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INFECTIOUS DISEASE EPIDEMIOLOGY (A REINGOLD, SECTION EDITOR)

The Epidemiology and Prevention of Hepatitis E Virus Infection

Kenrad E. Nelson[1] · **Christopher D. Heaney**[2] · **Brittany L. Kmush**[3]

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Abstract
Purpose of Review Hepatitis E virus (HEV) infections are a global public health problem. These viruses were originally identified as the cause of large waterborne outbreaks with increased mortality in pregnant women in developing countries in Asia and Africa in 1983. A decade later, locally acquired cases of acute hepatitis were reported in industrialized countries after food-borne transmission from an animal reservoir, especially swine, wild boar, and deer. However, the knowledge about the clinical features of HEV infection, the animal reservoirs, and virus characteristics has expanded substantially in recent years.
Recent Findings HEV infections in patients who are immunosuppressed after a solid organ transplant and AIDS or cancer chemotherapy frequently develop chronic hepatitis. Some patients with chronic HEV infection develop extra-hepatic manifestations, especially neurologic symptoms. Clinical observations support the effectiveness of ribavirin therapy from chronic HEV. Recent research has found an expanded animal reservoir of *Hepeviridae* that are human pathogens and strains that are only animal pathogens. A consensus classification of *Hepeviridae* has been published recently. The risk of transfusion transmission of HEV has been quantified and selected donor screening implemented in two countries in the last few years.
Summary Recent research has greatly expanded scientific information on the diversity and zoonotic reservoirs of *Hepeviridae* as well as the epidemiology and clinical features of HEV infection in humans.

Keywords Hepatitis E virus · Hepatitis epidemics · Waterborne infections · Food-borne infections · Hepatitis · Ribavirin · Hepatitis E vaccine · Viral replication · Zoonoses · Swine · Camels

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✉ Kenrad E. Nelson
knelson3@jhu.edu

Christopher D. Heaney
cheaney1@jhu.edu

Brittany L. Kmush
blkmush@syr.edu

[1] Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, 615 N. Wolfe Street, Baltimore, MD 21205, USA

[2] Department of Environmental Health and Engineering and Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, 615 N. Wolfe Street, Baltimore, MD 21205, USA

[3] Department of Public Health, Food Studies, and Nutrition, Falk College of Sport and Human Dynamics, Syracuse University, 150 Crouse Dr, Syracuse, NY 13244, USA

Introduction

Outbreaks of jaundice have been recorded throughout history. The hypothesis that acute hepatitis might be caused by a viral infection was proposed in 1931 [1]. The concept that more than one hepatitis virus with different transmission routes might commonly infect humans was documented by Krugman and colleagues in studies in the 1960s [2]. Large waterborne outbreaks of hepatitis have been reported since the eighteenth century [3]. An outbreak of over 29,000 cases of waterborne hepatitis occurred in Delhi, India in December 1955 after flooding caused contamination of the urban water supply [4]. This outbreak was of particular interest because it involved mainly adults; there was little evidence of person-to-

person transmission of infection, and 102 of the 250 deaths (41%) occurred in pregnant women [4]. During the next two decades, many similar outbreaks of hepatitis occurred in South Asia during the rainy season (Table 1). The hypothesis that these recurring waterborne outbreaks were from an infection with a different hepatitis virus than those responsible for sporadic endemic hepatitis was proposed by Khuroo after an outbreak in Kashmir in 1978 [5]. After the hepatitis A virus (HAV) was identified by immune electron microscopy (IEM) visualization of viral particles in stool samples from infected patients, it became possible to develop serologic assays of HAV. Patients with acute hepatitis during the 1955 outbreak in Delhi and other similar outbreaks were found not to have serological evidence of HAV infection [6]. Subsequently, Balayan observed an outbreak in Afghanistan in 1982 with similar clinical and epidemiological features of the Indian outbreaks. He passed fecal samples through a bacterial filter from nine patients with acute hepatitis and ingested the filtrate. About 30 days later, he developed symptoms of acute hepatitis and demonstrated clusters of 32–34 nm viral particles in his feces by IEM after mixing his stool with convalescent sera from infected patients [7]. The virus which had caused enteric non-A-non-B hepatitis was named hepatitis E virus (HEV).

An HEV cDNA isolation and complete sequencing of the viral genome was reported in 1991 [8, 9]. Serologic studies in industrialized countries in Europe and North America found seroprevalence of 5–21% among adults in the general population [10–12]. Although most of the seropositive subjects did not have a history of acute hepatitis, many patients with acute hepatitis from HEV infections were identified in the 1990s in several European countries [11]. Patients who had acquired their infection in Asia or Africa had HEV genotype 1 virus isolated, whereas genotype 3 infection were recovered from patients with locally acquired infections in Europe [11–13]. Research in the last few years has detected five HEV genotypes that infect humans and a major zoonotic reservoir of HEV genotype 3 and 4 strains in swine, wild boar, and deer.

