotypes 1 and 2 HEV.⁵³ The avian HEV from a chicken successfully infected turkeys,⁶⁰ but failed to infect two rhesus monkeys,³² suggesting that avian HEV is likely not zoonotic and may not infect humans. The strains of HEV from rabbits infected pigs³⁸ and genotypes 1 and 4 human HEV also reportedly infected rabbits.⁶¹ The mechanisms and genetic determinant(s) of cross-species HEV infection remain unknown.

Pigs as a Reservoir for Zoonotic HEV Transmission

It has been demonstrated that pig handlers such as pig farmers and swine veterinarians are at increased risk of HEV infection.^{62–67} For example, swine veterinarians in the United States were 1.51 times more likely to be positive for HEV antibodies than age- and geography-matched normal blood donors.⁶² Individuals from traditionally major swine states such as Minnesota are more likely seropositive for HEV antibodies than those from traditionally nonswine States such as Alabama. In North Carolina, swine workers had a 4.5-fold higher HEV antibody prevalence rate than the control subjects.⁶⁸ In Moldova, approximately 51% of swine farmers were seropositive for HEV antibodies, whereas only 25% of control subjects with no occupational exposure to swine were seropositive.⁶⁵ Pig is now a recognized reservoir for zoonotic HEV infection, and direct human contact with infected pigs poses a risk for HEV infection.

Other Animal Reservoirs for Zoonotic HEV Transmission

In addition to pigs, other animal species such as deer and rabbit also serve as potential reservoirs for HEV. For examples, zoonotic transmissions of hepatitis E from deer to humans and from a pet cat to human owner were reported.^{44,45,69,70} Workers from the Iowa Department of Natural Resources (DNR) who had contacts with wildlife animal species had a higher HEV antibody prevalence rate than normal blood donors ($p < 0.05$).⁷¹ Understanding the natural history and mechanisms of cross-species infection of HEV will be critical for effectively preventing zoonotic human infection by HEV.

Zoonotic Source of Virus for Persistent Infection in Immunocompromised Individuals

Recently, persistent HEV infection has become an emerging and significant clinical problem with considerable morbidity and mortality in immunocompromised individuals such as organ transplant recipients,^{6,7,72–75} patients with HIV infections,^{76–80} non-Hodgkin lymphoma,⁸¹ and lymphoblastic leukemia.⁸² Approximately 58 to 92% of the HEV-infected organ transplant recipients developed persistent infection.^{7,83,84} Thus far, cases of persistent infections are almost exclusively caused by strains of HEV belonging to the genotype 3,^{72,84} suggesting that the source of infection is likely zoonotic in nature.^{83,85} In immunocompetent individuals, a lower dose of virus exposure through direct contact with infected animals or consumption of undercooked animal meat may only result in subclinical or self-limiting acute infection because hepatitis E is known to be a dose-dependent disease: A high dose causes biochemical and clinical hepatitis whereas a low dose causes only subclinical infection.⁸⁶

However, in immunocompromised individuals that cannot effectively clear the virus even exposed at a low dose, the infection can progress into chronicity. Therefore, individuals with immunosuppressive conditions should avoid eating undercooked animal meat or contact with potentially HEV-infected animals.

Foodborne Transmission of HEV

Animal Meat Products as the Sources for Foodborne Transmission

Approximately 2% of the pig livers sold in local grocery stores in Japan,⁸⁷ 4% in Germany,⁸⁸ 6.5% in the Netherlands,⁸⁹ and 11% in the United States⁹⁰ tested positive for the zoonotic genotype 3 HEV RNA. The contaminating virus in the commercial pig livers remains fully infectious,⁹⁰ and incubation of the contaminated meat at a temperature (56°C) equivalent to a medium-to-rare cooking condition did not inactivate the virus completely.⁹¹ Many sporadic and cluster cases of hepatitis E have been linked to the consumption of contaminated raw or undercooked animal meat and meat products.^{92–95} For example, severe hepatitis E developed in a Japanese man after consumption of contaminated wild boar meat; another man contracted fulminant hepatitis after eating the same wild boar meat.^{93,94} The zoonotic genotype 4 HEV was detected from the patient serum and wild boars with indistinguishable nucleotide sequences. A cluster case of hepatitis E patients was linked to the consumption of raw deer meats in Japan.⁴⁴ Importantly, the HEV sequence amplified from the leftover frozen deer meat was nearly identical to the HEV sequence amplified from the patients. Additionally, consumption of game meat is also a risk factor for HEV infection.⁸³

It appears that large pork production chains in some countries are contaminated by HEV, which raises a public health concern for potential foodborne HEV transmission because of the high-volume consumption of pork products worldwide. In the United Kingdom, HEV was detected in pig livers in a slaughterhouse, in surface samples from a processing plant, and in pork sausages and surface samples at the point of sale.⁹⁶ In Czech Republic, Italy, and Spain, among the 337 fecal, liver, and meat samples from pigs at slaughterhouses tested, HEV RNA was detected in 41% (Italy) and 41% (Spain) fecal samples, 5% liver and 2.5% meat (Czech Republic).⁹⁷ Approximately 6% of the sausages sampled at processing and at the point of sale in Spain were also positive for genotype 3 HEV RNA.⁹⁷ In France, pig liver sausages (figatelli) were responsible for some sporadic cases of hepatitis E.⁹⁸ Acute or recent HEV infection was observed in 7 of 13 individuals who ate figatelli, but in none of the 5 individuals who did not eat figatelli. The genotype 3 HEV sequences amplified from 7 of the 12 figatelli from supermarkets were genetically linked to the patients who ate figatelli. In Japan, foodborne HEV transmission has been demonstrated in Kitami and Abashiri via consumption of grilled pig entrails.⁹⁹

The potential widespread dissemination of HEV through pork production chains and the hidden danger of potential subsequent foodborne transmission especially in immunocompromised individuals are of significant concerns.¹⁰⁰

Taken together, these data clearly showed that foodborne transmission is an important route of HEV transmission that is responsible for the sporadic and cluster cases of hepatitis E worldwide.

