



Hepatitis E

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Abstract

is inflammation of the liver caused by [infection](#) with the [hepatitis E virus](#).^{[1][2]} It is one of five known human [hepatitis](#) viruses: [A](#), [B](#), [C](#), [D](#), and [E](#). HEV is a [positive-sense](#), single-stranded, nonenveloped, RNA icosahedral [virus](#). HEV has mainly a fecal-oral transmission route.^{[3][4][5]} Infection with this virus was first documented in 1955 during an outbreak in [New Delhi, India](#)^[6]. A [preventive vaccine](#) (HEV 239) is approved for use in [China](#).^[7]

Although hepatitis E often causes an acute and [self-limiting infection](#) (the viral infection is temporary and the individual recovers) with low death rates in the western world, it bears a high risk of developing chronic hepatitis in people with a [weakened immune system](#) with substantially higher death rates. [Organ transplant](#) recipients who receive medications to weaken the immune system and prevent organ rejection are thought to be the main population at risk for chronic hepatitis E.^[8]

Hepatitis E infection has a clinical course comparable to hepatitis A, but in [pregnant women](#), the disease is more often severe and is associated with a clinical syndrome called [fulminant liver failure](#). Pregnant women, especially those in the third trimester, have a higher rate of death from the disease of around 20%.^{[9][10][4]} In total there are 8 genotypes; genotypes 3 and 4 cause chronic hepatitis in the immunosuppressed.^{[11][12]} Hepatitis E incidence in 2017 was more than 19 million.^[13]

Signs and symptoms

The incubation period of hepatitis E varies from 2 to 8 weeks. After a short [prodromal phase](#) symptoms lasting from days to weeks follow. They may include [jaundice](#), fatigue, and [nausea](#), though the majority of HEV infections are asymptomatic. The asymptomatic phase coincides with elevated hepatic [aminotransferase](#) levels.^{[14][15]}

Viral RNA becomes detectable in [stool](#)



Pregnant women show a more severe course of infection than other populations. Mortality rates of 20% to 25% and hepatic failure have been reported from outbreaks of genotype 1 and 2 HEV in developing countries. Besides signs of an acute infections, adverse maternal and fetal outcomes may include [preterm delivery](#), abortion, [stillbirth](#), and intrauterine fetal and neonatal death.^{[23][9][24]}

The pathologic and biologic mechanisms behind the adverse outcomes of [pregnancy](#) infections remain largely unclear so far. Mainly, increased [viral replication](#) and influence of hormonal changes on the immune system have been discussed lately.^[25] Furthermore, studies showing evidence for viral replication in the placenta or reporting the full [viral life cycle](#) in placental-derived cells in vitro implicate the human [placenta](#) as site of extra-hepatic replication.^[26]

Virology

HEV is classified into the family Hepeviridae, which is divided in two genera, Orthohepevirus (all mammalian and avian HEV isolates) and Piscihepevirus (cutthroat trout HEV).^[25] Only one [serotype](#) of the virus is known, and classification is based on the [nucleotide](#) sequences of the genome.^[27] [Genotype](#) 1 has been classified into five subtypes^[28], genotype 2 into two subtypes^{[28]pg 10}, and genotypes 3 and 4 have been divided into 10^[29] and seven subtypes^[29]. Additionally there are genotypes 5, 6, 7 and 8.^[12] Rat HEV was first isolated from Norway rats in Germany^[30], a 2018 CDC article indicated the detection of rat HEV RNA in a transplant recipient.^[31]

has been isolated from tropical and several subtropical countries in [Asia](#) and [Africa](#).^[32]

has been isolated from [Mexico](#), [Nigeria](#), and [Chad](#).^[33]

has been isolated almost worldwide including [Asia](#), [Europe](#), [Oceania](#), and [North](#) and [South America](#).^[34]

appears to be limited to Asia and indigenous cases from Europe.^{[32][35][36]}

Genotypes 1 and 2 are restricted to humans and often associated with large outbreaks and epidemics in developing countries with poor sanitation conditions.^[32] Genotypes 3 and 4 infect humans, pigs, and other animal species and have been responsible for sporadic cases of