Hepeviridae

After HEV was isolated initially, it was grouped with the *Caliciviridae* because of its similar structure with these viruses. However, it has subsequently been classified into the family, *Hepeviridae*. HEV has a non-enveloped icosahedral capsid that is about 32–34 nm in diameter. The viral genome is a single-stranded positive sense RNA that is 7.2 kb in length with three open reading frames (ORF-1, 2, and 3). ORF-1 contains over 5 kb and codes for several essential enzymes for virus assemble, including a methyltransferase, cysteine protease, RNA helicase, and a RNA-dependent polymerase [14]. ORF-2 encodes the viral capsid protein. ORF-3 encodes

Table 1 Morbidity and mortality from selected waterborne hepatitis E virus epidemics

Site	Years	Cases	Deaths—total	Deaths—pregnant women
Delhi, India	1954–1955	29,300	266	102
Bosnia, Yugoslavia	1964	4984	98	82
Kathmandu, Nepal	1973	10,000	118	30
Kashmir, India	1978–1979	20,000	600	436
Xinjiang, China	1986–1988	119,280	705	51
Shebeli, Somalia	1988–1989	11,413	346	48
Maharashtra, India	1989–1990	3580	50	32
Kanpur, India	1991	70,000	48	13
Islamabad, Pakistan	1993–1994	3458	8	4
Darfur, Sudan	2004	2621	45	19
Kitgum, Uganda	2007–2009	4789	72	13
Nellore, Andhra Pradesh, India	2008–2009	23,915	315	Unknown
Dhaka, Bangladesh	2008–2009	4751	18	4
Rajshahi, Bangladesh	2010	2162	12	3
Ichalkaranji/Kolhapur, Maharashtra, India	2012	5165	36	5
Refugee Camps, Upper Nile, South Sudan	2012–2013	10,055	214	22
Biratnagar, Morang, Nepal	2014	7000	17	2
Raipur, Chhattisgarh, India	2014	5000	31	12
Napak, Karamoja, Uganda	2013–2014	1498	32	18
Sambalpur, Odisha, India	2014–2015	3000	50	2
Refugee Camps, Gambella, Ethiopia	2014–2015	1117	21	2
Shimla/Solan, Himachal Pradesh, India	2015–2016	5000–10,000	22	3
Beria, South Sudan	2015–2016	2475	21	Unknown

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proteins that interact with other viral proteins and are important for virus egress from the host cell [15].

The primary site of HEV replication is in hepatocytes. Assembled HEV particles are released into the bile canaliculi as non-enveloped viruses. However, a minority of particles that are released into the sinusoidal blood stream contain envelope components from the hepatocytes [16]. Cell attachment of enveloped HEV strains is less efficient than non-enveloped HEV, and enveloped strains are less sensitive to neutralization

Four genotypes of HEV are common human pathogens but there is only one serotype [12] (Table 2). Genotypes 1 and 2 are exclusively human pathogens and are usually transmitted by fecally contaminated water. Person-to-person transmission is uncommon; therefore, a high proportion of adults remain susceptible in areas where epidemics are common. Genotype 3 and 4 strains have a zoonotic reservoir, primarily including domestic swine, wild boar, deer, rabbits, and shellfish [17, 18]. However, several other genotype 3 viruses have been isolated from goats, mongoose, and moose [19–21]. A genotype 4 virus has been isolated from cows and yaks in China [22, 23, 24••]. Recently, HEV genotype 7 viruses have been isolated from a patient in Saudi Arabia who developed hepatitis after having had a liver transplant. The identical virus was isolated from his camel, with which he had frequent contact [25••].

Genotype 1 viruses are endemic in Southern Asia, especially the Indian subcontinent, and Africa. Genotype 2 viruses have been found in Mexico and West Africa. Genotype 3 viruses are present throughout the industrialized countries in Europe, North and South America, central and southern Japan, and Australia. Genotype 4 strains are endemic in China, northern Japan, India, and Australia [12] (Fig. 1). Genotype 7 viruses have only been isolated from camels and a patient in the Middle East [25••].

Research during the past few years has identified *Hepeviridae* among a wide variety of animal species. A consensus classification of related viruses within the family *Hepeviridae* was published in 2014 [26••]. In this classification, there are two genera, *Orthohepevirus*, consisting of all mammalian and avian isolates, and *Piscihepevirus*, consisting of cutthroat trout virus. Species within the genus *Orthohepevirus* include *Orthohepevirus A* consisting of isolates from humans, pigs, wild boar, deer, mongoose, rabbit, and camel; *Orthohepevirus B* consisting of chicken and avian isolates; *Orthohepevirus C* consisting of isolates from rats, bandicoot, shrew, ferret, and mink; and *Orthohepevirus D* containing isolates from bats (Table 3). Consensus reference sequences for HEV subtypes in *Orthohepevirus A* genus have been published in 2016 [27].

