



Zoonotic Hepatitis E Virus: Epidemiology, Animal Reservoirs, and Control Strategies

I Made Kardena^{1*}, Palagan Senopati Sewoyo¹, Anak Agung Gde Oka Dharmayudha², I Wayan Nico Fajar Gunawan², Putu Devi Jayanti², I Nyoman Mantik Astawa¹, Anak Agung Ayu Mirah Adi¹, I Nyoman Suarsana³, I Nyoman Suartha², and Alan P. Dargantes⁴

¹Department of Pathobiology, Faculty of Veterinary Medicine, Udayana University, Bali, 80234, Indonesia

²Department of Veterinary Clinic, Faculty of Veterinary Medicine, Udayana University, Denpasar, Bali, 80234, Indonesia

³Department of Veterinary Basic Sciences, Faculty of Veterinary Medicine, Udayana University, Denpasar, Bali, 80234, Indonesia

⁴Department of Medicine, Surgery, and Zootechnics, College of Veterinary Medicine, Central Mindanao University, Musuan, Maramag, Bukidnon, 8714, The Philippines

*Corresponding author's Email: imadekardena@unud.ac.id

ABSTRACT

Hepatitis E virus (HEV) is a leading cause of acute hepatitis transmitted through the enteric route, impacting millions of individuals worldwide annually. While HEV is generally self-limiting, it can lead to considerable illness and death, particularly in gestating women, immunocompromised individuals, and those with pre-existing conditions, such as chronic liver disease. Hepatitis E virus genotypes 1 and 2 infect solely humans and are prevalent in areas with poor sanitation, whereas genotypes 3 and 4 are zoonotic, infecting both animals and humans. Hepatitis E virus genotype 7 has been reported to infect both humans and animals; however, further research is needed to clarify its zoonotic potential. Zoonotic transmission occurs primarily through the consumption of contaminated meat and close contact with infected animals, posing significant public health risks. Epidemiological studies indicated an increasing seroprevalence of HEV in humans and animals across diverse regions, highlighting the need for strengthened public health measures. While HEV infections in animal reservoirs are generally asymptomatic, they represent a critical source of human infections. The present review aimed to highlight HEV's current classification, epidemiology, modes of transmission from animals to humans, prevention, and control measures, with a special focus on HEV zoonotic genotypes and their animal reservoirs.

Keywords: Control measure, Epidemiology, Hepatitis E virus, Public health, Zoonotic genotype

INTRODUCTION

Hepatitis E Virus (HEV) is a major etiology of acute hepatitis transmitted via the enteric route, affecting millions of people worldwide annually. While HEV infections are often self-limiting (Nimgaonkar et al., 2018), they result in an estimated 3.3 million symptomatic cases and up to 44,000 mortalities each year (Rein et al., 2012). This virus is classified as a single-stranded RNA virus within the *Hepeviridae* family and the *Orthohepevirus* genus (Purdy et al., 2022). Currently, HEV includes eight classified genotypes. HEV-1 and HEV-2 solely infect humans and are generally found in areas with inadequate sanitation, including developing nations in Africa and South Asia (Nelson et al., 2019).

In contrast, HEV-3 and HEV-4 are zoonotic and can infect both humans and various animals. The global significance of HEV-3 and HEV-4 lies in their wide geographical distribution, being detected in both industrialized and low-income countries. Their distribution includes regions such as North America, Europe, and Asia, including Indonesia (Meng et al., 2010; Widasari et al., 2013). These genotypes can be transmitted through the consumption of raw or inadequately cooked meat or direct contact with infected animals (Colson et al., 2010; Primadharsini et al., 2019). Several recent hepatitis E cases have been identified that are not linked to travel in endemic areas, suggesting autochthonous or locally acquired infections. The majority of these cases are associated with genotypes 3 and 4, particularly in regions where these infections are not traditionally endemic (Samala and Ghany, 2013).

The case fatality rate of this disease is generally low, but it can rise in pregnant women, with the possibility of vertical transmission to the fetus (Berglöv et al., 2019). Fetal mortality is most likely to occur during the third trimester. Additionally, these patients may experience preterm delivery, low birth weight, or stillbirth of the fetus (Wu et al., 2020). The fatality rate is also observed to be high in individuals with immunocompromised conditions and patients with prior

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health issues, such as chronic liver (Santos-Silva et al., 2023). Although the overall number of hepatitis E cases remains low, the incidence of this disease is increasing in advanced countries (Fukuda et al., 2004; Olsen et al., 2006; Clemente-Casares et al., 2016). Wild boars (*Suis scrofa*) and domestic pigs (*Suis scrofa domesticus*) are the main reservoirs for HEV-3 and HEV-4 genotypes (Pavio et al., 2015). While these animals are identified as main reservoirs, other animal species, such as deer (*Cervidae*) and rabbit (*Oryctolagus cuniculus*), may also serve as potential reservoirs (Izopet et al., 2012; Karlsen et al., 2023). Deer, for instance, has been identified as a source of zoonotic food-borne HEV infection in humans (Tei et al., 2003). Although deer have been proven as a potential reservoir, domestic pigs have a significant impact on the spread of zoonotic HEV, particularly in regions with extensive pig farming (Kardena et al., 2024). Infected pigs usually do not show clear clinical symptoms of HEV infection, but they can release large amounts of the virus through feces, contaminating the environment and human food supplies (Salines et al., 2017). Pig farmers who have close contact with livestock are at heightened risk of HEV infection (Cossaboom et al., 2016; Hoan et al., 2019). Therefore, an in-depth understanding of HEV epidemiology in swine populations is critical for developing effective control strategies and reducing the risk of zoonotic transmission. In Indonesia, HEV is thought to be highly endemic, with several reports showing seroprevalence of the virus in humans and pigs, which serve as its main reservoirs.

This literature review aimed to comprehensively examine the general classification of HEV and animal reservoirs, with a particular emphasis on the zoonotic genotype, their animal reservoirs, associated epidemiology, transmission mechanisms, and control measures.

MATERIALS AND METHODS

This literature review was conducted using the literature study method, focusing on identifying and synthesizing existing research on HEV zoonotic genotypes, with a particular emphasis on epidemiology, transmission, and control measures. A narrative review approach was employed to collate, analyze, and summarize findings from selected sources. The review involved accessing scientific articles through ScienceDirect and PubMed. The search for relevant articles was carried out between March 2024 and September 2024. These databases were selected for their extensive coverage of biomedical and public health publications. Search terms included zoonotic HEV, HEV epidemiology, HEV transmission, HEV in Indonesia, zoonotic HEV reservoir, HEV risk factors, HEV control, and HEV prevention. The keywords were used individually and in various combinations to ensure comprehensive retrieval of relevant studies. Based on predefined inclusion and exclusion criteria, 94 articles were included in this review. Inclusion criteria required that articles were peer-reviewed, written in English, and focused on HEV zoonotic genotypes, transmission, epidemiology, and control measures. Non-English articles lacked available full text, focused exclusively on non-zoonotic HEV genotypes, or were excluded. The collected data were systematically compiled, analyzed, and synthesized to conclude.

Overview and classification of virus genotypes

The HEV is a non-enveloped, single-stranded RNA virus with an icosahedral shape and a diameter of approximately 32-34 nm (Cancela et al., 2023). The HEV virus has been successfully detected in humans and several animals (Pavio et al., 2015; Smith et al., 2020; Karlsen et al., 2023). The taxonomic classification of the virus family is based on the complete genome sequence of HEV isolates. The Hepatitis E virus belongs to the *Hepeviridae* family and the *Orthohepevirus* genus. The *Orthohepevirus* genus consists of four species, including *Orthohepevirus* A, B, C, and D. *Orthohepevirus* A includes four genotypes of HEV, namely HEV-1 to HEV-4, all of which are capable of infecting humans (Park et al., 2016).

Hepatitis E virus genotypes 1 and 2 are exclusively found in humans and are mainly found in Africa and South Asia. These genotypes are generally linked to contaminated water and inadequate hygiene and sanitation (Doceul et al., 2016; Fenaux et al., 2019). Meanwhile, HEV-3 and HEV-4 have been isolated from both human and animal hosts (Smith et al., 2020; Garbuglia et al., 2024). These genotypes are distributed across America, Europe, and Asia (Figure 1; Doceul et al., 2016), typically transmitted through eating undercooked or raw meat (Meng, 2013).

Hepatitis E virus genotype 3 is the most widely studied and well-documented in GenBank, with sequences primarily obtained from humans, pigs, and wild boars. However, HEV-3 strains have also been identified in various animal species, including mongoose (*Herpestidae*), deer, rabbits (Kenney and Meng, 2019), domestic ruminants (Wu et al., 2015; Huang et al., 2016), and white-collared peccaries (*Pecari tajacu*; Table 1; Ferreira et al., 2020). This genotype is classified into 14 subtypes and three clades (3abchijk, 3efg, and 3ra; Smith et al. 2020). Recently, a study by Cancela et al. (2023) proposed a new subtype named 3o.

