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# Hepatitis E Virus; An Underestimated Threat for the Viral Hepatitis Elimination Program

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Since the launch of the viral hepatitis elimination program in 2016 (1), major actions have been taken to eliminate Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) (2-4), both accounting for the majority of hepatitis cases globally (5). However, recent comprehensive investigations show that Hepatitis E Virus (HEV) is a neglected pathogen that can seriously threaten public health and the global success of the hepatitis elimination program. An estimated 70,000 global deaths are linked to HEV (6).

Comparable to HBV and HCV, HEV can cause a wide range of liver diseases. Depending on the immune status of infected individuals, HEV can cause acute and chronic infections triggering advanced liver diseases such as liver cirrhosis and liver failure that might result in death (7). Like HBV and HCV, HEV strains are classified into different genotypes with various geographical distribution and prevalence (8-10). Socio-economic conditions and food habits of different communities substantially impact circulating genotypes, prevalence, and transmission routes of HEV (11). For instance, while HEV-3 mainly contributes to the infection burden in developed countries, HEV-4 is the primary cause of HEV infection in developing countries. Both HEV-1 and HEV-2 are prevalent in endemic and hyperendemic regions (11, 12).

The routes of HEV transmission allow the virus to spread widely and make it more difficult to counteract its dispersal. Unlike HBV and HCV, the transmission of HEV is not restricted to contact with an infected person (4). Also, HEV is classified among viruses that can be transmitted through the fecal-oral route (e.g., rotaviruses (13), noroviruses (14), and HAV (15)). Furthermore, similar to HBV, some HEV genotypes can transmit prenatally and parentally (16). Surprisingly, the vertical transmission of HEV can be fatal for pregnant women, their fetuses, or newborns (17). Due to suboptimal cellular immunity, pregnant women are much more vulnerable to HEV (18), and some strains of this virus can cause fulminant hepatitis, spontaneous abortion, and neonatal complications (19). In contrast to HBV, safe antiviral treatments are unavailable to prevent the vertical transmission of HEV (20, 21).

The transmission of HEV through blood transfusion and organ transplantation has added concerns to public health (22, 23). Like other blood-borne pathogens, which are not routinely screened at blood banks, the prevalence of HEV in multi-transfused cohorts is considerable (24, 25), which reflects the circulation of viral strains in blood donor pools (26, 27). Together with other non-enveloped viruses, HEV is a challenge for pathogen reduction strategies and could impede the safety of plasma therapy (28, 29). Identifying HEV-RNA in the absence of elevated liver enzymes or HEV anti-IgM in blood donors pinpoints that rigorous regulations are critical for donor recruitment and nucleic acid testing (NAT) in blood screening (30). Accordingly, HEV is routinely tested in donated blood in a few European countries, while in other countries, only blood for high-risk recipients is screened (31). Besides, applying NAT platforms for donated blood can significantly reduce HEV transmission and enormously scale down the associated economic burden (32, 33).

Similar to HBV and HCV, clinical diagnostic assays of HEV have been improved by applying RT-PCR and Next-generation Sequencing (NGS) techniques that even allow the differentiation of HEV genotypes (34-36).

Some distinct features of HEV impede its eradication. For instance, unlike HBV, there is no efficient vaccine, and unlike HCV, there is no specific antiviral against HEV (12).

The absence of these two vital tools is a significant drawback for any elimination program. Furthermore, food- and water-borne transmission allows HEV to infect people in regions with poor water sanitary systems. Also, unsafe food processing and contamination in developed countries elevate the chance of HEV outbreaks (37). Small changes in climate parameters have been shown to promote outbreaks of food- and water-borne infectious diseases (38). Accordingly, natural disasters such as floods or earthquakes can damage water supplies and sewage systems and favor the spread of HEV and HAV (39).

In contrast to other hepatitis viruses, HEV can infect a wide range of non-human hosts such as bats, swine, deer, camel, rabbit, wild boar, and non-human primates (11). Two genotypes of HEV (HEV-3 and HEV-4) are associated with zoonotic transmissions (11, 16). The cross-species transmission of HEV has been demonstrated experimentally and in natural conditions (30, 40, 41). It is a serious concern that converging mutants or recombinants of viruses in animal reservoirs can be more contagious or invasive to humans. Remarkably, some animals like wild boar and Mongolia gerbils can be infected by human-infecting HEV, such as HEV-4, and a broad range of non-human-infecting HEV genotypes (11, 42). These animal reservoirs for HEV hamper the elimination and could potentially cause large-scale epidemics, particularly in immune-compromised individuals (43).

In conclusion, the above-presented data shed light on the neglected importance of HEV and the difficulties of its elimination. Accordingly, suitable strategies to raise public awareness (44, 45), elevate the level of food and water safety, and implement blood screening strategies should be a cornerstone of control measures in the agenda of elimination programs.

## Footnotes

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