Natural History and Clinical Course

Detection of Infection

The mean incubation period of HEV is about 6 weeks, with a range of 2–9 weeks. Infectious virus can be detected in the stool a week or more prior to symptoms and prior to virus in the blood. Viremia occurs with the onset of symptoms and persists for a few weeks in a person with normal immune function. However, virus can be excreted in the stool for 2 months or longer [12]. Alanine aminotransferase (ALT) levels increase with the onset of clinical symptoms and also in asymptomatic persons at the end of the incubation period. Anti-HEV IgM titers increase with the onset of clinical symptoms, or at the end of the incubation period in asymptomatic persons, and decline in 4 to 6 months. Anti-HEV IgG titers increase with the onset of clinical symptoms and persist for several years. Lifelong persistence of antibodies does not occur in all subjects. Reversion to seronegative is fairly common [12]. However, it is not clear whether or not subjects who lose antibodies are completely susceptible to re-infection.

Interpreting serological data from population-based studies has been very difficult because of the varying sensitivity and

Table 2 Epidemiological characteristics and genotype distribution of hepatitis E viruses that infect humans

Characteristic	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 7
Geographical location	Africa and Asia	Mexico, Africa	Developed countries	China, Taiwan, Japan	Middle East
Transmission route	Waterborne; fecal-oral; person-to-person	Waterborne; fecal-oral	Food-borne	Food-borne	Food-borne
Groups at high risk for infection	Young adults	Young adults	Older adults (>40 years) and males, immunocompromised persons	Young adults	Young and older adults, immunocompromised persons
Zoonotic transmission	No	No	Yes	Yes	Yes
Chronic infection	No	No	Yes	Yes	Yes