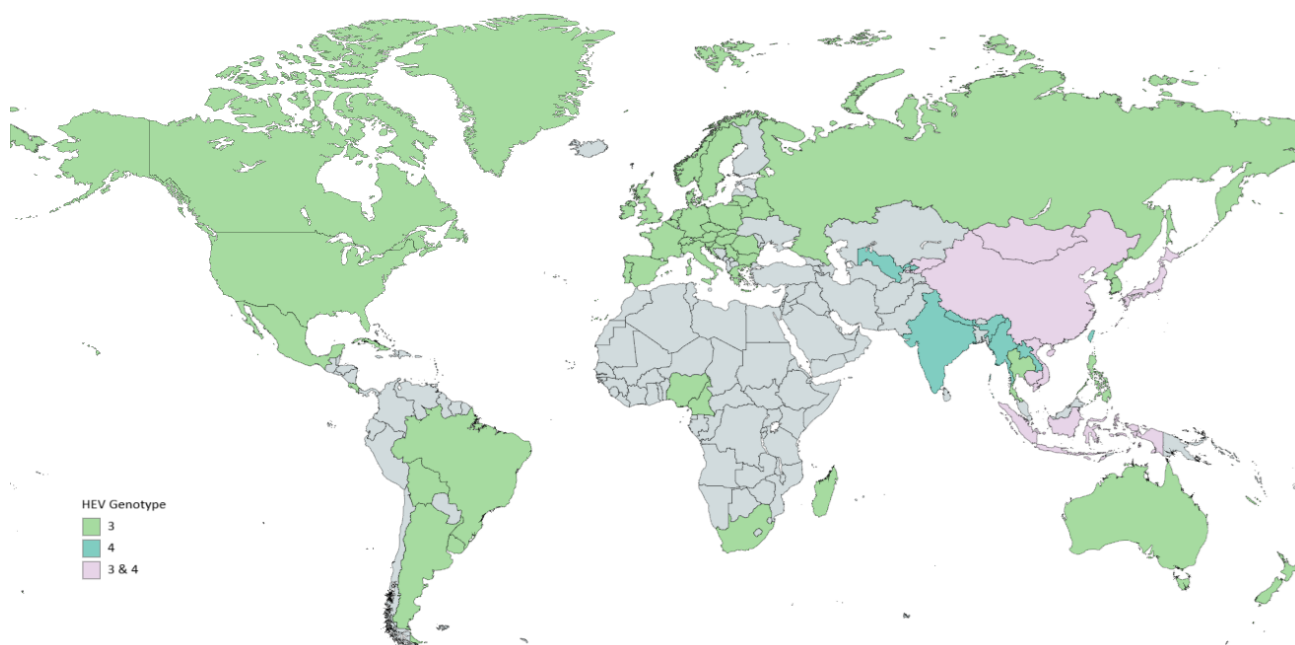


Figure 1. Geographical distribution of zoonotic HEV genotypes (3 and 4). The map was created using MapChart with the World Countries template. Source of the data: [Okamoto \(2007\)](#) and [Treagus et al. \(2021\)](#).

Table 1. Zoonotic hepatitis E virus genotypes, subtypes, and host

Family	Genus	Genotype	Subtypes*	Host	References
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	3	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3l, 3m, 3ra	Human, domestic pig, wild boar, mongoose, deer, rabbit, domestic ruminants, and white- collared peccaries	Wu et al. (2015) Hu et al. (2016) Kenney and Meng (2019) Ferreiro et al. (2020) Castagna et al. (2024)
		4	4a, 4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i	Human, domestic pig, wild boar, cattle, sheep, goat, yak	Xu et al. (2014) Wu et al. (2015) Huang et al. (2016) Garbuglia et al. (2024)
		7	7, 7a	Camel	Lee et al. (2016)

*Source of the data: [Smith et al. \(2020\)](#)

Hepatitis E virus genotype 4 exhibits nucleotide similarities ranging from 71.79% to 77.38% with other genotypes and is classified into nine subtypes. Similar to HEV-3, this genotype has been detected and isolated from humans, domestic pigs, and wild boars ([Garbuglia et al., 2024](#)). Research by [Wu et al. \(2015\)](#) and [Huang et al. \(2016\)](#) also reported the presence of HEV-4 in other animals, such as cattle, sheep, and goats, in China. [Xu et al. \(2014\)](#) reported HEV-4 infection in Yak (*Bos grunniens*). However, further studies are required to ascertain whether these animals serve as reservoirs of HEV-4 or merely as incidental hosts.

So far, HEV-5, HEV-6, and HEV-8 have only been reported to infect animals, with no confirmed cases of human infection ([Doceul et al., 2016](#)). However, these genotypes have demonstrated the ability to infect non-human primates, indicating a potential for zoonotic transmission to humans ([Li et al., 2016; 2019; Wang et al., 2019](#)). Notably, HEV-7 has been reported to infect a human liver transplantation recipient who consumed meat and milk from camel products ([Lee et al., 2016](#)). Further investigation is needed into the zoonotic potential of this genotype due to date, there has been only one reported case of human infection with HEV-7. Hepatitis E virus genotype 7 has two subtypes, but the second subtype has not been named ([Smith et al., 2020](#)).

Epidemiology

Hepatitis E is endemic in both industrial and low-income countries worldwide, with epidemic outbreaks predominantly occurring in developing regions across Mexico, Africa, and Asia ([Meng, 2010](#)). Following the discovery of HEV infection in pigs by [Meng et al. \(1997\)](#), concerns arose regarding the risk of zoonotic transmission, posing a significant public health concern. Worldwide, the prevalence of anti-HEV IgG among domestically raised pigs varies

widely, ranging from 20% to 100%, while the prevalence of HEV RNA is reported between 0% and 20% (Salines et al., 2017). Hepatitis E virus prevalence differs considerably between countries, regions, and even individual farms within the same country (Sooryanarain and Meng, 2020).

The prevalence of HEV-3 subtypes varies significantly between countries. In the United States, subtype 3a is the most common, while in Japan, subtypes 3a, 3b, and 3e are prevalent (Sooryanarain and Meng, 2020). In Europe, the distribution of HEV-3 subtypes varies by geographic location and country, including subtypes 3a, 3b, 3c, 3e, 3f, 3h, 3i, and 3j (Lapa et al., 2015). New subtypes continue to be identified, with 3k found in Japan (Miura et al., 2017), 3l in Switzerland (Wang et al., 2017a), and Northern Italy (De Sabato et al., 2018). In China, rabbit hepatitis E virus (rHEV) exhibits a high genetic similarity to HEV-3, leading to its classification as a genotype of HEV-3, subtype 3ra (Wang et al., 2017b; Smith et al., 2020). In South America, several studies have identified HEV-3 infections in humans and animals, including pigs, white-collared peccaries, and wild boars in Uruguay (Mirazo et al., 2018; Ferreiro et al., 2020). The anti-HEV-3 IgG seropositivity rate on Uruguayan pig farms was reported to be 46.8% (103/220), while in wild boars, it was 22.1% (31/140; Mirazo et al., 2018).

HEV-4 is predominantly endemic in Asia but has recently been detected in several European countries (Primadharsini et al., 2019). Subtypes 4c and 4i have been identified in Japan (Sato et al., 2011). According to Nakano et al. (2016), HEV-4 likely originated in Japan before spreading to China and other parts of Asia, with the global pork trade playing a significant role in its distribution. Among HEV-4 subtypes, 4a, 4b, 4d, and 4h are the most commonly isolated, while subtypes 4c, 4e, 4f, 4g, and 4i remained restricted to specific periods. All HEV-4 subtypes have been reported in China and Japan (Li et al., 2022).

Data on the seroprevalence of hepatitis E in various countries have been reported by several studies. Wu et al. (2022) conducted a study in Guangzhou, China, comparing HEV seroprevalence among swine workers, poultry workers, and the general population. The findings revealed significantly higher seroprevalence rates in swine workers (47%, 156/332) and poultry workers (40.2%, 119/296) compared to the general population (26.1%, 35/134).

In southern France, traditional liver pork sausages known as figatelli, often consumed raw or undercooked as part of local customs, have been identified as a source of HEV transmission to humans (Colson et al., 2010). A case-control study by Colson et al. (2010) reported that the seroprevalence of anti-HEV IgG among individuals consuming raw figatelli reached 54 percent, highlighting the significant risk associated with this dietary practice. The seroprevalence of HEV-3 in domestic pigs in France was 31% (1069/6565, Rose et al., 2011).