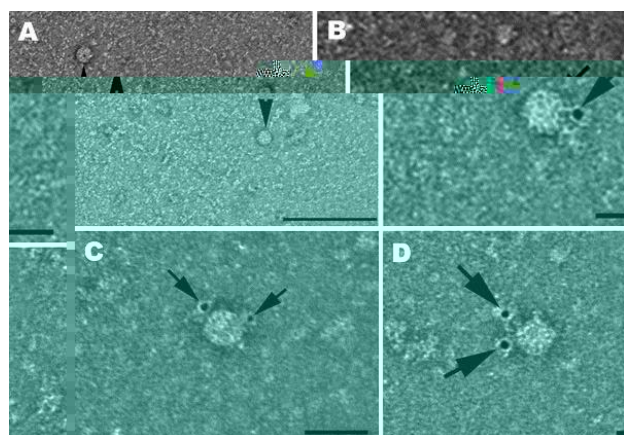
hepatitis E in both developing and industrialized countries.^{[37][38]}

In the United Kingdom, the [Department for Environment, Food and Rural Affairs](#) said that the number of human hepatitis E cases increased by 39% between 2011 and 2012.^[39]

Hepatitis E is widespread in Southeast Asia, northern and central Africa, India, and Central America.^[40] It is spread mainly by the [fecal-oral route](#) due to fecal contamination of water supplies or food; person-to-person transmission is uncommon.^[41] Genotypes 1 and 2 cause outbreaks, while the other genotypes cause sporadic cases.^[42]

As mentioned, the incubation period following exposure to the hepatitis E virus ranges from 3 to 8 weeks, with a mean of 40 days.^[41] Outbreaks of epidemic hepatitis E most commonly occur after heavy rainfalls and [monsoons](#) because of their disruption of water supplies.^[43] Major outbreaks have occurred in New Delhi, India (30,000 cases in 1955–1956),^[44] [Burma](#) (20,000 cases in 1976–1977),^[45] [Kashmir, India](#) (52,000 cases in 1978),^[46] [Kanpur, India](#) (79,000 cases in 1991),^[44] and China (100,000 cases between 1986 and 1988).^[47] According to Rein et al., HEV genotypes 1 and 2 caused some 20.1 million Hepatitis E infections, along with 3.4 million cases of symptomatic disease, and 70,000 deaths in 2005; however the aforementioned paper did not estimate the burden of genotypes 3 and 4.^[48]

According to the Department for Environment, Food and Rural Affairs, evidence indicated the increase in hepatitis E in the U.K. was due to food-borne [zoonoses](#), citing a study that found in the U.K. that 10% of pork



Hepatitis E virus in pork liver sausage (the arrows in panel A point to the virion, those in B, C & D point to bound gold nanoparticles used in virus detection)



sausages contained the Hepatitis E virus. Some research suggests that food must reach a temperature of 70 °C for 20 minutes to eliminate the risk of infection. The [Animal Health and Veterinary Laboratories Agency](#) discovered hepatitis E in almost half of all pigs in Scotland.^[39]

Hepatitis E infection appeared to be more common in people on hemodialysis, although the specific risk factors for transmission are not clear.^[49]

The disease is thought to be a zoonosis in that animals are thought to be the source. Both deer and swine have been implicated.^[50] Domestic animals have been reported as a reservoir for the hepatitis E virus, with some surveys showing infection rates exceeding 95% among domestic pigs.^[51] Replicative virus has been found in the [small intestine](#), [lymph nodes](#), [colon](#), and [liver](#) of experimentally infected [pigs](#). Transmission after consumption of [wild boar](#) meat and uncooked deer meat has been reported as well.^[52] The rate of transmission to humans by this route and the public health importance of this are, however, still unclear.^[53]

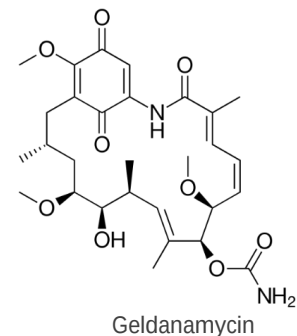
A number of other small mammals have been identified as potential reservoirs: the lesser bandicoot rat ([Bandicota indica](#)), the black rat ([Rattus norvegicus](#)) and the Asian house shrew ([Suncus murinus](#)). A new virus designated rat hepatitis E virus has been isolated.^[54]

HEV has three [open reading frames \(ORFs\)](#) encoding two polyproteins (O1 and O2 protein). ORF2 encodes three capsid proteins whereas O1 encodes seven fragments involved in viral replication, among others.^{[55][56][57]}