Adapted from Centers for Disease Control and Prevention

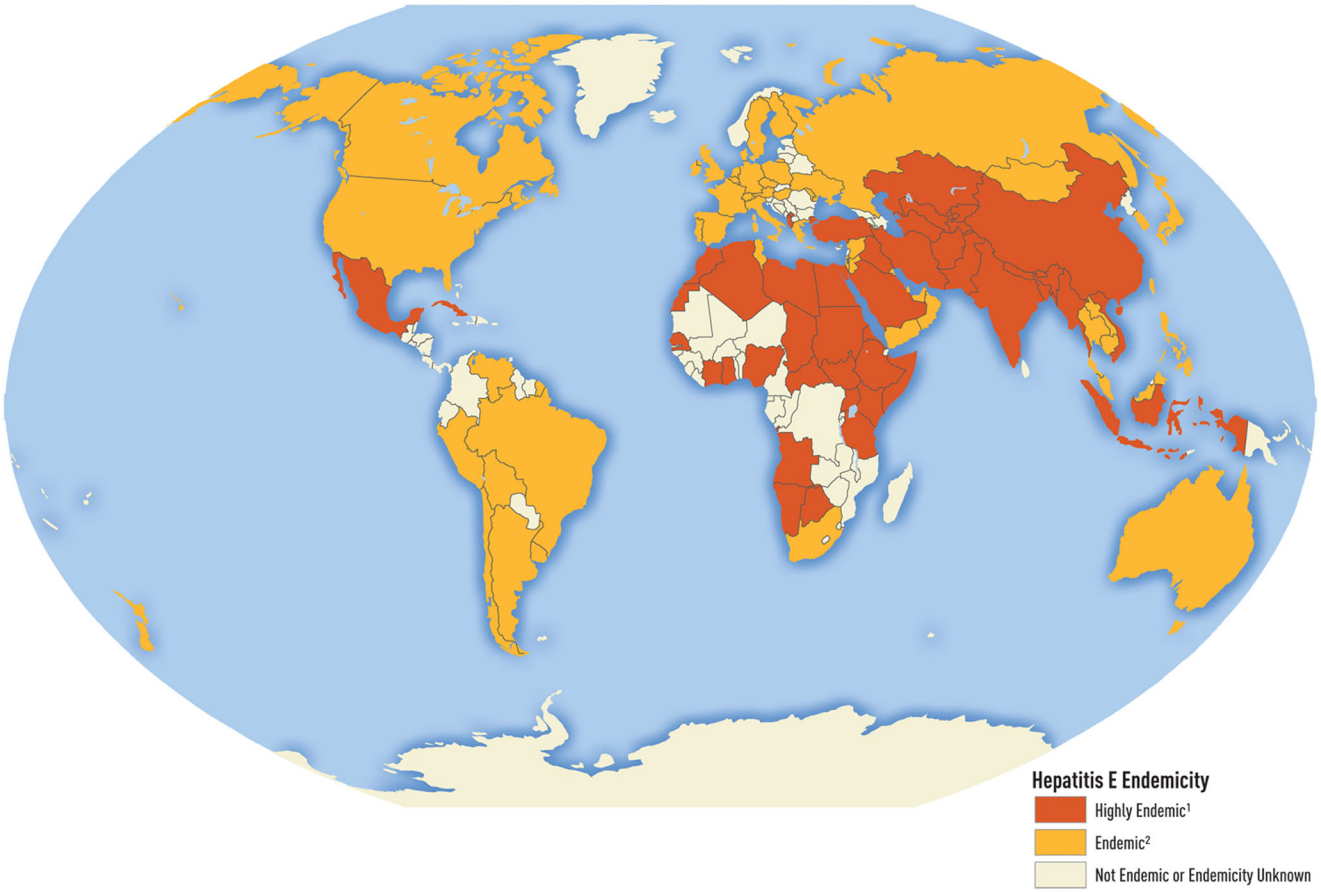

Fig. 1 Global distribution and levels of endemicity of hepatitis E virus (*HEV*). From Centers for Disease Control and Prevention

specificity of available assays [28–31]. Although some current serologic assays commonly used throughout the world perform reliably, no commercial assays have been approved and licensed by the US Food and Drug Administration for use in the USA. The Centers for Disease Control and Prevention will test subjects for HEV infection using reliable assays. However, many clinicians are unaware of this resource, which severely impedes the diagnosis and reporting of HEV in the USA. Confirmation of active HEV-infection is done by detecting HEV RNA in the serum; in addition, serologic assays for HEV antigen have been reported to detect active infection [32, 33].

Clinical Symptoms

The majority of HEV infections are subclinical. A prospective study in Bangladesh found that only 20% of participants with infection from HEV genotype 1 viruses were symptomatic [34]. The proportion of subclinical infection with genotype 3 and 4 viruses may be even higher [12]. The most common symptoms associated with acute HEV infection include jaundice, malaise, and anorexia. Some patients may also have fever, nausea, vomiting, abdominal pain, and pruritus [12]. These symptoms usually persist for 2–6 weeks; then, they resolve. A small subset of patients develops fulminant

Table 3 *Hepeviridae* family classification and reservoirs

Genus	Species	Reservoir
Orthohepevirus		
	Orthohepevirus A	Human, pig, wild boar, deer, mongoose, rate camel
	Orthohepevirus B	Chicken and other birds
	Orthohepevirus C	Greater bandicoot, Asian musk shrew, ferret, mink
	Orthohepevirus D	Bat
Piscihepevirus		Cutthroat trout and other fish

hepatitis. The mortality from HEV has been reported to be about 1%, except in pregnant women and immune compromised patients.

HEV in Pregnant Women

High mortality rates among pregnant women have been consistently reported during large waterborne epidemics of HEV genotype 1 strains in Africa and Asia [35–38]. The mortality among pregnant women has been reported to vary from 18 to 25% or higher, whereas it is only about 1% in the general population during these outbreaks [35]. Consequently, about a third or more of all fatal cases in these outbreaks occur in pregnant women. Two studies in Bangladesh have estimated that HEV infection may account for 9.5–23.0% of all maternal mortality, based on verbal autopsy reports [39, 40].

The pathogenesis of the more severe HEV infections during pregnancy is not completely understood [41]. Most reported cases of fulminant hepatitis during pregnancy have been reported among women who were infected during waterborne epidemics of HEV genotype 1 in developing countries. However, a recent study from Israel described two of nine pregnant women with autochthonous HEV infections from genotype 3 strains who developed fulminant hepatitis requiring liver transplants [42•]. The other seven patients recovered after a brief illness with acute hepatitis. Severe infections among pregnant women during epidemics in developing countries commonly involve women during the last trimester, when they are the most physiologically immune suppressed during their pregnancy [41]. They are often reported to develop fulminant hepatic failure, bleeding, eclampsia, and disseminated intravascular coagulation [43–45]. Their illness is often complicated by miscarriage and fetal death. One hypothesis is that HEV may replicate in the fetus as well as the placenta and liver leading to a higher viral load [46].

Negative strand HEV RNA has been found in the placenta, implying viral replication at this site [46]. Although termination of the pregnancy has been suggested, whether termination of the pregnancy of a patient with severe hepatitis would help alleviate the symptoms is not clear [47]. Some ORF-3-encoded proteins from genotype 1 strains have been found to interact with proteins in the clotting pathway leading to hemorrhagic manifestations [48]. In addition, nutritional deficiencies that are more common among pregnant women in developing countries may be a cofactor in the increased susceptibility and pathogenesis of more severe infections in these women [49, 50].

Immunocompromised Patients

Chronic HEV infections have been reported among immunocompromised patients in recent years [51]. Most of these reports have involved patients with solid organ transplants, who are receiving immune suppressive drug therapy to prevent rejection of their transplanted organs [52–54]. However, several AIDS patients and cancer patients with chronic HEV viremia persisting for over 6 months have also been reported [54–61]. Most of these chronic HEV infections have been associated with genotype 3 infections in Europe [54].