In Indonesia, zoonotic HEV genotypes, both HEV-3 and HEV-4, have been detected (Wibawa et al., 2007; Widasari et al., 2013). Wibawa et al. (2004) reported that IgG antibody testing against HEV (anti-HEV) detected a 20% (54/276) seroprevalence in the human population tested in Bali. This percentage is notably higher than the findings from Lombok, which reported 4 percent (17/446), and Surabaya, East Java, which recorded just 0.5 percent (2/393). Utsumi et al. (2011) found that the seroprevalence of anti-HEV in people over 20 years old in Bali was higher than in Java. In the pig population, Wibawa et al. (2004) reported a seroprevalence rate of 72% (51/71), while Utsumi et al. (2011) and Widasari et al. (2013) reported a prevalence of HEV antibodies in pigs from Bali at 82.4% and 81.5%, respectively. A more recent study by Kardena et al. (2024) observed a low seroprevalence of 23.5% (43/183) in pigs collected from rural areas of Karangasem and urban areas of Denpasar, Bali. The decline in prevalence is thought to be due to a pig disease outbreak in 2020-2021 that affected the pig populations and led the farmers to adopt more cautious practices and implement improved livestock systems with enhanced biosecurity measures (Kardena et al., 2024).

Widasari et al. (2013) studied the presence of anti-HEV genotype 3 antibodies among the general population and pig farm workers in Java and Bali, Indonesia, with seroprevalence rates of 5.1% (15/291) and 11.6% (23/199), respectively. This study also examined pig serum samples, showing high prevalence rates of swine HEV antibodies, including 70.3% (114/162) in Java and 81.5% (97/119) in Bali. All studies consistently show that seropositivity for anti-HEV antibodies is higher in Bali than in Java. This discrepancy is likely due to the dietary habits and cultural practices in Bali, where pork consumption is common, and many pig farms exist due to the predominantly Hindu population (Kardena et al., 2021). In contrast, other areas in Indonesia have a majority Muslim population, where pork farming is rare. Furthermore, Balinese people are closely associated with pigs in their daily lives, keeping them as domestic animals and using them in religious ceremonies (Widasari et al., 2013; Kardena et al., 2023).

Zoonotic hepatitis E virus reservoir

The primary reservoirs for zoonotic HEVs are wild boars and domestic pigs (Figure 2). Numerous studies have indicated a high prevalence of HEV among domestic pig populations globally since the first discovery of HEV infection in pigs in 1997 (Wibawa et al., 2004; Rose et al., 2011; Widasari et al., 2013; Mirazo et al., 2018; Hoan et al., 2019; Kardena et al., 2024). A rise in sporadic human cases has also been documented in developed countries (Clemente-Casares et al., 2016; Guillois et al., 2016). In pigs, infection typically occurs at an early age, following the loss of

maternal antibodies (Feng et al., 2011). Virus excretion in fecal samples peaks between 3 to 8 weeks after weaning, followed by a decline at 15-18 weeks of age (Kantala et al., 2015). However, the length of immunity gained after viral exposure is still unclear. The possibility of reinfection due to decreased immunity (postpartum or during coinfection) cannot be ruled out. Loss of protection due to decreasing antibody levels may occur in older animals, particularly in sows (Casas et al., 2011).

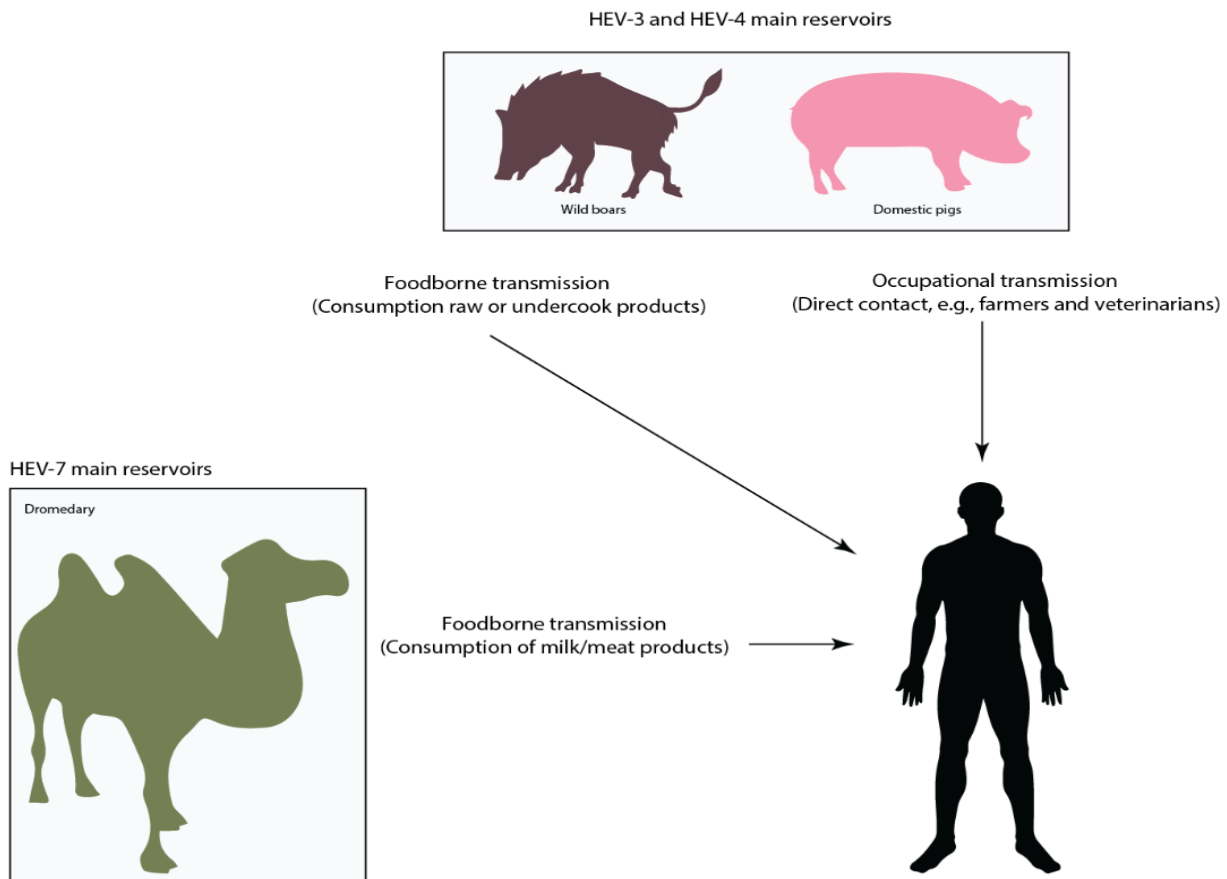


Figure 2. Transmission pathways of zoonotic hepatitis E virus genotypes (HEV-3, HEV-4, and HEV-7)

The presence of viral RNA in serum samples (viremia) is minimally documented compared to samples from the liver or feces (Grierson et al., 2015). Thus, searching for viral RNA in blood or serum samples is not an optimal method for diagnosing acute HEV infection or conducting prevalence studies in natural settings. Hepatitis E virus infection in animals does not significantly impact their health as it does not exhibit clear clinical signs (Song et al., 2013). The absence of these clinical signs complicates the surveillance and reporting of infections in livestock flocks (Pavio et al., 2017).

Several factors influence the level of viremia in pigs at slaughterhouses. Infection typically occurs before slaughter, with the spread of infection within livestock populations resulting in a high proportion of virus shedding in their feces, creating a continuous loop of new infections (Salines et al., 2017). Mirazo et al. (2018) reported that HEV-3 infection was most frequently observed in slaughter-age animals (57.3%, 70/122), which was higher than in younger animals (33.6%, 33/98). This age-related difference in infection rates is further supported by Kardena et al. (2024), who stated that pigs older than six months were four times more likely to be seropositive for HEV antibodies compared to the younger ones.

Factors contributing to the highest risk of HEV infection in pig livers include slaughtering animals at too young an age, specific pig breeds, lack of biosecurity, and using drinking water from nearby sources (Pavio et al., 2017). Kardena et al. (2024) reported several potential risk factors associated with HEV seropositivity in pig farms in Bali, Indonesia, including the type of maintenance management (extensive versus semi-intensive), type of pen floor, sewage (piled versus non-piled), cleanliness of the feed trough, the presence of domestic animals around the farm, type of drinking water, the presence of water sources around the farm, and feed processing (cooked versus not cooked). In France, identified risk factors include direct contact with wild boars, hunting, and residing in rural areas (Carpentier et al., 2012). Furthermore,

HEV exposure may result from drinking water from rivers frequented by wild boars or through contact with feces in these environments (Carpentier et al., 2012).

