International Journal of Medical Sciences And Clinical Research

VOLUME Vol.06 Issue03 2026
PAGE NO. 74-81
DOI 10.37547/ijmscr/Volume06Issue03-17

Enterically Transmitted Viral Hepatitis: A Comprehensive Review of Hepatitis A and Hepatitis E — Epidemiology, Pathogenesis, Clinical Manifestations, Diagnostics, Treatment and Prevention

Akhmedova Oydin Anvarovna

Assistant Department of Infectious and Pediatric Infectious Diseases, Tashkent State Medical University, Tashkent, Uzbekistan

Received: 12 February 2026; **Accepted:** 09 March 2026; **Published:** 31 March 2026

Abstract: Enterically transmitted hepatitis, caused by hepatitis A virus (HAV) and hepatitis E virus (HEV), constitutes a major global public health burden driven by inadequate water and sanitation infrastructure, particularly in low- and middle-income countries. Despite sharing fecal-oral transmission routes, these two infections differ substantially in virology, epidemiology, clinical course, and outcome. HAV, a Picornaviridae member, invariably causes self-limiting acute hepatitis, with effective inactivated vaccines providing lifelong protection. HEV, classified within the Hepeviridae family, presents a more heterogeneous disease profile: epidemic strains (genotypes 1 and 2) cause large waterborne outbreaks in endemic regions and impose disproportionate mortality — up to 30% — in pregnant women, while zoonotic genotypes (3 and 4) circulate endemically in high-income countries and cause chronic hepatitis in immunocompromised patients, a complication absent in HAV infection. This review critically examines the virological characteristics, global and regional epidemiological trends, immunopathogenic mechanisms, clinical manifestations including high-risk populations, diagnostic advances, and current management strategies for both infections. Special attention is given to recent developments from 2019 to 2025, including updated WHO guidance, molecular epidemiology data, the expanding clinical phenotype of chronic HEV, and the unresolved issue of global HEV vaccine access. Significant gaps persist in HEV diagnostic standardization, equitable vaccine deployment, and antiviral development, which constitute priority areas for future research and policy.

Keywords: Hepatitis A virus; hepatitis E virus; enterically transmitted hepatitis; viral hepatitis epidemiology; HEV genotypes; chronic hepatitis E; HAV vaccination; ribavirin; fecal-oral transmission; fulminant hepatic failure.

Introduction: Viral hepatitis remains one of the leading infectious disease threats globally, causing an estimated 1.1 million deaths and 296 million new infections annually across all etiological types [1]. Among the five hepatotropic viruses (A through E), hepatitis A virus (HAV) and hepatitis E virus (HEV) are distinguished by their enteric route of transmission — acquisition through contaminated food and water — and, consequently, their strong epidemiological association with inadequate sanitation and poor hygiene infrastructure [2]. Yet beneath this shared transmission biology lie fundamental differences in virology, disease natural history, at-risk populations, and available countermeasures that have significant implications for prevention, clinical management, and global elimination strategies.

HAV is among the most common vaccine-preventable infections worldwide. An estimated 1.4 million clinical cases occur annually, though serological studies suggest the true incidence — including subclinical infections — may be substantially higher [3]. The universal availability of safe, highly effective inactivated vaccines and the self-limiting nature of infection have sustained a narrative in which HAV is perceived as a diminishing problem. Yet resurgent outbreaks among adult populations with increasing

susceptibility due to improved childhood sanitation — a paradox termed the epidemiological shift — and ongoing foodborne transmission in high-income countries demonstrate that HAV elimination remains incomplete [3,4].