A multicenter study from 17 transplant centers in Europe reported 56 patients with chronic HEV infection, of whom 18 (32%) cleared their infection after reduction of the dose of immunosuppressive drugs [54]. When HEV is not cleared, ribavirin therapy is often effective in resolving chronic HEV infections in transplant patients. In a group of 59 patients with chronic HEV who were treated with a mean does of 600 mg/day of ribavirin for 3 months, 46 (78%) had a sustained virological response [55]. However, failure of ribavirin therapy has been reported, associated with a mutation in the HEV polymerase gene [62]. Chronic HEV infections have been reported less frequently from the USA. A study of 311 patients who had solid organ transplant at Johns Hopkins University hospital found several patients who had serological evidence of HEV infection after their transplant and four were HEV RNA positive but all of these patients resolved their infection [63]. An AIDS patient with chronic HEV that remained undiagnosed for over 2 years was reported from the Women's Interagency HIV study in the USA [64]. Although most patients who have developed chronic hepatitis E have been infected with genotype 3 strains, a patient from the United Arab Emirates who developed chronic HEV after infection with genotype 7 HEV acquired from his camel has been reported recently [25••].

Although large waterborne outbreaks of HEV have been reported in Africa, especially in northern and eastern Africa, there have been few reports from other areas in the continent. One group has evaluated the acute risk for HEV infection in HIV-1 positive pregnant women in central Africa [65]. Another study reported a strong association between HEV seroprevalence, HIV infection, and environmental enteropathy in urban Zambia [66]. A population that is at increased risk of fulminant hepatitis from an HEV infection are patients with chronic liver disease [12, 13, 67]. However, a recent investigation in patients in the USA with acute liver failure reported HEV infection to be uncommon [68].

Extra-hepatic Manifestations

Although HEV replicates in the liver, and the predominant symptoms are from acute hepatitis, extra-hepatic symptoms also have been reported from patients, especially those who develop chronic HEV. The most frequent extra-hepatic symptoms are neurological. These include meningitis, encephalitis, Guillain-Barre syndrome, and brachial neuritis [69–71]. A study of patients diagnosed with acute HEV infection in the UK reported that 8% had neurological manifestations [69]. In some patients, the extra-hepatic symptoms dominated the clinical findings. Some patients have evidence of extra-hepatic replication of HEV. HEV RNA has been recovered from the

cerebrospinal fluid of a patient with encephalitis [69]. In addition, patients with HEV infection have been reported to present with symptoms of acute pancreatitis, aplastic anemia, or glomerulonephritis [70]. A genotype 3 HEV isolate from a patient with chronic infection and neurologic symptoms in the UK was found to replicate in Hep G2C3A cells, a hepatoma cell line. The viral genome from the cultured virus was found to contain an insertion of 171 nucleotides from the human ribosome protein in the hypervariable region [72]. The recombinant virus, the Kernow-C1 strain, has been quite useful for in vitro studies of the replication cycle of HEV. When the same ribosome insertion was placed in a genotype 1 strain, the virus could be grown in cell lines from several animal species, including cows, chickens, dogs, cats, and hamsters [72].

Means of Transmission

Waterborne

There are several means of transmission of HEV that differ by genotype (Table 2). Large outbreaks in developing countries in Asia occur with genotype 1 strains from waterborne transmission [36, 37, 73–77]. There has been minimal direct person-to-person transmission from patients who acquire their infection from contaminated water to their contacts in these outbreaks. However, one outbreak in Uganda, which lasted over a year, had some features suggesting that significant person-to-person transmission prolonged the outbreak [38]. In this outbreak, most cases occurred secondary to an index case in a household, separated by an incubation period. In India and Pakistan, outbreaks occur seasonally during or directly following the rainy season, when flooding increases the levels of pollution of the water supply. An outbreak in 1993 in Pakistan of 3500 cases was associated with a malfunctioning water treatment plant [78].

Food-borne

Sporadic cases and clusters of infections from HEV genotype 3 and 4 strains are transmitted as a food-borne illness from a zoonotic source (Table 4). One of the earliest reports that identified the zoonotic reservoir of HEV was a case in Japan who prepared sushi from a Sitka deer he had hunted. After consuming the sushi, both he and a friend developed acute hepatitis. The identified virus was recovered from the sushi [79]. Another cluster of four cases was subsequently reported from Japan after consumption of contaminated meat from a deer and a wild boar [80]. In Southern France, a cluster of seven patients with HEV genotype 3 infections were traced to the consumption of *figatellu*, a sausage containing uncooked pig liver served during a wedding party [81]. A recent outbreak in Australia involving 24 people was associated with consumption of pork liver pate [82]. An outbreak of 33 cases among passengers on a cruise ship was attributed to the consumption of raw shellfish [83]. Contaminated water that is used for irrigation can be a source of infection. A study in Canada found HEV contamination of strawberries with viruses identified to neighboring swine farms [84]. A recent study of HEV in cows in China found HEV RNA in their milk [24••]. The HEV was transmitted to monkeys with oral ingestion of the milk, even after the milk was pasteurized [24••]. Other investigators have detected HEV genotype 4 RNA in cows and yaks in China [22, 23]. Although HEV RNA has not been detected among cows in the USA, a serologic study to identify the range of the zoonotic reservoir among animals in the USA found 15% of cows to be HEV seropositive [85]. However, attempts to detect HEV RNA in cows in the USA and Europe, where genotype 3 virus is endemic, have not been successful, thus far [86]. A patient from the United Arab Emirates contracted an HEV genotype 7 infection from drinking camel's milk and eating camel meat after having a liver transplant [25••].