Rabbits are recognized as the natural hosts of HEV-3ra and are considered a significant reservoir of HEV alongside pigs (Wang et al., 2017). Experimental studies have demonstrated that HEV-3ra is capable of infecting both non-human primates and humans. However, under natural conditions, no evidence of rHEV has been detected in pig populations located near rabbit farms, and cross-species infection has never been reported (Geng et al., 2013).

In addition to wild boars and domestic pigs, recent research by Karlsen et al. (2023) identified deer as a potential true reservoir for HEV-3 and HEV-4, based on phylodynamic analyses. Supporting this, several studies have detected anti-HEV antibodies in various deer species from regions where pig farming is uncommon (Di Profio et al., 2022). Furthermore, HEV RNA has been identified in deer liver tissue, providing direct evidence of viral presence. Histopathological examinations revealed lymphocytic inflammatory cell infiltration in deer, a finding consistent with observations in other confirmed HEV hosts, further substantiating the role of deer as true hosts for HEV-3 (Fonti et al., 2022). Hepatitis E virus strains isolated from deer in Italy demonstrated a nucleotide similarity of 90%-91.5% with strains from humans (Romano et al., 2011) and pigs (Di Bartolo et al., 2017). Takahashi et al. (2004) reported that the HEV genome isolated from wild boars had a high similarity (99.7%) to HEV isolated from wild deer and patients infected with HEV after consuming raw deer meat. These findings reinforce the hypothesis that deer may contribute to the transmission of HEV-3 and HEV-4 in wildlife, potentially serving as a true reservoir for these HEV genotypes.

Zoonotic hepatitis E virus transmission

Occupational-related transmission

Hepatitis E virus infection among workers in slaughterhouses or on pig farms has been documented in several studies. Perez-Gracia et al. (2007) reported HEV-3 infection in workers at a slaughterhouse in Spain. Similarly, Acosta et al. (2022) reported that a pig farmer in Argentina suffered an acute symptomatic hepatitis E. A study conducted in Moldova found significantly higher HEV seroprevalence rates among pig farmers (51%) compared to the general population not involved in pig farming (25%). Farmers with a history of cleaning pig pens or assisting with farrowing were 2.46 times more likely to test seropositive than controls (Drobeniuc et al., 2001). Similarly, a Bayesian estimation approach in the Netherlands reported HEV seroprevalence rates of 11% among swine veterinarians, 6% among non-swine veterinarians, and 2% in the general population (Bouwknegt et al., 2008). Wu et al. (2022) conducted a multivariate analysis indicating that individuals who work in pig slaughterhouses had an elevated risk of HEV infection. In Indonesia, studies by Utsumi et al. (2011) and Widasari et al. (2013) reported several pig farmers in Java and Bali who tested seropositive for anti-HEV antibodies. The likelihood of HEV infection rises with prolonged exposure and is influenced by gender, with men generally exhibiting higher seroprevalence rates. Additionally, prevalence tends to increase with age (De Schryver et al., 2015). Although the specific transmission route in occupational exposure requires further investigation, the role of direct contact with infected animals is evident (Mrzljak et al., 2021). These findings highlight that swine workers have the highest seroprevalence, likely due to their frequent and direct contact with pigs, further emphasizing occupational risk as a significant factor in HEV exposure.

Forest workers, in addition to pig farm workers, are at risk of HEV exposure from wild animals, such as wild boars and deer. Hepatitis E virus transmission is suspected to occur through environmental contamination by wild boar feces, with forest workers becoming exposed through direct contact with contaminated environments or by consuming wild boar meat. Carpentier et al. (2012) observed a seroprevalence rate of 31% among forestry workers in France and 14% in wild boars. The study identified woodcutters as having the highest risk of HEV exposure among forestry workers (Carpentier et al., 2012).

Foodborne transmission by consuming contaminated meat

The Hepatitis E virus has been identified at the start of the food chain supply, particularly in slaughterhouses where meat processing occurs. Research has detected HEV RNA in the serum of pigs in slaughterhouses (Sooryanarain and Meng, 2020) and various commercial pork products (Cossaboom et al., 2016). For instance, HEV RNA was found in 58% (7/12) of figatelli in France (Colson et al., 2010). Similar findings have been reported in HEV RNA in raw liver samples in the United States and France (Cossaboom et al., 2016; Feurer et al., 2018), as well as in raw sausages in Italy and Germany (Di Bartolo et al., 2015; Szabo et al., 2015). In the United States slaughterhouses, approximately 40% of pigs tested positive for HEV antibodies, with around 6% exhibiting HEV-3 viremia (Sooryanarain and Meng, 2020).

The presence of viremia during the slaughter process raised significant food safety concerns, as blood containing HEV can contaminate food supplies. Foodborne transmission occurs through the consumption of raw or undercooked pork products contaminated with the virus (Meng, 2013). In Indonesia, there have been no reports regarding research on the presence of viral RNA in pork food products to date, according to the author's knowledge.

Zhang et al. (2023) investigated HEV prevalence in rabbits and rabbit meat at a slaughterhouse in Hebei Province, China. The study reported a seroprevalence of 10.9% (50/459) in slaughter-age rabbits, with HEV RNA detected in 11.7% (7/60) of rabbit livers. All identified HEV strains were classified as HEV-3ra. These findings highlighted the potential risk of HEV transmission to humans through the consumption of rabbit-derived animal products.

Control and prevention

Exposure to HEV primarily occurs through the consumption of meat from infected animals and direct contact with them. Consequently, an effective preventive strategy is to minimize human exposure, particularly among individuals who have direct contact with reservoir animals or consume them.

Food safety measures

Effective food processing techniques are essential for preventing foodborne HEV outbreaks. Several studies have demonstrated that cooking meat at 71°C for 20 minutes effectively inactivates the virus (Barnaud et al., 2012). Ensuring that animal products are thoroughly cooked before consumption can significantly reduce the risk of HEV transmission through contaminated meat (Castagna et al., 2024).

Occupational safety measures

For workers who have direct contact with reservoir animals, several measures can reduce the risk of HEV infection. These include proper handwashing after contact with animals, the use of Personal Protective Equipment (PPE), such as gloves and masks to minimize direct contact with animal fluid, and the implementation of stringent biosecurity protocols on farms and in slaughterhouses to prevent the spread of HEV among animals and from animals to humans (Mrzljak et al., 2021).

Surveillance and control

Surveillance and control of HEV infection are crucial to bridging the knowledge gap regarding its transmission and reservoirs. Regular monitoring of HEV prevalence in pig populations and pork products can help to identify and manage potential outbreaks. Enhanced surveillance can provide data for developing targeted interventions (Mrzljak et al., 2021).

In HEV surveillance, enzyme-linked immunosorbent assay (ELISA) is commonly employed to detect anti-HEV antibodies in various biological samples, including serum, body cavity transudates, and meat juices (Khudyakov and Kamili, 2011). Additionally, reverse transcription polymerase chain reaction (RT-PCR) is widely used to detect HEV RNA in diverse sample types, such as food products such as meat, sausages, semen, muscle tissue, serum, and liver tissue (Krumova-Valcheva et al., 2023).

Hepatitis E virus vaccines

Due to the widespread prevalence of HEV infection among various animal species, developing an HEV vaccine for animals is a key strategy to prevent transmission from animals to humans (Huang et al., 2024). Vaccines derived from a single genotype may achieve cross-protection across different genotypes. However, the development of a vaccine that provides cross-species immunity in pigs necessitates further studies (Park et al., 2016). In humans, vaccine development efforts include the HEV P179 vaccine, designed based on the amino acids 439-617 of the HEV-4 capsid protein. This vaccine already passed Phase I clinical trials in China (Cao et al., 2017).

Another vaccine, HEV 239, is a recombinant vaccine that has been extensively studied. The antigen in this vaccine is derived from pORF2 amino acids 368-606 of HEV-1 (Li et al., 2015). Multiple clinical trials have demonstrated its efficacy and safety, with the vaccine successfully passing Phase I through Phase IV trials (Yu et al., 2019; Zaman et al., 2024). Although developed based on HEV-1, Phase III clinical trials revealed that HEV 239 also provides cross-protection against HEV-4 infections but does not confer protection against other HEV genotypes (Huang et al., 2024).

In contrast to its performance in humans, a study by Dähnert et al. (2024) reported that the HEV 239 vaccine failed to protect pigs experimentally infected with HEV-3, highlighting limitations in its interspecies cross-protection. This underscores the need for a universal HEV vaccine capable of providing cross-protection across all genotypes and species. The successful development of such a vaccine would enable widespread immunization efforts, significantly reducing the global burden of HEV infections and improving public health outcomes.

