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Review

WORLDWIDE DISTRIBUTION OF HEPATITIS E VIRUS AMONG DOMESTIC RUMINANTS AND THEIR ROLE IN VIRUS TRANSMISSION – A REVIEW

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Summary

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Hepatitis E virus (HEV) is a small RNA virus from the *Hepeviridae* family, causing acute viral hepatitis in humans. The first reports of the infection date back to the 1980s among soldiers in Afghanistan. However, modern data indicate that the virus is globally distributed and infects millions of people annually. HEV has a zoonotic potential, with pigs and wild boars considered the main reservoirs of the virus. However, there is convincing evidence that HEV circulate among other animal species, including domestic and wild ruminants, in which the infection proceeds asymptomatically, making them into important viral reservoirs. There is considerable variation in the prevalence depending on animal species, geography, and sample type. The seroprevalence in cattle in China ranges from 0.8% to 18.7%. In Europe, most investigations report negative results, except for Turkey (29.16% HEV RNA-positive milk samples) and Bulgaria (7.7% seropositivity). In sheep, natural infection was first described in China, with prevalence between 0.7% and 11.1%. The seroprevalence in Africa varies from 4.4% to 31.8%, while in Europe it ranges from 1.9% to 32.2%, the highest rate recorded in Bulgaria. Goats have also been confirmed as natural HEV hosts, with viral RNA detected in faeces (up to 74% in China) and seroprevalence up to 24.4% in Bulgaria. Detection of HEV RNA in milk and the genetic similarity between animal and human strains highlight the zoonotic potential of ruminants and the need for continued molecular surveillance. Therefore, the present review aims to present the available epidemiological data on the spread of HEV in ruminants and their role in virus transmission.

Key words: hepatitis E virus, HEV RNA, milk-borne transmission, ruminants, seroprevalence, zoonotic transmission

INTRODUCTION

Hepatitis E virus is classified within the *Hepeviridae* family, which includes small enterically transmitted quasi-enveloped viruses with a single-stranded, positive-sense RNA genome. According to the latest classification published by International Committee on Taxonomy of Viruses (ICTV) (Purdy *et al.,* 2022), this family is divided into two subfamilies: *Orthohepevirinae* and *Parahepevirinae*. The *Orthohepeviridae* subfamily comprises four genera, each specifically adapted to different species of mammals and birds.

Zoonotic acute hepatitis E in humans is caused primarily by *Paslahepevirus balayani* and *Rocahepevirus ratti* (Purdy *et al.,* 2022). *Paslahepevirus balayani* is the main species associated with human infection. Based on full-genome analysis, eight distinct genotypes (designated as gt) have been identified, four of which (gt1–gt4) are known to cause disease in humans (Wang & Meng, 2021).

HEV gt1 and HEV gt2 are restricted to humans and are responsible for large-scale outbreaks in developing countries, where the lack of clean drinking water and poor sanitary conditions facilitate transmission of the infection. Such epidemics are most frequently reported in Asia and Africa (Raji *et al.,* 2022). In contrast, HEV gt3 and HEV gt4 have a well-documented zoonotic potential and are responsible for both sporadic and clustered cases of hepatitis E in both industrialised and developing countries. These genotypes are widely distributed across Europe, Asia, and North America (Smith *et al.,* 2020). HEV gt5 and HEV gt6 are limited to wild boars and have been isolated in Japan (Takahashi *et al.,* 2014), whereas HEV gt7 and HEV gt8 have been detected in camels. Evidence supporting the ability of HEV gt7 to infect humans was presented in the study by Lee *et al.* (2016).

Infection caused by *Orthohepevirus C* (currently *Rocahepevirus ratti*) was first documented in a human patient in Hong Kong (Sridhar *et al.,* 2018), with subsequent cases reported in Spain, Canada, France, and Central Africa (Benavent *et al.,* 2023; Casares-Jimenez *et al.,* 2024).

Although the HEV infection is usually asymptomatic in animals, hepatitis E virus is one of the leading causes of acute viral hepatitis in humans,, widely prevalent in several European countries (Adlhoch *et al.,* 2016). Immunocompetent patients typically clear the virus spontaneously, which is the probably reason why many cases remaining undiagnosed. During pregnancy, HEV infection can be transmitted transplacentally, causing severe damage and foetal death. Foetal hepatitis E is often accompanied by disseminated intravascular coagulation (DIC) syndrome in the mother (Khuroo, 2023). In immunocompromised patients, HEV infection can become chronic, requiring antiviral therapy and, in some cases, progress to liver cirrhosis necessitating transplantation (Kamar *et al.,* 2014).