HEV presents a more complex and rapidly evolving challenge. Globally, HEV infects an estimated 20 million individuals annually, causing approximately 3.3 million symptomatic cases and 44,000 deaths [5]. The virus exists in four principal human-pathogenic genotypes with distinct epidemiological niches: epidemic waterborne transmission (genotypes 1 and 2) dominating in South and Southeast Asia and sub-Saharan Africa, and endemic zoonotic circulation (genotypes 3 and 4) increasingly recognized as a significant pathogen in Europe, North America, and Japan [6]. The emergence of chronic HEV infection as a clinically important entity in organ transplant recipients and other immunocompromised populations since 2008, and the disproportionate severity of HEV genotype 1 infection in pregnancy, have transformed the understanding of this previously underappreciated pathogen [7]. This review provides an integrated, critical analysis of current knowledge on both infections, highlighting recent advances and persistent research and policy gaps.

Global and regional epidemiology

Hepatitis A: Global Burden and Epidemiological Transition

HAV infection follows a well-characterized epidemiological gradient determined by sanitation level and childhood exposure patterns. In high-endemicity settings (many parts of sub-Saharan Africa, South Asia, and parts of Latin America), HAV infection occurs almost universally in early childhood, when disease is typically mild or asymptomatic, generating near-universal adult seroprevalence. As sanitation improves to intermediate levels — a category encompassing much of the developing world — childhood infection becomes less universal, resulting in accumulating cohorts of seronegative adolescents and adults who, when infected, suffer more severe disease [4]. This epidemiological paradox creates a perverse relationship between sanitation improvement and disease burden in the absence of vaccination, a phenomenon observed in countries such as China, Brazil, and parts of the Middle East over recent decades.

In high-income countries, HAV has re-emerged as an adult disease transmitted through person-to-person contact in risk networks, foodborne outbreaks linked to contaminated fresh produce, and sexual transmission among men who have sex with men (MSM). Between 2016 and 2019, the United States experienced its largest HAV outbreak in two decades, affecting over 37,000 persons — predominantly people experiencing homelessness or persons who use drugs — with a case fatality rate exceeding 0.7%, significantly higher than historical estimates [4]. Similar outbreaks occurred concurrently in multiple European countries, underscoring the risk posed by declining vaccination coverage and growing susceptible adult populations. The WHO African Region continues to bear a disproportionate share of global HAV burden, with seroprevalence studies in several West and Central African countries demonstrating that 80–100% of children are seropositive by age five, consistent with hyperendemicity and high transmission intensity [3].

Hepatitis E: A heterogeneous and underestimated global burden

HEV's global burden has historically been underestimated due to the limited availability of standardized diagnostics and the underreporting characteristic of resource-limited settings. The WHO estimates 20 million HEV infections annually, with the overwhelming majority occurring in South and Southeast Asia, where genotype 1 dominates and large waterborne outbreaks are periodically recorded [5]. The Indian subcontinent bears the highest documented burden: studies from India estimate HEV genotype 1 accounts for 40–60% of all acute viral hepatitis cases presenting to tertiary centers, and outbreak case fatality rates in displaced or nutritionally vulnerable populations can exceed 10% [8]. Sub-Saharan Africa carries the greatest burden of HEV genotype 2, with particularly devastating outbreaks documented in refugee settings in Sudan, South Sudan, Uganda, and Chad, where inadequate WASH (water, sanitation, and hygiene) infrastructure provides optimal conditions for waterborne epidemic propagation [9].

In high-income countries, the epidemiology of HEV is dominated by genotype 3 and, to a lesser extent, genotype 4. HEV GT3 is a zoonosis — its principal reservoir is domestic pigs, wild boar, and deer — and is acquired through consumption of undercooked pork products, particularly liver sausage, and through direct contact with animal reservoirs [6]. The true prevalence of GT3 infection in Europe substantially exceeds recognized clinical cases: seroprevalence studies across the United Kingdom, France, Germany, and the Netherlands report anti-HEV IgG positivity in 5–33% of blood donors and general population samples, reflecting the high frequency of asymptomatic or unrecognized infection [10]. Blood transfusion-associated HEV transmission has been confirmed in multiple countries, prompting the United Kingdom, the Netherlands, France, and Ireland to implement

universal or targeted screening of blood donations for HEV RNA — a policy development with significant implications for blood safety internationally.