Table 4 Food sources of human HEV infection

Food source	Location
Figatellu (smoked pig liver sausage)	France
Wild deer sushi	Japan
Raw oysters	UK
Wild boar meat	Japan, German
Larb Loo (pig liver and blood)	Thailand
Riverine water epidemics	Thailand, Cambodia
Camel meat and milk	Saudi Arabia
Pig liver pate	Australia

Despite these well-documented examples of food-borne transmission from a zoonotic reservoir, the source of infection in most patients with HEV is not identified. However, HEV RNA has been detected in 11% of pork liver for sale in supermarkets in the USA and is frequently found in commercial pork liver sold in Europe [87–89]. These contaminated food products could be a source of cross-contamination of other food in the kitchen, as well as a direct source of infection if the pork is inadequately cooked prior to consumption.

Transfusion and Parenteral Transmission

Since most infections with genotype 3 and 4 HEV viruses are asymptomatic and involve adults, transmission by transfusion of blood products is a risk. Several cases of transfusion transmitted HEV have been reported from Japan [90•, 91, 92]. In the Hokkaido area of northern Japan, genotype 4 HEV strains are common. Routine screening of donors for HEV RNA was instituted in Hokkaido in 2008. Among over 2 million donations that were screened, 231 were HEV RNA positive [93]. Throughout Japan, 19 transfusion-transmitted cases have been

detected in the last 15 years [90•]. A study of 225,000 blood donors in the UK found 78 HEV RNA-positive donors [94]. The investigators followed 44 patients who had been transfused with HEV RNA-positive blood products, and 18 of the recipients were infected [94]. Ten of these patients developed chronic infections. The investigators found the lowest viral load that transmitted infection to be 2×10^4 and 55% of components containing this dose transmitted infection [94]. However, transmission could have been prevented from transfusion of blood with lower viral loads by some partial immunity among recipients which was difficult to evaluate in this study. After this study in 2016, the UK blood services instituted a policy of only transfusing patients with a transplant or hematologic malignancy with screened HEV negative blood. Based on an estimated annual incidence of HEV in the general population of the UK of 0.2%, they estimated the risk ratio of food-borne to transfusion transmission of HEV among recipients to be 13:1 [95•].

Vertical Transmission

Transmission of HEV to the fetus of a woman who develops infection during pregnancy or to the infant at delivery is very common. Various studies have estimated the rate of vertical transmission to be 33–67% [44, 45, 96, 97]. Although fetal death after vertical infection is common, many infants have recovered without sequelae [44, 45]. HEV RNA has been detected in the breast milk of a woman who was infected when she was breast-feeding [98•]. Data on the risk to the infant of continual breast-feeding when this occurs are needed.

Occupational Transmission

Several occupations carry an increased risk of exposure to infectious HEV, including swine farmers, butchers, abattoir workers, and workers in contact with sewage. Some studies have shown these occupations to have higher seroprevalence of HEV IgG than the general population [99–102]. However, some studies have not found these occupations to carry a higher risk [102]. A recent study of HEV seroprevalence among wild boar hunters in central Germany found them to have higher rates. The hunters who wore gloves during disemboweling wild boars had significantly lower HEV seroprevalence (age-adjusted OR 0.12; 95% CI 0.02, 0.86) [103]. A case was reported recently of transmission of HEV from a scalpel injury in a laboratory worker performing research on a pig [104].

Animal Reservoirs for HEV Genotypes 3, 4, and 7

Swine and Wild Boar

The animals that are most commonly reported to be infected with HEV genotype 3 and 4 strains are domestic swine and wild boar [18, 105]. Swine in Europe and North America are infected with genotype 3 strains, while in Asia, swine are infected with genotype 4 viruses [106]. The pigs commonly develop an HEV infection at 2 to 4 months of age. They excrete virus in their feces for 4–7 weeks or longer and viremia lasts 1 to 2 weeks, but is delayed when their sow is HEV IgG seropositive [17]. The infected animals are asymptomatic; however, microscopic lesions of hepatitis have been demonstrated in the liver of some animals. Importantly, 11% of pig livers for sale in grocery stores in the USA have been found to be HEV RNA positive [18]. Heating the infected liver at 56 °C, similar to "medium-rare" cooking, did not eliminate infectivity [107–109].