One Health strategy

The One Health strategy, emphasizing the interconnectedness of human, animal, and environmental health, plays a vital role in HEV control and prevention. Collaborative efforts among veterinarians, public health professionals, and

environmental scientists are essential for establishing and implementing comprehensive surveillance systems, promoting research on HEV transmission dynamics and reservoirs, and designing and enforcing biosecurity measures across animal and human health sectors. Implementing these measures can substantially lower the risk of HEV transmission by reducing human exposure to the virus and limiting its spread within animal populations, thereby protecting public health (Kardena et al., 2024). Interdisciplinary collaboration is highly recommended in all disease cases (Castagna et al., 2024).

CONCLUSION

The Hepatitis E virus poses a significant global public health challenge due to its zoonotic potential and wide distribution across different regions. The Hepatitis E virus is primarily transmitted through foodborne routes, such as consuming undercooked meat and occupational exposure from direct contact with infected animals. While pigs are key reservoirs, other species contribute to transmission, emphasizing the complexity of HEV epidemiology. Preventive strategies, such as implementing biosecurity measures, promoting food safety through proper cooking practices, and enhancing surveillance systems, are essential for controlling HEV spread. The integration of the one health approach, which considers the interconnectedness of human, animal, and environmental health, is critical for the development of comprehensive control measures. Future research should focus on understanding the full spectrum of HEV reservoirs, refining diagnostic tools, and developing universal vaccines that provide cross-genotype and interspecies protection to reduce the global burden of HEV-related illnesses.

DECLARATIONS

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Ethical considerations

Ethical issues, including plagiarism, consent to publish, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy, have been checked by all the authors.

Authors' contributions

I Made Kardena and Alan P. Dargantes conducted the conceptualization and design of the study. I Made Kardena, Palagan Senopati Sewoyo, Anak Agung Gde Oka Dharmayudha, I Wayan Nico Fajar Gunawan, and Putu Devi Jayanti contributed to data collection and the drafting of the manuscript. Palagan Senopati Sewoyo contributed to the visualization/images. I Nyoman Mantik Astawa, Anak Agung Ayu Mirah Adi, I Nyoman Suarsana, I Nyoman Suartha, and Alan P. Dargantes reviewed and revised the manuscript. All authors checked and approved the final edition of the manuscript.

Competing interests

All authors declare that there are no competing interests.

Availability of data and materials

The datasets and materials analyzed in this review are derived from publicly available articles, reports, and databases, which are cited throughout the manuscript. No new data were generated or analyzed during this study.

REFERENCES

- Acosta J, Galimberti A, Marziali F, Costaguta A, Bessone F, Tanno H, Gardiol D, Reggiardo MV, and Cavatorta AL (2022). Zoonotic transmission of hepatitis E virus in a pig farmer from Argentina: A case report. *Zoonoses Public Health*, 69(3): 235-241. DOI: <https://www.doi.org/10.1111/zph.12902>
- Barnaud E, Rogee S, Garry P, Rose N, and Pavio N (2012). Thermal inactivation of infectious hepatitis E virus in experimentally contaminated food. *Applied and Environmental Microbiology*, 78(15): 5153-5159. DOI: <https://www.doi.org/10.1128/aem.00436-12>

- Berglöv A, Hallager S, and Weis N (2019). Hepatitis E during pregnancy: Maternal and fetal case-fatality rates and adverse outcomes—A systematic review. *Journal of Viral Hepatitis*, 26(11): 1240-1248. DOI: <https://www.doi.org/10.1111/jvh.13129>
- Bouwknegt M, Engel B, Herremans MMPT, Widdowson MA, Worm HC, Koopmans MPG, Frankena K, de Roda Husman AM, de Jong MCM, and van der Poel WHM (2008). Bayesian estimation of hepatitis E virus seroprevalence for populations with different exposure levels to swine in the Netherlands. *Epidemiology and Infection*, 136(4): 567-576. DOI: <https://www.doi.org/10.1017/s0950268807008941>
- Cancela F, Icasuriaga R, Cuevas S, Hergatacorzian V, Olivera M, Panzera Y, Perez R, Lopez J, Borzacconi L, Gonzalez E et al. (2023). Epidemiology update of hepatitis E virus (HEV) in Uruguay: Subtyping, environmental surveillance, and zoonotic transmission. *Viruses*, 15(10): 2006. DOI: <https://www.doi.org/10.3390/v15102006>
- Cao YF, Tao H, Hu YM, Shi CB, Wu X, Liang Q, Chi CP, Li L, Liang ZL, Meng JH et al. (2017). A phase I randomized open-label clinical study to evaluate the safety and tolerability of a novel recombinant hepatitis E vaccine. *Vaccine*, 35(37): 5073-5080. DOI: <https://www.doi.org/10.1016/j.vaccine.2017.05.072>
- Carpentier A, Chaussade H, Rigaud E, Rodriguez J, Berthault C, Boue F, Tognon M, Touze A, Garcia-Bonnet N, Choutet P et al. (2012). High hepatitis E virus seroprevalence in forestry workers and in wild boars in France. *Journal of Clinical Microbiology*, 50(9): 2888-2893. DOI: <https://www.doi.org/10.1128/JCM.00989-12>
- Casas M, Cortés R, Pina S, Peralta B, Allepuz A, Cortey M, Casal J, and Martín M (2011). Longitudinal study of hepatitis E virus infection in Spanish farrow-to-finish swine herds. *Veterinary Microbiology*, 148(1): 27-34. DOI: <https://www.doi.org/10.1016/j.vetmic.2010.08.010>
- Castagna F, Liguori G, Lombardi R, Bava R, Costagliola A, Giordano A, Quintiliani M, Giacomini D, Albergo F, Gigliotti A et al. (2024). Hepatitis E and potential public health implications from a One-Health perspective: Special focus on the European wild boar (*Sus scrofa*). *Pathogens*, 13(10): 840. DOI: <https://www.doi.org/10.3390/pathogens13100840>
- Clemente-Casares P, Ramos-Romero C, Ramirez-Gonzales E, and Mas A (2016). Hepatitis E virus in industrialized countries: The silent threat. *Biomed Research International*, 2016(1): 1-17. DOI: <https://www.doi.org/10.1155/2016/9838041>
- Colson P, Borentain P, Queyriaux B, Kaba M, Moal V, Gallian P, Heyries L, Raoult D, and Gerolami R (2010). Pig liver sausage as a source of hepatitis E virus transmission to humans. *The Journal of Infectious Diseases*, 202(6): 825-834. DOI: <https://www.doi.org/10.1086/655898>
- Cossaboom C, Heffron C, Cao D, Yugo D, Houk-Miles A, Lindsay D, Zajac A, Bertke A, Elvinger F, and Meng X (2016). Risk factors and sources of foodborne hepatitis E virus infection in the United States. *Journal of Medical Virology*, 88(9): 1641-1645. DOI: <https://www.doi.org/10.1002/jmv.24497>
- Dähnert L, Aliabadi E, Fast C, Hrabal I, Schröder C, Behrendt P, Protzer U, Groschup MH, and Eiden M (2024). Immunisation of pigs with recombinant HEV vaccines does not protect from infection with HEV genotype 3. *One Health*, 18: 100674. DOI: <https://www.doi.org/10.1016/j.onehlt.2023.100674>
- De Sabato L, Lemey P, Vrancken B, Bonfanti L, Ceglie L, Vaccari G, and Di Bartolo I (2018). Proposal for a new subtype of the zoonotic genotype 3 Hepatitis E virus: HEV-3I. *Virus Research*, 248: 1-4. DOI: <https://www.doi.org/10.1016/j.virusres.2018.02.010>
- De Schryver A, De Schrijver K, Francois G, Hambach R, van Sprundel M, Tabibi R, and Colosio C (2015). Hepatitis E virus infection: An emerging occupational risk?. *Occupational Medicine*, 65: 667-672. DOI: <https://www.doi.org/10.1093/occmed/kqv154>
- Di Bartolo I, Angeloni G, Ponterio E, Ostanello F, and Ruggeri FM (2015). Detection of hepatitis E virus in pork liver sausages. *International Journal of Food Microbiology*, 193: 29-33. DOI: <https://www.doi.org/10.1016/j.ijfoodmicro.2014.10.005>
- Di Bartolo I, Ponterio E, Angeloni G, Morandi F, Ostanello F, Nicoloso S, and Ruggeri FM (2017). Presence of hepatitis E virus in a red deer (*Cervus elaphus*) population in Central Italy. *Transboundary and Emerging Diseases*, 64(1): 137-143. DOI: <https://www.doi.org/10.1111/tbed.12353>
- Di Profio F, Sarchese V, Palombieri A, Fruci P, Lanave G, Robetto S, Martella V, and Di Martino B (2022). Current knowledge of hepatitis E virus (HEV) epidemiology in ruminants. *Pathogens*, 11(10): 1124. DOI: <https://www.doi.org/10.3390/pathogens11101124>
- Doceul V, Bagdassarian E, Demange A, and Pavio N (2016). Zoonotic hepatitis E virus: Classification, animal reservoirs and transmission routes. *Viruses*, 8: 270. DOI: <https://www.doi.org/10.3390/v8100270>
- Drobeniuc J, Fovarov MO, Shapiro CN, Bell BP, Mast EE, Dadu A, Culver D, Iarovoi P, Robertson BH, and Margolis HS (2001). Hepatitis E virus antibody prevalence among persons who work with swine. *The Journal of Infectious Diseases*, 184(12): 1594-1597. DOI: <https://www.doi.org/10.1086/324566>
- Fenaux H, Chassaing M, Berger S, Gantzer C, Bertrand I, and Schvoerer E (2019). Transmission of hepatitis E virus by water: An issue still pending in industrialized countries. *Water Research*, 151: 144-157. DOI: <https://www.doi.org/10.1016/j.watres.2018.12.014>
- Feng R, Zhao C, Li M, Harrison TJ, Qiao Z, Feng Y, Ma Z, and Wang Y (2011). Infection dynamics of hepatitis E virus in naturally infected pigs in a Chinese farrow-to-finish farm. *Infection Genetics and Evolution*, 11(7): 1727-1731. DOI: <https://www.doi.org/10.1016/j.meegid.2011.07.009>
- Ferreiro I, Herrera ML, González I, Cancela F, Leizagoyen C, Loureiro M, Arellano H, Echaidés C, Bon B, Castro G et al. (2021). Hepatitis E virus (HEV) infection in captive white-collared peccaries (*Pecari tajacu*) from Uruguay. *Transboundary and Emerging Diseases*, 68(3): 1040-1045. DOI: <https://www.doi.org/10.1111/tbed.13790>
- Feurer C, Le Roux A, Rossel R, Barnaud E, Dumarest M, Garry P, and Pavio N (2018). High load of hepatitis E viral RNA in pork livers but absence in pork muscle at French slaughterhouse. *International Journal of Food Microbiology*, 264: 25-30. DOI: <https://www.doi.org/10.1016/j.ijfoodmicro.2017.10.013>
- Fonti N, Pacini MI, Forzan M, Parisi F, Periccioli M, Mazzei M, and Poli A (2022). Molecular and pathological detection of hepatitis E virus in Roe deer (*Capreolus capreolus*) and Fallow deer (*Dama dama*) in Central Italy. *Veterinary Sciences*, 9(3): 100. DOI: <https://www.doi.org/10.3390/vetsci9030100>
- Fukuda S, Sunaga J, Saito N, Fujimura K, Itoh Y, Sasaki M, Tsuda F, Takahashi M, Nishizawa T, and Okamoto H (2004). Prevalence of antibodies to hepatitis E virus among Japanese blood donors: Identification of three blood donors infected with a genotype 3 hepatitis E virus. *Journal of Medical Virology*, 73(4): 554-561. DOI: <https://www.doi.org/10.1002/jmv.20125>
- Garbuglia AR, Koja G, Villano U, Minosse C, Equestre M, Pauciuolo S, Coppola A, Madonna E, Picchi G, Biase JD et al. (2024). HEV-3 subtypes and strain detected in cases of HEV infection in central Italy from 2015 to 2023. *Infection*, pp. 2-12. DOI: <https://www.doi.org/10.1007/s15010-024-02348-0>
- Geng Y, Zhang H, Li J, Huang W, Harrison TJ, Zaho C, Zhou Y, Lian H, and Wang Y (2013). Comparison of hepatitis E virus genotypes from rabbits and pigs in the same geographic area: No evidence of natural cross-species transmission between the two animals. *Infection, Genetics and Evolution*, 13: 304-309. DOI: <https://www.doi.org/10.1016/j.meegid.2012.11.006>