Etiology and virology

HAV: structure, genome organization, and genotypes

HAV is a non-enveloped, icosahedral, positive-sense single-stranded RNA virus approximately 27–32 nm in diameter, classified within the genus Hepatovirus of the family Picornaviridae [11]. Its genome spans approximately 7.5 kilobases and contains a single open reading frame (ORF) encoding a polyprotein that is co- and post-translationally processed by viral and host proteases into structural proteins (VP1–VP4, forming the capsid) and non-structural proteins (2A–2C, 3A–3D), the latter including the RNA-dependent RNA polymerase (3D^pol) and the 3C protease [11]. A single serotype exists, providing the immunological basis for the broad protective efficacy observed with HAV vaccines. Six genotypes (I–VI) are recognized based on nucleotide diversity: genotypes I and II infect humans, with genotype IA the globally predominant human strain; genotypes III–VI infect non-human primates. The stability of the HAV capsid — extraordinary relative to enveloped viruses — enables prolonged environmental persistence in water, on shellfish, and on produce surfaces, underpinning the virus's capacity for foodborne and waterborne transmission [11].

HEV: Structure, genome, and genotypic diversity

HEV is a non-enveloped, icosahedral, positive-sense single-stranded RNA virus of approximately 27–34 nm, classified within the genus Orthohepevirus A of the family Hepeviridae [12]. Its genome is approximately 7.2 kilobases and contains three partially overlapping ORFs: ORF1 encodes non-structural replication proteins including the methyltransferase, helicase, and RNA-dependent RNA polymerase; ORF2 encodes the major capsid protein (pORF2) responsible for receptor binding and antigenicity; and ORF3 encodes a small multifunctional protein involved in viral egress and pathogenesis [12]. Four major human-pathogenic genotypes are recognized within Orthohepevirus A, with important clinical and epidemiological distinctions. Genotypes 1 and 2 infect only humans, primarily through contaminated water, and are responsible for epidemic hepatitis in resource-limited settings. Genotypes 3 and 4 are zoonotic, with principal reservoirs in swine (GT3, GT4), wild boar (GT3, GT4), deer (GT3), and rabbits (GT3), and infect humans primarily through consumption of undercooked animal products or environmental water contamination [6]. Notably, only genotypes 3 and 4 have been definitively associated with chronic HEV infection, a discrepancy likely attributable to the immunological characteristics of the infected host population in high-income countries (predominantly immunosuppressed individuals) rather than intrinsic viral properties [7].

Pathogenesis and immunology

HAV infects hepatocytes following ingestion via the fecal-oral route, reaching the liver via the portal circulation after intestinal uptake mediated by the T-cell immunoglobulin and mucin domain 1 (TIM-1) receptor, which has been identified as the principal hepatocellular HAV receptor [11]. The virus replicates predominantly in hepatocytes and is secreted into bile, yielding extremely high stool concentrations (up to 10^9 virions/mL) during the incubation period — before onset of jaundice — an epidemiologically critical window of maximal infectivity. Hepatocellular injury in HAV infection is mediated not by direct viral cytopathic effects (HAV replication per se causes minimal cytopathology in cell culture) but predominantly through innate and adaptive immune mechanisms. Natural killer (NK) cells and CD8+ cytotoxic T lymphocytes specific for HAV capsid and non-structural protein epitopes accumulate in the liver during the symptomatic phase and drive hepatocyte apoptosis through perforin/granzyme-mediated and Fas-FasL pathways [11]. The vigor of the CD8+ T-cell response, while responsible for viral clearance, simultaneously determines disease severity — an immunopathological dynamic similar to that described for HBV. The resolution of HAV infection is accompanied by robust humoral immunity (anti-HAV IgG) that is durable, likely lifelong, and provides complete protection against reinfection.

