Hepatitis E is inflammation of the liver caused by infection with the hepatitis E virus.\(^1\) 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 a fecal-oral transmission route.\(^2\)\(^3\) Infection with this virus was first documented in 1955 during an outbreak in New Delhi, India.\(^4\) A preventive vaccine (HEV 239) is approved for use in China.\(^5\)

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.\(^6\)

Clinically, it is 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 hepatitis E.
failure. Pregnant women, especially those in the third trimester, have a higher rate of death from the disease of around 20%.\textsuperscript{(7)} Hepatitis E newly infected about 28 million people in 2013.\textsuperscript{(8)}

## Signs and symptoms

### Acute infection

The incubation period of hepatitis E varies from 3 to 8 weeks, after a short prodromal phase symptoms lasting from days to weeks follow. They may include jaundice, fatigue, and nausea. The symptomatic phase coincides with elevated hepatic aminotransferase levels.\textsuperscript{(9)}

Viral RNA becomes detectable in stool and blood serum during incubation period. Serum IgM and IgG antibodies against HEV appear just before onset of clinical symptoms. Recovery leads to virus clearance from the blood, while the virus may persist in stool for much longer. Recovery is also marked by disappearance of IgM antibodies and increase of levels of IgG antibodies.\textsuperscript{(3)}\textsuperscript{(9)}

### Chronic infection

While usually an acute disease, in immunocompromised subjects—particularly in solid organ transplant patients—hepatitis E may cause a chronic infection.\textsuperscript{(10)} Occasionally this may cause liver fibrosis and cirrhosis.\textsuperscript{(11)}

### Other organs

Infection with hepatitis E virus can also lead to problems in other organs. For some of these reported conditions the relationship is tenuous, but for several neurological and blood conditions the relationship appears causal.\textsuperscript{(12)}

- Acute pancreatitis
- Guillain-Barré syndrome (acute limb weakness due to nerve involvement) and neuralgic amyotrophy (arm and shoulder weakness)
- Hemolytic anemia in people with the hereditary risk factor glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency)
- Glomerulonephritis with nephrotic syndrome and/or cryoglobulinemia
- Mixed cryoglobulinemia, where antibodies in the bloodstream react inappropriately at low temperatures
- Severe thrombocytopenia (low platelet count in the blood) which confers a risk of dangerous bleeding

### Infection in pregnancy

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 \textsuperscript{H} 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.\textsuperscript{(13)}\textsuperscript{(14)}

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.\textsuperscript{(15)} 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.

### Virology

### Classification
Only one serotype of the virus is known, and classification is based on the nucleotide sequences of the genome. Genotype 1 has been classified into five subtypes, genotype 2 into two subtypes, and genotypes 3 and 4 have been into 10 and seven subtypes, respectively.

**Distribution**

- **Genotype 1** has been isolated from tropical and several subtropical countries in Asia and Africa. Genotype 1 has been isolated from tropical and several subtropical countries in Asia and Africa. Genotype 2 has been isolated from Mexico, Nigeria, and Chad. Genotype 3 has been isolated almost worldwide including Asia, Europe, Oceania, and North and South America. Genotype 4 appears to be limited.

Genotypes 1 and 2 are restricted to humans and often associated with large outbreaks and epidemics in developing countries with poor sanitation conditions. 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.

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.

**Transmission**

Hepatitis E is widespread in Southeast Asia, northern and central Africa, India, and Central America. It is spread mainly by the fecal-oral route due to fecal contamination of water supplies or food; person-to-person transmission is uncommon.

The incubation period following exposure to the hepatitis E virus ranges from 3 to 8 weeks, with a mean of 40 days. Outbreaks of epidemic hepatitis E most commonly occur after heavy rainfalls and monsoons because of their disruption of water supplies. Major outbreaks have occurred in New Delhi, India (30,000 cases in 1955–1956), Burma (20,000 cases in 1976–1977), Kashmir, India (52,000 cases in 1978), Kanpur, India (79,000 cases in 1991), and China (100,000 cases between 1986 and 1988).

DEFRA said that evidence indicated the increase in hepatitis E in the UK was due to food-borne zoonoses, citing a study that found 10% of pork 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.

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

**Animal reservoir**

The disease is thought to be a zoonosis in that animals are thought to be the source. Both deer and swine have been implicated. Domestic animals have been reported as a reservoir for the hepatitis E virus, with some surveys showing infection rates exceeding 95% among domestic pigs. 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. The rate of transmission to humans by this route and the public health importance of this are, however, still unclear.
A number of other small mammals have been identified as potential reservoirs: the lesser bandicoot rat (*Bandicota bengalensis*), the black rat (*Rattus rattus brunneusculus*) and the Asian house shrew (*Suncus murinus*). A new virus designated rat hepatitis E virus has been isolated.[37]