- Grierson S, Heaney J, Cheney T, Morgan D, Wyllie S, Powell L, Smith D, Ijaz S, Steinbach F, Choudhury B, Tedder RS et al. (2015). Prevalence of hepatitis E virus infection in pigs at the time of slaughter, United Kingdom, 2013. *Emerging Infectious Diseases*, 21(8): 1396-1401. DOI: <https://www.doi.org/10.3201/eid2108.141995>
- Guillois Y, Abravanel F, Miura T, Pavio N, Vaillant V, Lhomme S, Guyader FSL, Rose N, Saux JCL, King LA et al. (2016). High proportion of asymptomatic infections in an outbreak of hepatitis E associated with a spit-roasted piglet, France, 2013. *Clinical Infectious Diseases*, 62(3): 351-357. DOI: <https://www.doi.org/10.1093/cid/civ862>
- Hoan NX, Huy PX, Sy BT, Meyer CG, Son TV, Binh MT, and Velavan TP (2019). High hepatitis E virus (HEV) positivity among domestic pigs and risk of HEV infection of individuals occupationally exposed to pigs and pork meat in Hanoi, Vietnam. *Open Forum Infectious Diseases*, 6(9): ofz306. DOI: <https://www.doi.org/10.1093/ofid/ofz306>
- Huang F, Li Y, Yu W, Jing S, Wang J, Long F, He Z, Yang C, Bi Y, and Cao W (2016). Excretion of infectious hepatitis E virus into milk in cows imposes high risks of zoonosis. *Hepatology*, 64(2): 350-359. DOI: <https://www.doi.org/10.1002/hep.28668>
- Huang X, Lu J, Liao M, Huang Y, Wu T, and Xia N (2024). Progress and challenges to hepatitis E vaccine development and deployment. *Vaccines*, 12(7): 719. DOI: <https://www.doi.org/10.3390/vaccines12070719>
- Izopet J, Dubois M, Bertagnoli S, Lhomme S, Marchandeau S, Boucher S, Kamar N, Abravanel F, and Guérin JL (2012). Hepatitis E virus strains in rabbits and evidence of a closely related strain in humans, France. *Emerging Infectious Diseases*, 18(8): 1274-1281. DOI: <https://www.doi.org/10.3201/eid1808.120057>
- Kantala T, Heinonen M, Oristo S, von Bonsdorff CH, and Maunula L (2015). Hepatitis E virus in young pigs in Finland and characterization of the isolated partial genomic sequences of genotype 3 HEV. *Foodborne Pathogens and Disease*, 12(3): 253-260. DOI: <https://www.doi.org/10.1089/fpd.2014.1841>
- Kardena IM, Adi AAAM, Astawa INM, O'Dea M, Laurence M, Sahibzada S, and Bruce M (2021). Japanese encephalitis in Bali, Indonesia: Ecological and socio-cultural perspectives. *International Journal of Veterinary Science and Medicine*, 9(1): 31-43. DOI: <https://www.doi.org/10.1080/23144599.2021.1975879>
- Kardena IM, Adi AAAM, Astawa INM, O'Dea M, Robertson I, Sahibzada S, and Bruce M (2023). Individual and herd-level seroprevalence in association with potential risk factors of Japanese encephalitis in pigs collected from urban, periurban, and rural areas of Bali, Indonesia. *Veterinary Medicine International*, 2023(1): 9682657. DOI: <https://www.doi.org/10.1155/2023/9682657>
- Kardena IM, Dharmayudha AAGO, Gunawan IWN, Jayanti PD, Astawa INM, Adi AAAM, Suarsana IN, Suartha IN, and Dargantes AP (2024). Seroprevalence of swine hepatitis E virus and the farmers' potential risk of infection in the Province of Bali, Indonesia. *Veterinary World*, 17(8): 1810. DOI: <https://www.doi.org/10.14202/vetworld.2024.1810-1820>
- Karlsen AA, Kichatova VS, Kyuregyan KK, and Mikhailov MI (2023). Phylogenetic analysis suggests that deer species may be a true reservoir for hepatitis E virus genotypes 3 and 4. *Microorganisms*, 11(2): 375. DOI: <https://www.doi.org/10.3390/microorganisms11020375>
- Kenney SP and Meng XJ (2019). Hepatitis E virus genome structure and replication strategy. *Cold Spring Harbor Perspectives in Medicine*, 9(1): a031724. DOI: <https://www.doi.org/10.1101/cshperspect.a031724>
- Khudyakov Y and Kamili S (2011). Serological diagnostics of hepatitis E virus infection. *Virus Research*, 161(1): 84-92. DOI: <https://www.doi.org/10.1016/j.virusres.2011.06.006>
- Krumova-Valcheva GL, Di Bartolo I, Smith RP, Gyurova E, Mateva G, Milanov M, Dimitrova A, Burow E, and Daskalov H (2023). Detection of HEV RNA using one-step real-time RT-PCR in farrow-to-finish pig farms in Bulgaria. *Pathogens*, 12(5): 673. DOI: <https://www.doi.org/10.3390/pathogens12050673>
- Lapa D, Capobianchi MR, and Garbuglia AR (2015). Epidemiology of hepatitis E virus in European countries. *International Journal of Molecular Sciences*, 16(10): 25711-25743. DOI: <https://www.doi.org/10.3390/ijms161025711>
- Lee GH, Tan BH, Teo EC, Lim SG, Dan YY, Wee A, Aw PP, Zhu Y, Hibberd ML, Tan CK et al. (2016). Chronic infection with camelid hepatitis E virus in a liver transplant recipient who regularly consumes camel meat and milk. *Gastroenterology*, 150(2): 355-357.e353. DOI: <https://www.doi.org/10.1053/j.gastro.2015.10.048>
- Li B, Wagner AL, Song Y, Chen X, and Lu Y (2022). Distribution and phylogenetics of hepatitis E virus genotype 4 in humans and animals. *Zoonoses and Public Health*, 69(5): 458-467. DOI: <https://www.doi.org/10.1111/zph.12934>
- Li SW, Zhao Q, Wu T, Chen S, Zhang J, and Xia NS (2015). The development of a recombinant hepatitis E vaccine HEV 239. *Human Vaccines & Immunotherapeutics*, 11(4): 908-914. DOI: <https://www.doi.org/10.1080/21645515.2015.1008870>
- Li TC, Bai H, Yoshizaki S, Ami Y, Suzaki Y, Doan YH, Takahashi K, Mishiro S, Takeda N, and Wakita T (2019). Genotype 5 hepatitis E virus produced by a reverse genetics system has the potential for zoonotic infection. *Hepatology Communications*, 3(1): 160-172. DOI: <https://www.doi.org/10.1002/hep4.1288>
- Li TC, Zhou X, Yoshizaki S, Ami Y, Suzaki Y, Nakamura T, Takeda N, and Wakita T (2016). Production of infectious dromedary camel hepatitis E virus by a reverse genetic system: Potential for zoonotic infection. *Journal of Hepatology*, 65(6): 1104-1111. DOI: <https://www.doi.org/10.1016/j.jhep.2016.07.013>
- Liang H, Chen J, Xie J, Sun L, Ji F, He S, Zeng Y, Liang C, Zhang G, Su S et al. (2014). Hepatitis E virus serosurvey among pet dogs and cats in several developed cities in China. *PLoS One*, 9: e98068. DOI: <https://www.doi.org/10.1371/journal.pone.0098068>
- Meng XJ (2010). Hepatitis E virus: Animal reservoirs and zoonotic risk. *Veterinary Microbiology*, 140(3-4): 256-265. DOI: <https://www.doi.org/10.1016/j.vetmic.2009.03.017>
- Meng XJ (2013). Zoonotic and foodborne transmission of hepatitis E virus. *Seminars in Liver Disease*, 33(1): 41-49. DOI: <https://www.doi.org/10.1055/s-0033-1338113>
- Meng XJ, Purcell RH, Halbur PG, Lehman JR, Webb DM, and Tsareva TS (1997). A novel virus in swine is closely related to the human hepatitis E virus. *Proceedings of the National Academy of Sciences of the United States of America* 94(18): 9860-9865. DOI: <https://www.doi.org/10.1073/pnas.94.18.9860>
- Mirazo S, Gardinali NR, Verger L, Ottonelli F, Ramos N, Castro G, Pinto MA, Re V, Pisano B, Lozano A et al. (2018). Serological and virological survey of hepatitis E virus (HEV) in animal reservoirs from Uruguay reveals elevated prevalences and a very close phylogenetic relationship between swine and human strains. *Veterinary Microbiology*, 213: 21-27. DOI: <https://www.doi.org/10.1016/j.vetmic.2017.11.013>
- Miura M, Inoue J, Tsuruoka M, Nishizawa T, Nagashima S, Takahashi M, Shimosegawa T, and Okamoto H (2017). Full-length genomic sequence analysis of new subtype 3k hepatitis E virus isolates with 99.97 nucleotide identity obtained from two consecutive acute hepatitis patients in a city in northeast Japan. *Journal of Medical Virology*, 89(6): 1116-1120. DOI: <https://www.doi.org/10.1002/jmv.24743>