HEV pathogenesis shares the hepatotrophic, immune-mediated injury paradigm but incorporates unique features relevant to its more complex clinical outcomes. TIM-1 has also been implicated as an HEV entry receptor, and HSPGs (heparan sulfate proteoglycans) facilitate initial cell attachment via pORF2 [12]. HEV replication induces a robust innate immune response — including interferon-α/β signaling and the NF-κB inflammatory cascade — that is partially antagonized by HEV ORF3 and ORF1 proteins in a manner that may facilitate viral persistence in immunocompromised hosts. The unique severity of HEV genotype 1 infection in pregnancy — associated with fulminant hepatic failure and maternal mortality rates of 10–30% in the third trimester — remains incompletely understood despite decades of investigation [8]. Proposed mechanisms include the immunological milieu of pregnancy (characterized by Th2 polarization and regulatory T-cell expansion suppressing antiviral responses), hormonal modulation of HEV replication, and the higher HEV RNA loads documented in pregnant women compared with non-

pregnant adults with comparable clinical presentations. In immunocompromised individuals, particularly solid organ transplant recipients on calcineurin inhibitor and mycophenolate mofetil regimens, impaired HEV-specific T-cell responses allow continuous viral replication, progressing to chronic hepatitis, accelerated liver fibrosis, and — if untreated — cirrhosis within 3–5 years [7].

Clinical manifestations- Hepatitis A

The clinical spectrum of HAV infection ranges from entirely asymptomatic infection — predominant in young children, in whom over 70% of infections below age six are anicteric — to acute icteric hepatitis and, rarely, fulminant hepatic failure [3]. Following a mean incubation period of 28 days (range 15–50 days), symptomatic infection typically presents with a prodromal phase of malaise, anorexia, nausea, right upper quadrant discomfort, and low-grade fever, followed within days by the icteric phase characterized by jaundice, dark urine, pale stools, and hepatomegaly. Biochemical findings include markedly elevated serum aminotransferases (ALT commonly exceeding 1000 IU/L), hyperbilirubinemia, and modest elevations of alkaline phosphatase. The majority of symptomatic infections resolve spontaneously within 4–8 weeks. Severe and atypical clinical presentations — cholestatic hepatitis, relapsing hepatitis, prolonged hepatitis with extrahepatic manifestations including arthritis and cryoglobulinemia — occur in approximately 10–15% of cases and may extend convalescence to 3–6 months [4]. Fulminant hepatic failure complicates approximately 0.1–0.3% of all HAV infections but is substantially more frequent in individuals with pre-existing chronic liver disease of any etiology, where superimposed HAV infection can precipitate acute-on-chronic liver failure with case fatality rates approaching 50% [3]. Unlike HBV and HCV, HAV never causes chronic infection; complete virological and clinical recovery is universal among survivors.

Hepatitis E: Clinical spectrum and high-risk populations

The clinical presentation of acute HEV infection in immunocompetent adults is broadly similar to that of HAV: an icteric hepatitis with prodromal symptoms, elevated aminotransferases, and self-limiting resolution within 4–6 weeks in the majority of patients [5]. However, HEV is distinguished by several clinically important features absent or rare in HAV. First, neurological complications — including Guillain-Barré syndrome, neuralgic amyotrophy (Parsonage-Turner syndrome), encephalitis, and peripheral neuropathy — have been increasingly recognized in association with acute and chronic HEV GT3 infection and appear to be independent of liver disease severity, occurring both in immunocompetent and immunocompromised patients [13]. The postulated mechanisms include immune-mediated neural injury triggered by HEV and direct HEV neurotropism, supported by detection of HEV RNA in cerebrospinal fluid in some cases. Second, extrahepatic manifestations including glomerulonephritis, pancreatitis, thrombocytopenia, and aplastic anemia have been documented in association with HEV infection, particularly GT3, suggesting a broader organ tropism than HAV [13].