Contaminated Shellfish as the Source for Foodborne Transmission

HEV replicates in the liver as well as in gastrointestinal tract,^{56,101} and infected humans and other animals excreted large amounts of HEV in feces,^{57,102} which poses a concern for environmental contamination and food safety. HEV has been detected in swine manure and wastewater associated with hog operations,⁷¹ and in concrete pits and lagoons of swine manure storage facilities in the United States.¹⁰² Genotype 3 HEV RNA was detected in swine manure collected from concrete holding pits and from lagoons on pig farms; importantly, the HEV detected in pig manure slurry remains infectious.¹⁰² In Korea, HEV RNA resembling the genotype 3 swine HEV was detected in oysters.¹⁰³ Consumption of contaminated shellfish has been implicated in sporadic cases of acute hepatitis E.^{104–106} An outbreak of hepatitis E on a cruise ship was linked to the consumption of shellfish while on board.¹⁰⁷ Therefore, contaminated shellfish is an emerging source of foodborne HEV transmission.

Contaminated Water as the Source for Foodborne and Waterborne Transmission

Contamination of water by HEV from human and other animal wastes can lead to subsequent contamination of food and produce, and thus leading to potential foodborne transmission.^{3,108,109} Historically, waterborne epidemics are the characteristic of hepatitis E outbreaks in humans in regions where sanitation conditions are poor.¹ Untreated sewage water contamination of drinking water and contaminated well or river water used for washing and drinking purpose are the main sources of HEV transmission in developing countries.¹¹⁰ In India, a significantly higher prevalence of HEV antibodies was detected in sewage workers (57%) than in controls (19%), and sewage workers with >5 years of employment history had a much higher seropositivity rate.¹¹¹ In HEV endemic regions, the use of river water for bathing, waste disposal, and drinking purposes is also a significant risk factor.^{112–115} In Turkey, individuals who used untreated waste water for irrigation purposes have a significant higher HEV antibody prevalence rate (34.8%) than the control subjects with similar age and socioeconomic status.¹¹⁶

In industrialized countries with good sanitation conditions and water treatment measures, outbreaks of waterborne HEV transmission are rare. However, the existence of numerous zoonotic strains of HEV from various animal species implies that land application and runoffs of HEV-containing animal manure and feces could contaminate irrigation or coastal water with concomitant contamination of produce or shellfish,^{3,102,109} thus posing a risk of foodborne and waterborne HEV transmission. For example, in Canada, genotype 3 HEV of swine origin was detected on irrigated field-grown strawberries; irrigation water was suspected as the source of the strawberry contamination.¹¹⁷ Strains of

infectious HEV of both human and swine origins have been detected in sewage water in industrialized countries.^{118–122} Therefore, contaminated water could be a source of food contamination, thus leading to foodborne HEV transmission.

Other Uncommon Routes of HEV Transmission

Vertical Transmission

Vertical HEV transmissions from mother-to-fetus were reportedly associated with a high neonatal mortality, including premature birth, increased fetal loss and acute hepatitis in the newborns.^{123–125} For example, vertical HEV transmission was detected in approximately 33% of HEV-infected pregnant women.¹²⁴ HEV RNA was reportedly detected in the colostrum of HEV-infected mothers, although breast-feeding appears to be safe for the infants.¹²⁶ Under experimental conditions, however, vertical HEV transmission in animal models has not been demonstrated. For example, infectious HEV was detected in egg whites from embryonated eggs hatched from chickens infected experimentally with an avian strain of HEV, but there was no evidence of complete vertical transmission.¹²⁷ Also, pregnant sows inoculated with a genotype 3 HEV became infected, but vertical transmission to the fetuses was not detected.¹²⁸ Similarly, pregnant rhesus macaques experimentally infected with HEV failed to transmit the virus to offspring.¹²⁹ Therefore, further in-depth studies are warranted to definitively understand the potential risk of vertical HEV transmission.

Blood-Borne Transmission

Bloodborne transmission of HEV through blood transfusions, although rare, has been documented.^{95,130–134} For example, some blood donors have tested positive for HEV RNA. In Japan, HEV RNA was detected in 8 of the 41 blood donors with elevated ALT levels.^{135–138} Screening donor blood for acute markers of HEV infection will reduce the risk of potential bloodborne transmission.

Prevention of Foodborne and Zoonotic Transmission of HEV

A vaccine against HEV in humans was recently licensed for use in China, but not in other countries.¹³⁹ In the absence of a vaccine in most parts of the world, preventive measures such as good hygiene practice and avoidance of drinking water of unknown purity are necessary to minimize the risk of HEV infection. Because swine and several other animal species are reservoirs for HEV, an important measure to prevent zoonotic infection is to wash hands thoroughly with soap and water after handling pigs and other infected animals. The majority of the sporadic and cluster cases of hepatitis E are associated with the consumption of raw or undercooked animal meat products; therefore, an important preventive measure for foodborne HEV transmission, especially in immunocompromised individuals, is to avoid eating undercooked animal meat. Even though HEV infection in pigs is nonpathogenic, it will still be advantageous for the swine industry to develop

a vaccine against HEV infections in pigs because such an animal vaccine will minimize the risk of zoonotic transmission and increase pork safety.³

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