- Mrzljak A, Balen I, Barbic L, Ilic M, and Vilbic-Cavlek T (2021). Hepatitis E virus in professionally exposed: A reason for concern?. *World Journal of Hepatology*, 13(7): 723. DOI: <https://www.doi.org/10.4254/wjh.v13.i7.723>
- Nakano T, Takahashi K, Takahashi M, Nishigaki Y, Watanabe N, Ishida S, Fujimoto S, Kato H, Okano H, Takei Y et al. (2016). Investigating the origin and global dispersal history of hepatitis E virus genotype 4 using phylogeographical analysis. *Liver International*, 36(1): 31-41. DOI: <https://www.doi.org/10.1111/liv.12880>
- Nelson KE, Labrique AB, and Kmush BL (2019). Epidemiology of genotype 1 and 2 hepatitis E virus infections. *Cold Spring Harbor Perspectives in Medicine*, 9: a031732. DOI: <https://www.doi.org/10.1101/cshperspect.a031732>
- Nimgaonkar I, Ding Q, Schwartz RE, and Ploss A (2017). Hepatitis E virus: Advances and challenges. *Nature Reviews Gastroenterology & Hepatology*, 15: 96-110. DOI: <https://www.doi.org/10.1038/nrgastro.2017.150>
- Okamoto H (2007). Genetic variability and evolution of hepatitis E virus. *Virus Research*, 127(2): 216-228. DOI: <https://www.doi.org/10.1016/j.virusres.2007.02.002>
- Olsen B, Axelsson-Olsson D, Thelin A, and Weiland O (2006). Unexpected high prevalence of IgG-antibodies to hepatitis E virus in Swedish pig farmers and controls. *Scandinavian Journal of Infectious Diseases*, 38(1): 55-58. DOI: <https://www.doi.org/10.1080/00365540500321470>
- Park WJ, Park BJ, Ahn HS, Lee JB, Park SY, Song CS, and Choi IS (2016). Hepatitis E virus as an emerging zoonotic pathogen. *Journal of Veterinary Science*, 17(1): 1-11. DOI: <https://www.doi.org/10.4142/jvs.2016.17.1.1>
- Pavio N, Doceul V, Bagdassarian E, and John R (2017). Recent knowledge on hepatitis E virus in Suidae reservoirs and transmission routes to human. *Veterinary Research*, 48: 1-14. DOI: <https://www.doi.org/10.1186/s13567-017-0483-9>
- Pavio N, Meng XJ, and Doceul V (2015). Zoonotic origin of hepatitis E. *Current Opinion in Virology*, 10: 34-41. DOI: <https://www.doi.org/10.1016/j.coviro.2014.12.006>
- Perez-Gracia MT, Mateos ML, Galiana C, Fernandez-Barredo S, Garcia A, Gomez MT, and Moreira V (2007). Autochthonous hepatitis E infection in a slaughterhouse worker. *American Journal of Tropical Medicine and Hygiene*, 77(5): 893-896. DOI: <https://www.doi.org/10.4269/ajtmh.2007.77.893>
- Primadharsini PP, Nagashima S, and Okamoto H (2019). Genetic variability and evolution of hepatitis E virus. *Viruses*, 11(5): 456. DOI: <https://www.doi.org/10.3390/v11050456>
- Purdy MA, Drexler JF, Meng XJ, Norder H, Okamoto H, Van der Poel WHM, Reuter G, de Souza WM, Ulrich RG, and Smith DB (2022). ICTV virus taxonomy profile: Hepeviridae 2022. *Journal of General Virology*, 103(9): 001778. DOI: <https://www.doi.org/10.1099/jgv.0.001778>
- Rein DB, Stevens GA, Theaker J, Wittenborn JS, and Wiersma ST (2012). The global burden of hepatitis E virus genotypes 1 and 2 in 2005. *Hepatology*, 55(4): 988-997. DOI: <https://www.doi.org/10.1002/hep.25505>
- Romano L, Paladini S, Tagliacarne C, Canuti M, Bianchi S, and Zanetti AR (2011). Hepatitis E in Italy: A long-term prospective study. *Journal of Hepatology*, 54(1): 34-40. DOI: <https://www.doi.org/10.1016/j.jhep.2010.06.017>
- Rose N, Lunazzi A, Dorenlor V, Merbah T, Eono F, Eloit M, Madec F, and Pavio N (2011). High prevalence of Hepatitis E virus in French domestic pigs. *Comparative Immunology, Microbiology and Infectious Diseases*, 34(5): 419-427. DOI: <https://www.doi.org/10.1016/j.cimid.2011.07.003>
- Salines M, Andraud M, and Rose N (2017). From the epidemiology of hepatitis E virus (HEV) within the swine reservoir to public health risk mitigation strategies: A comprehensive review. *Veterinary Research*, 48: 31. DOI: <https://www.doi.org/10.1186/s13567-017-0436-3>
- Samala N and Ghany MG (2013). Hepatitis E: The nonendemic perspective. *Clinical Liver Disease*, 2: 245-249. DOI: <https://www.doi.org/10.1002/cld.256>
- Santos-Silva S, Hemnani M, Lopez-Lopez P, Gonçalves HM, Rivero-Juarez A, der Poel WHV, Nascimento MSJ, and Mesquita JR (2023). A systematic review of hepatitis E virus detection in camels. *Veterinary Sciences*, 10(5): 323. DOI: <https://www.doi.org/10.3390/vetsci10050323>
- Sato Y, Sato H, Naka K, Furuya S, Tsukiji H, Kitagawa K, and Okamoto H (2011). A nationwide survey of hepatitis E virus (HEV) infection in wild boars in Japan: Identification of boar HEV strains of genotypes 3 and 4 and unrecognized genotypes. *Archives of Virology*, 156: 1345-1358. DOI: <https://www.doi.org/10.1007/s00705-011-0988-x>
- Smith DB, Izopet J, Nicot F, Simmonds P, Jameel S, and Meng XJ (2020). Update: Proposed reference sequences for subtypes of hepatitis E virus (species *Orthohepevirus A*). *Journal of General Virology*, 101(7): 692-698. DOI: <https://www.doi.org/10.1099/jgv.0.001435>
- Song YJ, Park WJ, Park BJ, Lee JB, Park SY, Song CS, Lee NH, Seo KH, Kang YS, and Choi IS (2013). Hepatitis E virus infections in humans and animals. *Clinical and Experimental Vaccine Research*, 3(1): 29-36. DOI: <https://www.doi.org/10.7774/cevr.2014.3.1.29>
- Sooryanarain H and Meng XJ (2020). Swine hepatitis E virus: Cross-species infection, pork safety, and chronic infection. *Virus Research*, 284: 197985. DOI: <https://www.doi.org/10.1016/j.virusres.2020.197985>
- Szabo K, Trojnar E, Anheyer-Behmenburg H, Binder A, Schotte U, Ellerbroek L, Klein G, and John R (2015). Detection of hepatitis E virus RNA in raw sausages and liver sausages from retail in Germany using an optimized method. *International Journal of Food Microbiology*, 215: 149-156. DOI: <https://www.doi.org/10.1016/j.ijfoodmicro.2015.09.013>
- Takahashi K, Kitajima N, Abe N, and Mishiro S (2004). Complete or near-complete nucleotide sequences of hepatitis E virus genome recovered from a wild boar, a deer, and four patients who ate the deer. *Virology*, 330(2): 501-505. DOI: <https://www.doi.org/10.1016/j.virol.2004.10.006>
- Tei S, Kajima N, Takahashi K, and Mishiro S (2003). Zoonotic transmission of hepatitis E virus from deer to human beings. *Lancet*, 362(9381): 371-373. DOI: [https://www.doi.org/10.1016/s0140-6736\(03\)14025-1](https://www.doi.org/10.1016/s0140-6736(03)14025-1)
- Treagus S, Wright C, Baker-Austin C, Longdon B, and Lowther J (2021). The Foodborne Transmission of Hepatitis E Virus to Humans. *Food and Environmental Virology*, 13: 127-145. DOI: <https://www.doi.org/10.1007/s12560-021-09461-5>
- Utsumi T, Hayashi Y, Lusida MI, Amin M, Soetjpto, Hendra A, and Hotta H (2010). Prevalence of hepatitis E virus among swine and humans in two different ethnic communities in Indonesia. *Archives of Virology*, 156: 689-693. DOI: <https://www.doi.org/10.1007/s00705-010-0883-x>
- Wang B, Harms D, Hofmann J, Ciardo D, Kneubühl A, and Bock CT (2017a). Identification of a novel hepatitis E virus genotype 3 strain isolated from a chronic hepatitis E virus infection in a kidney transplant recipient in Switzerland. *Genome Announcements*, 5(20): 10-1128. DOI: <https://www.doi.org/10.1128/genomea.00345-17>
- Wang L, Liu L, and Wang L (2017b). An overview: Rabbit hepatitis E virus (HEV) and rabbit providing an animal model for HEV study. *Reviews in Medical Virology*, 28(1): e1961. DOI: <https://www.doi.org/10.1002/rmv.1961>