The smallest ORF of the HEV genome, ORF3 is translated from a subgenomic RNA into O3, a protein of 113–115 amino acids. ORF3 is proposed to play critical roles in immune evasion by HEV. Previous studies showed that ORF3 is bound to viral particles found in patient sera and produced in cell culture. Although in cultured cells ORF3 has not appeared essential for HEV RNA replication, viral assembly, or infection, it is required for particle release.^[58]

The lifecycle of hepatitis E virus is unknown; the capsid protein obtains viral entry by binding to a cellular receptor. ORF2 (c-terminal) moderates viral entry by binding to HSC70.^{[59][60]}

[Geldanamycin](#) blocks the transport of HEV239 capsid protein, but not the binding/entry of the truncated capsid protein, which indicates that HSP90 plays an important part in HEV transport.^[59]



Diagnosis

In terms of the diagnosis of hepatitis E, only a laboratory test that confirms antibodies present for HEV RNA or HEV can be trusted as conclusive for the virus in any individual tested for it.^{[10][61]} In the United States no serologic tests for diagnosis of HEV infection have ever been authorized by the Food and Drug Administration.^[10] The World Health Organization has developed an international standard strain for detection and quantification of HEV RNA.^[62]

Assuming that vaccination has not occurred:

- with HEV-Ag and/or HEV-RNA indicates chronic infection, however if with Anti-HEV-Ag being 'positive' this indicates recent infection, if Anti-HEV-Ag is then there is cross reactivity.^[20]

- with HEV-Ag and/or HEV-RNA as well as Anti-HEV-Ag then it is acute infection, if the latter is then it is dependent on time taken for seroconversion. If HEV-Ag and/or HEV-RNA is with Anti-HEV-Ag being 'positive' it is a past infection, if the latter is then infection is not present.^[20]

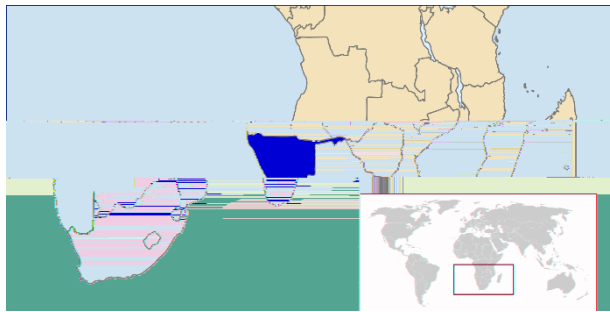
Prevention

[Sanitation](#) is the most important measure in prevention of hepatitis E; this consists of proper treatment and disposal of human waste, higher standards for public water supplies, improved personal hygiene procedures, and sanitary food preparation. Thus, prevention strategies of this disease are similar to those of many other diseases that plague developing nations.^[41] Cooking



meat at 71 degrees Celsius for 5 minutes kills the Hepatitis E virus.^[63]

The amount of virus present in blood products required to cause transfusion-transmitted infection (TTI) appears variable. Transfusion transmission of Hepatitis E virus can be screened via minipool HEV NAT (Nucleic acid testing) screening.^{[64][65]} NAT is a technique used to screen blood molecularly, when blood donations are received; it screens



Namibia, Africa

An outbreak was reported in [Namibia](#) which is located in Africa, in January 2018, the total infected is reported as 490.^[80] As of 14 April, 2019 according to the World Health Organization, there have been 5,014 cases and 42 deaths due to this Hepatitis E outbreak in the country of Namibia. The case fatality ratio for this outbreak is currently 0.8%.^[81]

History

The most recent common ancestor of hepatitis E evolved between 536 and 1344 years ago.^[82] It diverged into two [clades](#) — an anthropotropic form and an enzootic form — which subsequently evolved into genotypes 1 and 2 and genotypes 3 and 4, respectively.^[83]

Genotypes 1, 3, and 4 all increased their effective population sizes in the 20th century.^[82] The population size of genotype 1 increased noticeably in the last 30–35 years. Genotypes 3 and 4 population sizes began to increase in the late 19th century up to 1940–1945. Genotype 3 underwent a subsequent increase in population size until the 1960s. Since 1990, both genotypes' population sizes have been reduced back to levels last seen in the 19th century. The overall mutation rate for the genome has been estimated at roughly 1.4×10^{-3} substitutions/site/year.^[82]

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