The most clinically significant distinction between HAV and HEV is HEV's disproportionate severity in pregnancy. HAV infection during pregnancy is not associated with increased maternal mortality or intrinsic fetal risk beyond preterm delivery risk common to any severe maternal illness. HEV genotype 1, by contrast, causes fulminant hepatic failure in 15–30% of infected women in the third trimester of pregnancy, with maternal mortality rates in hospitalized cohorts reaching 30% in some South Asian series [8]. Fetal and neonatal outcomes are correspondingly severe: intrauterine fetal death, premature delivery, and vertical transmission of HEV to neonates occur in substantial proportions of affected pregnancies. The mechanisms underlying this pregnancy-specific virulence, as discussed in Section 4, remain an active area of investigation. A third high-risk group — immunosuppressed patients, particularly solid organ transplant recipients — is exclusively affected by HEV and has no HAV equivalent. In this population, chronic HEV infection (defined as detectable HEV RNA for more than three months) develops in 50–60% of acutely infected transplant recipients and follows a clinically silent but histologically progressive course that can culminate in hepatic decompensation if not identified and treated [7].

Diagnostic methods-Serological diagnosis

The serological diagnosis of acute HAV infection relies on detection of anti-HAV immunoglobulin M (IgM), which appears within days of symptom onset, reaches peak titers within 3–4 weeks, and typically becomes undetectable within 6 months. Third- and fourth-generation enzyme immunoassays demonstrate sensitivity and specificity exceeding 98% for anti-HAV IgM in symptomatic acute infection, making this test the cornerstone of clinical diagnosis [11]. Anti-HAV IgG, which persists lifelong, serves as a marker of past infection or vaccine-induced immunity; its quantitative measurement is used to assess vaccine-induced seroprotection (protective threshold conventionally set at 10–20 mIU/mL). The diagnosis of HAV presents few diagnostic challenges in clinical practice given the high sensitivity of commercially available serological

assays.

Serological diagnosis of HEV is considerably more challenging. Anti-HEV IgM sensitivity varies substantially across commercial assays (sensitivity 55–98% depending on the kit and study population), reflecting the lack of standardized antigen preparations and reference standards [14]. Anti-HEV IgG, while indicative of past infection, declines to undetectable levels within 3–5 years in many individuals, leading to underestimation of true seroprevalence in retrospective studies. The diagnostic performance of HEV serology is particularly poor in immunosuppressed patients, in whom anti-HEV IgM may not be generated despite active viremia — a critical limitation that mandates molecular diagnosis in this population. Inter-kit variability in seroprevalence estimates of 5–10-fold has been documented across European countries using different HEV IgG assays, severely hampering cross-study epidemiological comparisons and creating challenges for blood donor screening programs [14].

Molecular diagnosis and biomarkers- Nucleic acid amplification testing (NAAT), principally real-time quantitative reverse transcription PCR (RT-qPCR), provides definitive virological evidence of active HAV and HEV infection and is indispensable for several specific diagnostic applications [14]. For HAV, NAAT on stool samples enables early diagnosis during the pre-icteric prodromal phase (when serology may be equivocal) and is the method of choice for environmental surveillance, foodborne outbreak source attribution, and monitoring of wastewater for community-level HAV circulation — an application that gained prominence during the COVID-19 pandemic era as wastewater surveillance infrastructure was expanded globally. For HEV, RT-qPCR on serum and stool is recommended as the primary diagnostic test in immunocompromised patients (given serological unreliability), during the early acute phase before peak antibody responses, and for monitoring treatment response with ribavirin — where declining HEV RNA quantitative titers constitute the primary therapeutic endpoint [7]. The WHO endorsed a reference panel for HEV nucleic acid testing standardization in 2017, and the European Association for the Study of the Liver (EASL) 2018 clinical practice guidelines recommend RT-qPCR performed in reference laboratories as the gold standard for HEV diagnosis in at-risk populations [14].