**Genomics**

*Main article: Wikipedia:Hepatitis E Virus*

The virus has since been classified into the genus *Orthohepevirus*, and has been reassigned into the *Hepeviridae* family. The virus itself is a small nonenveloped particle. The genome is about 7200 bases in length, is a polyadenylated, single-strand RNA molecule that contains three discontinuous and partially overlapping open reading frames (ORFs) along with 5′ and 3′ cis-acting elements, which have important roles in HEV replication and transcription. ORF1 encodes a methyltransferase protease, helicase and replicase; ORF2 encodes the capsid protein and ORF3 encodes a protein of undefined function. A three-dimensional, atomic-resolution structure of the capsid protein in the context of a virus-like particle has been described.[38][39]

As of 2009, around 1,600 sequences of both human and animal isolates of HEV are available in open-access sequence databases. Species of this genus infect humans, pigs, boars, deer, rats, rabbits, and birds.[40]

**Virus lifecycle**

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.[38]

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.[38]

**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.[41][42]

**Prevention**

**Sanitation**

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 others that plague developing nations.[26]

**Vaccines**

A vaccine based on recombinant viral proteins was developed in the 1990s and tested in a high-risk population (Nepal) in 2001.[43] The vaccine appeared to be effective and safe, but development was stopped for lack of profitability, since hepatitis E is rare in developed countries.[44] No hepatitis E vaccine is licensed for use in the United States.[45]
Although other HEV vaccine trials have been successful, these vaccines have not yet been produced or made available to susceptible populations. The exception is China; after more than a year of scrutiny and inspection by China's State Food and Drug Administration (SFDA), a hepatitis E vaccine developed by Chinese scientists was available at the end of 2012. The vaccine—called HEV 239 by its developer Xiamen Innovax Biotech—was approved for prevention of hepatitis E in 2012 by the Chinese Ministry of Science and Technology, following a controlled trial on 100,000+ people from Jiangsu Province where none of those vaccinated became infected during a 12-month period, compared to 15 in the group given placebo. The first vaccine batches came out of Innovax' factory in late October 2012, to be sold to Chinese distributors.

Due to the lack of evidence, WHO as of 2015 did not make a recommendation regarding routine use of the HEV 239 vaccine. National authorities may however decide to use the vaccine based on the local epidemiology.

### Treatment

In terms of treatment, ribavirin is not registered for hepatitis E treatment, though off-label experience for treating chronic hepatitis E with this compound exists. The use of low doses of ribavirin over a three-month period has been associated with viral clearance in about two-thirds of chronic cases. Other possible treatments include pegylated interferon or a combination of ribavirin and pegylated interferon. In general, chronic HEV infection is associated with immunosuppressive therapies, but remarkably little is known about how different immunosuppressants affect HEV infection. In individuals with solid-organ transplantation viral clearance can be achieved by temporal reduction of the level of immunosuppression.

### Epidemiology

The hepatitis E virus causes around 20 million infections a year. These result in around three million acute illnesses and as of 2010, 57,000 deaths annually. It is particularly dangerous for pregnant women, who can develop an acute form of the disease that is lethal in 30% of cases or more. HEV is a major cause of illness and of death in the developing world and disproportionate cause of deaths among pregnant women. Hepatitis E is endemic in Central Asia, while Central America and the Middle East have reported outbreaks. Increasingly, hepatitis E is being seen in developed nations, with reports in 2005 of 329 cases of hepatitis E virus infection in England and Wales.

### Recent outbreaks

In October 2007, an epidemic of hepatitis E was suspected in Kitgum District of northern Uganda where no previous epidemics had been documented. This outbreak progressed to become one of the largest hepatitis E outbreaks in the world. By June 2009, the epidemic had caused illness in 10,196 persons and 160 deaths.

In July 2012, an outbreak was reported in South Sudanese refugee camps in Maban County near the Sudan border. South Sudan's Ministry of Health reported over 400 cases and 16 fatalities as of September 13, 2012. Progressing further as of February 2, 2013, 88 died due to the outbreak. The medical charity Medecins Sans Frontieres said it treated almost 4,000 patients. In April 2014, an outbreak in the Biratnagar Municipality of Nepal resulted in infection of over 6,000 locals and at least 9 dead. An outbreak was reported in Namibia in January 2018. Two mothers are dead and the total infected is reported as 49.

### History

The most recent common ancestor of hepatitis E evolved between 536 and 1344 years ago. 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.
Genotypes 1, 3, and 4 all increased their effective population sizes in the 20th century.[40] 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 $1.4 \times 10^{-3}$ substitutions/site/year.[40]

References

This article incorporates public domain text from the CDC as cited

6. Zhou, X; de Man, RA; de Knecht, RJ; Metselaar, HJ; Peppelenbosch, MP; Pan, Q; De Man, De Knecht; Metselaar; Peppelenbosch; Pan (2013). "Epidemiology and management of chronic hepatitis E infection in solid organ transplantation: a comprehensive literature review". Rev Med Virol. 23 (5): 295–304. doi:10.1002/rmv.1751. PMID 23813631.
7. WHO. "Global Alert and Response (GAR); Hepatitis E". Retrieved 26 January 2012.
Further reading


This page was last edited on 23 November 2018, at 20:11.

Text is available under the Creative Commons Attribution-ShareAlike License; additional terms may apply. By using this site, you agree to the Terms of Use and Privacy Policy.