- Wang L, Teng JLL, Lau SKP, Sridhar S, Fu H, Gong W, Li M, Xu Q, He Y, Zhuang H, Woo PCY, and Wang L (2019). Transmission of a novel genotype of hepatitis E virus from Bactrian camels to Cynomolgus macaques. *Journal of Virology*, 93(7): e02014-18. DOI: <https://www.doi.org/10.1128/jvi.02014-18>
- Wibawa IDN, Muljono DH, Mulyanto, Suryadarma IG, Tsuda F, Takahashi M, Nishizawa T, and Okamoto H (2004). Prevalence of antibodies to hepatitis E virus among apparently healthy humans and pigs in Bali, Indonesia: Identification of a pig infected with a genotype 4 hepatitis E virus. *Journal of Medical Virology*, 73(1): 38-44. DOI: <https://www.doi.org/10.1002/jmv.20059>
- Wibawa IDN, Suryadarma IGA, Mulyanto, Tsuda F, Matsumoto Y, Ninomiya M, and Okamoto H (2007). Identification of genotype 4 hepatitis E virus strains from a patient with acute hepatitis E and farm pigs in Bali, Indonesia. *Journal of Medical Virology*, 79(8): 1138-1146. DOI: <https://www.doi.org/10.1002/jmv.20904>
- Widasari DI, Yano Y, Utsumi T, Heriyanto DS, Anggorowati N, Rinonce HT, and Hayashi Y (2013). Hepatitis E virus infection in two different regions of Indonesia with identification of swine HEV genotype 3. *Microbiology and Immunology*, 57(10): 692-703. DOI: <https://www.doi.org/10.1111/1348-0421.12083>
- Wu C, Wu X, and Xia J (2020). Hepatitis E virus infection during pregnancy. *Virology Journal*, 17: 73. DOI: <https://www.doi.org/10.1186/s12985-020-01343-9>
- Wu J, Si F, Jiang C, Li T, and Jin M (2015). Molecular detection of hepatitis E virus in sheep from Southern Xinjiang, China. *Virus Genes*, 50: 410-417. DOI: <https://www.doi.org/10.1007/s11262-015-1194-9>
- Wu JY, Lau EHY, Lu ML, Guo C, Guo ZM, Yuan J, and Lu JH (2022). An occupational risk of hepatitis E virus infection in the workers along the meat supply chains in Guangzhou, China. *One Health*, 14: 100376. DOI: <https://www.doi.org/10.1016/j.onehlt.2022.100376>
- Xu F, Pan Y, Baloch AR, Tian L, Wang M, Na W, Ding L, and Zeng Q (2014). Hepatitis E virus genotype 4 in yak, Northwestern China. *Emerging Infectious Diseases*, 20(12): 2182-2184. DOI: <https://www.doi.org/10.3201/eid2012.131599>
- Yu XY, Chen ZP, Wang SY, Pan HR, Wang ZF, Zhang QF, Shen LZ, Zheng XP, Yan CF, Lu M et al. (2019). Safety and immunogenicity of hepatitis E vaccine in elderly people older than 65%. *Vaccine*, 37(32): 4581-4586. DOI: <https://www.doi.org/10.1016/j.vaccine.2019.04.006>
- Zaman K, Julin CH, Aziz AB, Stene-Johansen K, Yunus M, Qadri F, Gurley ES, Sandbu S, Overbo J, Dembinski JL et al. (2024). Safety and effectiveness of a recombinant hepatitis E vaccine in women of childbearing age in rural Bangladesh: A phase 4, double-blind, cluster-randomised, controlled trial. *Lancet*, 12(8): e1288-e1299. DOI: [https://www.doi.org/10.1016/s2214-109x\(24\)00192-x](https://www.doi.org/10.1016/s2214-109x(24)00192-x)
- Zhang H, Li X, Wang C, Shi T, Geng Y, and Zhao C (2023). Detection of hepatitis E virus in rabbits and rabbit meat from slaughterhouses in Hebei Province of China. *Vector-Borne and Zoonotic Diseases*, 23(11): 588-594 DOI: <https://www.doi.org/10.1089/vbz.2023.0010>

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