Deer

Several species of deer have been found to be HEV seropositive. HEV genotype 3 viruses have been identified in Sitka deer in Japan and deer in Hungary [80, 110]. Transmission of HEV from deer to humans has been reported in Japan [79, 80].

Camels

After the report of a post liver-transplant patient from the United Arab Emirates who developed chronic hepatitis from infection with HEV genotype 7 acquired from his camel, a survey of 2438 dromedary camels from five countries in the Middle East was reported [111, 112••]. The investigators found 12 (0.6%) of the 2171 serum samples and 5 (1.9%) of the 267 fecal samples to be HEV RNA positive. These were classified as HEV genotype 7 viruses. Another group of researchers from China reported an isolate of HEV from Bactrim (2-hump) camels, which differed in amino-acid distances by 0.095 to 0.148 from the dromedary (1-hump) isolates [113]. A recent study from the United Arab Emirates reported that HEV infection accounted for 40% of acute hepatitis cases [112••]. Clearly, more data are needed on the importance of the camel reservoir in HEV infections in Middle Eastern countries. Camels are clearly an important reservoir of HEV in some populations who do not have exposures to swine.

Rabbits

A genotype 3 HEV strain has been isolated from rabbits in China, the USA, and France [114, 115]. These viruses share about 95% nucleotide identity with human genotype 3 strains and have been successfully transmitted to pigs [115]. Although no human cases have been reported, thus far, these strains are likely infectious for humans.

Other Animal Reservoirs

Genotype 3 HEV strains have been isolated from mongooses in Japan. In addition, genotype 3 strains were isolated from rats in California, although most rat HEV strains have only 50% sequence identity with human viruses and are not infectious for primates [116, 117]. A genotype 3 strain has been isolated from a goat; however, no documented human infections have been reported to date from HEV genotype 3 from goats [19].

Although HEV does not replicate in shellfish, consumption of raw shellfish has been reported to transmit HEV when it concentrates virus from contaminated water [83]. Shellfish *Hepeviridae* isolates have been found to be genotype 3.

The zoonotic reservoir for HEV is likely to be more extensive than has been appreciated. Hopefully, additional research of the animal reservoir of human *Hepeviridae* will lead to a better understanding of the sources of human infections, as well as more effective prevention.

Epidemiology

The epidemiology of HEV differs substantially between populations in developing and industrialized countries (Table 2, Fig. 1). In developing countries, HE has been reported as large outbreaks of acute hepatitis from HEV genotype 1 and 2 infections transmitted by contaminated water. Many of these outbreaks are quite large, including thousands of reported cases. The largest reported outbreak occurred in Xinjiang, China involving 119,280 cases and 705 deaths in 1986–1988 [3] (Table 1). However, large outbreaks have been reported regularly after the 1955 outbreak in Delhi. Most of these outbreaks have occurred after monsoon rains, which causes fecal contamination of the water supply. In addition, some outbreaks have been secondary to residents tapping into water transport pipes, which then allowed contamination of the water [36]. It has been estimated that 20.1 million persons each year become infected with HEV genotype 1 leading to 70,000 deaths and 3000 stillbirths occur worldwide [75].

In addition to the large outbreaks, sporadic cases of hepatitis from HEV genotype 1 infection occur among persons who live in the endemic countries but often go undiagnosed [118•]. Sporadic cases of hepatitis from HEV-genotype 1 infection are diagnosed periodically by clinicians in Europe or the USA among travelers who acquired their infection in India or another endemic country [119, 120].

Acute hepatitis in India, Pakistan, Nepal, Bangladesh, and other countries where HEV genotype 1 is endemic is most often caused by an infection with this virus, rather than with one of the other human hepatitis viruses [35]. The distinctive epidemiologic characteristic of HEV infections include the following: (a) they involve adults much more frequently than children, (b) there is rarely person-to-person transmission, and (c) pregnant women have more severe morbidity and increased mortality.

However, there are some exceptions to these signature characteristics of HEV genotype 1 infections and outbreaks. Egypt is endemic for HEV genotype 1 infections, but subclinical infections commonly involve children in this country [121]. In addition, pregnant women commonly have inapparent HEV infections in Egypt [121]. The epidemiology of HEV in Egypt resembles hepatitis A virus (HAV). The reasons for this difference from the epidemiology of HEV in other countries where genotype 1 epidemics are common are not known. Perhaps pregnant women, who have experienced a primary HEV infection in childhood, have some residual immunity that modify the severity of a secondary infection.

The existence of genotype 3 and 4 HEV strains was appreciated in the 1990s; about a decade after, HEV was identified. These viruses were found to be infectious for pigs, monkeys, and other species [12]. Several case reports and small outbreaks have been directly linked to consumption of contaminated pork products. However, indirect exposure to HEV from pig manure can occur from sewage with animal manure run-off, surface water contamination, coastal water contamination, and cross-contamination of other food from pork in the kitchen [86]. Although the source of infection in patients with HEV infection is often not identified, several clinical and epidemiologic features of HEV may account for this problem. HEV infections are often asymptomatic, the incubation period is a month or more, and person-to-person transmission is very uncommon.