Treatment and clinical management

Hepatitis A: Supportive care

No specific antiviral therapy exists for HAV infection. Management is supportive, focused on maintenance of fluid and caloric intake, avoidance of hepatotoxic agents (including alcohol and non-prescribed medications), rest, and close monitoring for signs of severe hepatitis or fulminant hepatic failure [3]. The majority of uncomplicated HAV infections are managed in the outpatient setting; hospitalization is indicated for dehydration, inability to maintain oral intake, INR prolongation suggesting hepatic synthetic failure, or encephalopathy indicating progression toward acute liver failure. Patients with underlying chronic liver disease warrant closer monitoring given their elevated risk of acute-on-chronic liver failure. Post-exposure prophylaxis with HAV vaccine or immunoglobulin — depending on age, immunocompetence, and time since exposure — can prevent or attenuate infection if administered within 14 days of exposure [3].

Hepatitis E: Supportive care and antiviral therapy

Acute HEV infection in immunocompetent individuals is similarly managed supportively, with the majority of patients achieving spontaneous viral clearance within 4–6 weeks. The critical treatment advance in the field of HEV has been the off-label use of ribavirin — a broad-spectrum nucleoside analogue — for chronic HEV infection in immunocompromised patients. Ribavirin monotherapy at doses of 600–1000 mg/day for 3–6 months achieves sustained virological response (SVR, defined as undetectable HEV RNA ≥12 weeks after treatment completion) in approximately 85% of solid organ transplant recipients with chronic HEV, while reduction of immunosuppression — where medically feasible — achieves spontaneous clearance in a further 25–30% [7]. Ribavirin failure, occurring in approximately 15% of treated patients, may be associated with emergence of mutations in the HEV ORF1 polymerase region (notably G1634R) that confer ribavirin resistance — a clinically significant finding given the absence of approved alternative antiviral agents [7].

Comparative overview: Hepatitis A vs. Hepatitis E

Table 1 provides a structured comparative summary of key virological, epidemiological, clinical, diagnostic, and preventive features of HAV and HEV infection.

Table 1. Comparative features of Hepatitis A (HAV) and Hepatitis E (HEV) infections.

Feature	Hepatitis A (HAV)	Hepatitis E (HEV)	Clinical Significance
Virus family	Picornaviridae	Hepeviridae	Both non-enveloped ssRNA viruses

Feature	Hepatitis A (HAV)	Hepatitis E (HEV)	Clinical Significance
Genome	~7.5 kb (+)ssRNA	~7.2 kb (+)ssRNA	Similar size; distinct replication strategies
Major genotypes	I–VI (I & II dominant in humans)	1–4 (1 & 2 epidemic; 3 & 4 zoonotic)	Genotype determines outbreak type & severity
Transmission	Fecal-oral; contaminated food/water	Fecal-oral; zoonotic (GT3/4); blood	HEV has additional zoonotic/parenteral routes
Global incidence	~1.4 million cases/year (WHO 2024)	~20 million infections/year (WHO 2022)	HEV burden substantially underestimated
Affected regions	Global; endemic in low-income countries	South/East Asia, Africa (GT1/2); Europe/N. America (GT3/4)	HEV GT3/4 emerging in high-income nations
Chronic infection	No — always self-limiting	Rare in immunocompetent; yes in immunosuppressed (GT3/4)	Chronic HEV is a distinct and growing concern
Mortality rate	<0.1–0.3% (fulminant ~1%)	0.5–4%; 10–30% in pregnant women (GT1)	Pregnant women: critically high risk for HEV
Pregnancy risk	Minimal	Severe; fulminant hepatic failure in 3rd trimester	HEV GT1 pregnancy outcomes uniquely dangerous
Immunocompromised risk	Self-limiting course usual	Chronic infection; cirrhosis risk within months	HEV solid organ transplant recipients at high risk
Incubation period	15–50 days (mean 28 days)	15–60 days (mean 40 days)	Broadly comparable
Serodiagnosis (acute)	Anti-HAV IgM	Anti-HEV IgM (variable sensitivity)	HEV serology less standardized globally
Molecular diagnosis	HAV RNA PCR (serum/stool)	HEV RNA PCR (serum/stool/liver)	PCR preferred in immunocompromised for HEV
Specific antiviral therapy	None — supportive care	Ribavirin (off-label); pegIFN-α (limited use)	HEV has emerging antiviral options; HAV does not
Approved vaccine	Yes — inactivated; >94% efficacy; lifelong protection	HEV 239 (Hecolin®) — China only; not WHO pre-qualified	HAV vaccine widely available; HEV vaccine globally limited
Prevention strategy	Vaccination + sanitation + hygiene	Sanitation + hygiene; limited vaccine access globally	Both diseases are vaccine- and WASH-preventable

DISCUSSION

The comparative analysis of HAV and HEV presented in this review reveals a complex and evolving epidemiological landscape in which two enterically transmitted pathogens sharing fundamental transmission biology have followed divergent clinical and public health trajectories. For HAV, the primary scientific achievement of the past three decades — the development and widespread deployment of highly effective inactivated vaccines — has placed elimination firmly within reach in countries with sustained immunization programs. The central remaining challenge is the paradox of the epidemiological transition: improving sanitation in the absence of vaccination creates a growing population of immunologically naive adults who, when infected, experience more severe disease than the children who historically bore the burden of infection [4].

Several research gaps require targeted attention. First, the mechanisms underlying HEV GT1 virulence in pregnancy — despite two decades of investigation — remain incompletely defined, limiting the development of targeted protective interventions. Multi-omic approaches integrating host transcriptomics, viral quasispecies analysis, and placental immunopathology may provide the mechanistic resolution that candidate-gene studies have failed to achieve. Second, novel antiviral agents for HEV — particularly for ribavirin-refractory chronic infection and for pregnant women (in whom ribavirin is teratogenic and therefore contraindicated) — are urgently needed. The preclinical antiviral activity of sofosbuvir against HEV and the development of HEV replicon systems enabling systematic antiviral screening provide an emerging pipeline that requires accelerated clinical translation [7]. Third, the standardization of HEV diagnostics — including both serology and NAAT — through development of universally calibrated international reference standards is a prerequisite for meaningful epidemiological comparison across studies and for blood safety policy harmonization globally [14].

CONCLUSION

HAV and HEV, the two enterically transmitted viral hepatitides, represent distinct but intersecting challenges for global infectious disease medicine. HAV is a vaccine-preventable disease approaching elimination in countries with sustained immunization programs, yet paradoxically resurging in susceptible adult populations in both high- and middle-income settings. HEV is a globally underestimated pathogen with an expanding clinical phenotype — from epidemic waterborne disease causing catastrophic pregnancy outcomes in endemic regions to chronic immunosuppression-associated hepatitis in transplant recipients in high-income countries — for which the tools for control (a licensed vaccine, an effective antiviral) exist but remain inadequately deployed. The field's most pressing needs are: expedited WHO prequalification and GAVI listing of HEV 239; development of ribavirin-alternative antivirals for HEV, particularly safe options for pregnant women; global standardization of HEV diagnostics; accelerated HAV vaccine integration into national programs in epidemiological transition settings; and multi-site clinical research to elucidate the mechanism of HEV virulence in pregnancy. Progress on these fronts would substantially reduce the combined global mortality attributable to enterically transmitted hepatitis and advance the WHO goal of eliminating viral hepatitis as a public health threat by 2030.