The seroprevalence of HEV IgG antibodies in different populations is variable, but often quite high, around 15–40%. The prevalence of HEV IgG antibodies increases in late adolescence and young adults 20–30 years of age. The seroprevalence is usually similar in men and women. However, a study in Bangladesh found a higher seroprevalence among men who worked outside of the home [122]. In areas where genotypes 3 and 4 are common, the seroprevalence increase with age and is highest in men over age 50 years [12, 123].

Treatment and Prevention

There is no specific treatment for HEV infection. Immunocompromised patients with chronic HEV have been found to respond to ribavirin. In one study, 46 of 59 (78%) patients with solid organ transplants and chronic HEV resolved their infections after a treatment regimen of 600 mg/day of ribavirin for about 3 months. [55]. Among patients who cleared their HEV with ribavirin therapy, all had a 0.5 log decrease in their HEV viral load by 7 days of therapy [124]. Pegylated interferon has also been found to be successful in clearing chronic HEV in a few cases but can only be used in patients with liver transplants [125]. Sofosbuvir has been found to have antiviral activity against HEV in vitro [126].

However, it did not clear HEV viremia in one patient [125]. Ribavirin is not recommended for use in pregnant women because it has teratogenic properties.

A subunit HEV vaccine (Hecolin) was developed and tested in China in 2012 [127]. The vaccine is a truncated polypeptide containing amino acids 368 to 606 from an HEV genotype 1 strain that is expressed in *Escherichia coli* [128]. It forms virus-like particles (VLPs) that are highly immunogenic when administered by the intramuscular route. The vaccine was found to have high (100%) efficacy in a clinical trial including over 94,000 subjects aged 16–65 years in China [127]. The vaccine was given in three doses, at 0, 1, and 6 months. Although pregnant women were not intentionally enrolled, the vaccine was safe and immunogenic in 40 women in early pregnancy who were inadvertently vaccinated [129]. The vaccine was found to be 86.8% (95% CI 72.1–100%) effective in preventing clinical hepatitis in a 4.5-year follow-up in subjects who had received three doses [130]. Despite these encouraging results, the vaccine is not pre-qualified by WHO and is not available outside of China [131]. A WHO SAGE group reviewed the data on the vaccine and concluded that the data on the safety and immunogenicity were "promising." However, they recommended additional studies. Data are needed on the safety, immunogenicity, and efficacy of the vaccine in immunocompromised patients, pregnant women, patients with chronic liver disease, and those younger than 16 years and older than 65 years [132]. Nevertheless, the WHO commented that each country should be free to use vaccine in select populations during an emergency if they deemed it advisable. Clearly, additional data are needed on the efficacy of the Hecolin vaccine in preventing HEV when given in fewer doses in an accelerated schedule.

Control of large waterborne epidemics from genotype 1 strains is very challenging, since they occur in populations with limited resources. Boiling water is effective but often the fuel or other resources are scarce or unavailable. A recent study found that adding chlorine to non-potable water could be effective in eliminating the infectivity of HEV [133, 134]. However, in an outbreak among a displaced population in Darfur, Sudan in 2004, chlorination of contaminated water was ineffective in preventing HEV [37].

Food-borne infections from HEV have been very difficult to prevent because there are many sources of food-borne transmission of HEV (Table 4). The consumption of exotic foods, such as pig liver sausage in France or "larb loo" and raw pig liver covered with pig blood in Thailand, Laos, and other South East Asian countries, is hazardous but difficult dietary practices to change [86]. Nevertheless, it is good public health practice to advise high-risk patients who are immunocompromised after a transplant, a malignancy, or AIDS to avoid eating organ meats, pig liver patè, and raw shellfish. Food that could be contaminated with HEV, such as pork meat or liver, should be cooked to at least 70 °C (160 °F) for at least 20 min for it to be safe [108].

To prevent the transmission of HEV by transfusion, donor screening for HEV RNA will be required. Although the risk of food borne transmission of HEV exceeds that from transfusion, it is important to screen donors whose blood products will be transfused into patients at high risk of serious sequelae [93]. Unfortunately, a significant proportion of recipients of blood products are at high risk. Prevention in pregnant women is also very challenging. Certainly, the use of boiled water by pregnant women for drinking during an epidemic, when possible, should be practiced. Hopefully, the HEV vaccine could be employed in the future to prevent infection in persons at the highest risk of severe morbidity and mortality from an HEV infection.

Summary

The epidemiology of HEV infections is highly variable geographically and in different populations. Knowledge of the epidemiology, viral reservoirs, and transmission routes of these recently recognized viruses continues to expand.

Compliance with Ethical Standards

Conflict of Interest Kenrad E. Nelson, Chris Heaney, and Brittany L. Kmush each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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