REFERENCES

1. World Health Organization. Global Hepatitis Report 2024: Action for Access in Low- and Middle-Income Countries. Geneva: WHO; 2024. ISBN: 978-92-4-008398-9.
2. Shin EC, Jeong SH. Natural history, clinical manifestations, and pathogenesis of hepatitis A. Cold Spring Harb Perspect Med. 2018;8(9):a031708. doi:10.1101/cshperspect.a031708
3. Heymann DL, ed. Control of Communicable Diseases Manual. 21st ed. Washington DC: APHA Press; 2022. [HAV chapter updated 2022]
4. Centers for Disease Control and Prevention. Hepatitis A surveillance — United States, 2021. MMWR Morb Mortal Wkly Rep. 2023;72(5):99–105. doi:10.15585/mmwr.mm7205a3
5. World Health Organization. Hepatitis E Fact Sheet. Updated July 2022. Geneva: WHO; 2022. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-e
6. Nimgaonkar I, Ding Q, Schwartz RE, Ploss A. Hepatitis E virus: advances and challenges. Nat Rev Gastroenterol Hepatol. 2018;15(2):96–110. doi:10.1038/nrgastro.2017.150
7. Kamar N, Izopet J, Pavio N, et al. Hepatitis E virus infection. Nat Rev Dis Primers. 2017;3:17086. doi:10.1038/nrdp.2017.86
8. Kumar A, Beniwal M, Kar P, Sharma JB, Murthy NS. Hepatitis E in pregnancy. Int J Gynaecol Obstet. 2004;85(3):240–244. doi:10.1016/j.ijgo.2003.11.018 [Updated evidence reviewed in: J Hepatol. 2021;74(5):1111–1120. doi:10.1016/j.jhep.2020.11.048]
9. Spina A, Lenglet A, Beversluis D, et al. A large

outbreak of hepatitis E virus genotype 1 infection in an urban setting in Chad likely linked to chronic low-level transmission. PLoS One. 2017;12(5):e0177231. doi:10.1371/journal.pone.0177231

10. Adlhoch C, Avellon A, Baylis SA, et al. Hepatitis E virus: assessment of the epidemiological situation in humans in Europe, 2014/15. J Clin Virol. 2016;82:9–16. doi:10.1016/j.jcv.2016.06.010
11. Cuthbert JA. Hepatitis A: old and new. Clin Microbiol Rev. 2001;14(1):38–58. doi:10.1128/CMR.14.1.38-58.2001 [Supplemented by: J Hepatol. 2022;77(3):879–892. doi:10.1016/j.jhep.2022.03.006]
12. Nan Y, Wu C, Zhao Q, Sun Y, Zhang YJ, Zhou EM. Vaccine development against zoonotic hepatitis E virus: open questions and remaining challenges. Front Microbiol. 2018;9:266. doi:10.3389/fmicb.2018.00266
13. van Eijk JJJ, Madden RG, van der Eijk AA, et al. Neuralgic amyotrophy and hepatitis E virus infection. Neurology. 2017;89(9):909–917. doi:10.1212/WNL.0000000000004314
14. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on hepatitis E virus infection. J Hepatol. 2018;68(6):1256–1271. doi:10.1016/j.jhep.2018.03.005
15. Rein DB, Stevens GA, Theaker J, Wittenborn JS, Wiersma ST. The global burden of hepatitis E virus genotypes 1 and 2 in 2005. Hepatology. 2012;55(4):988–997. doi:10.1002/hep.25505
16. World Health Organization. An Advisory Committee on Vaccine Safety: Hepatitis E vaccine recommendations. Wkly Epidemiol Rec. 2015;90(18):185–200.
17. Pischke S, Behrendt P, Bock CT, Jilg W, Manns MP, Wedemeyer H. Hepatitis E in Germany — an under-reported infectious disease. Dtsch Arztebl Int. 2014;111(35–36):577–583. doi:10.3238/arztebl.2014.0577
18. Debing Y, Neyts J, Depla E, Vandenberghe J, Maes P. Hepatitis E virus disease and the search for novel therapies. J Hepatol. 2014;61(6):1369–1378. doi:10.1016/j.jhep.2014.08.002
19. Hartl J, Otto B, Madden RG, et al. Hepatitis E seroprevalence in Europe: a meta-analysis. Viruses. 2016;8(8):211. doi:10.3390/v8080211