Extrahepatic manifestations of the infection include neurological complications (Guillain-Barré syndrome and neuralgic amyotrophy), as well as kidney and pancreatic diseases (glomerulonephritis and pancreatitis) (Cheung *et al.,* 2012). According to the latest data from the World Health Organization (WHO, 2025), in 2021HEV caused 3450 deaths with estimated 19.47 million cases of acute hepatitis E globally. In Europe, HEV occurs both as sporadic cases and endemic outbreaks, with seroprevalence ranging between 0.6% and 52.5% (Mansuy *et al.,* 2011; Hartl *et al.,* 2016; Bura *et al.,* 2018). It is established that individuals in direct contact with animals (farmers, veterinarians, hunters) showed higher seroprevalence compared to the general population (Mrzljak *et al.,* 2021).

A recent study among blood donors in Bulgaria found anti-HEV IgG antibodies in 25.9% of the 555 individuals tested (Baymakova *et al.,* 2021). The same study presented the first results on seropositivity among hunters, with values reaching 48.7% for general hunters and 51.6% for wild boar hunters.

The widespread occurrence of hepatitis E among humans is probably related to the adaptation of the virus to various animal hosts. As early as the 1990s, suspicions about the zoonotic nature of the disease emerged when sporadic cases of acute HEV infection were registered in patients with no travel history to endemic areas (Jardi *et al.,* 1993). The first direct evidence of the zoonotic potential of HEV was presented by Japanese researchers. The cases of infection were documented in individuals who had consumed raw deer meat 6–7 weeks before the onset of clinical symptoms. Testing of leftover meat revealed the presence of HEV RNA, whose nucleotide sequence was identical to that detected in the patients (Tei *et al.,* 2003).

Further seroepidemiological studies confirmed that the main reservoirs of the zoonotic HEV genotypes gt3 and gt4 are domestic pigs and wild boars, with transmission occurring primarily via the faecal-oral route through direct contact or consumption of contaminated food and water (Bouwknegt *et al.,* 2008). Although domestic and wild pigs are considered the main reservoirs of HEV, the high seroprevalence worldwide suggests that other animal species, including large and small ruminants, may also be exposed to infection.

A structured search of the literature was conducted across on the electronic international databases PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Scopus (https://www.scopus.com/home.uri) using the following keywords: HEV, Hepatitis E Virus, ruminants, cow, buffalo, goat and sheep. Articles published before the year 2000 were selectively included for historical purposes.

PREVALENCE OF HEPATITIS E VIRUS IN CATTLE AND BUFFALOES

Determining the exact moment of establishing hepatitis E virus (HEV) infection in cattle is challenging. Based on the timeline of published studies, it is assumed that some of the earliest cases of HEV infection in domestic cattle were identified in China in 2002 and 2009. According to Wang *et al.* (2002), anti-HEV antibodies were detected in 6.3% of tested bovine serum samples. In a study by Yu *et al.* (2009), serum samples from various animal species and humans were analysed; of the 1612 samples from cattle, 301 (18.7%) were reported as seropositive. Another study in 2010, covering 17 regions in China, found anti-HEV antibodies in 7 out of 912 (0.8%) tested cattle (Geng *et al.,* 2010). In the same year, molecular genotyping of the virus in cattle was conducted for the first time in Xinjiang, an autonomous region of China (Hu *et al.,* 2010) with 91 samples (faecal and rectal swabs) from cattle that were seropositive for anti-HEV antibodies. Reverse transcription-nested PCR (RT-nPCR) detected HEV RNA in 8 of the samples (8.8%). The genetic analysis revealed high nucleotide identity between the isolates and human and swine strains belonging to HEV genotype 4 (gt4), suggesting a possible role of cattle as a reservoir for zoonotic transmission.

In 2016, a similar study was conducted in the Yunnan province, China, where mixed farming is a common practice. Active HEV infection was detected in blood, faecal and milk samples, with viral RNA found in faeces. A key finding was the detection of the virus in the milk of infected animals. The genetic analysis confirmed the isolates as belonging to HEV gt4. Subsequently, an experiment with rhesus macaques demonstrated that consumption of pasteurised milk containing the virus led to active infection. This finding questions the effectiveness of pasteurisation as a method for virus elimination and raises the hypothesis that milk from infected cattle may serve as a potential source of infection for humans (Huang *et al.,* 2016).

Other studies in China have identified HEV RNA in various biological samples. The prevalence in milk ranged from 0% (Khuroo *et al.,* 2016) to 100% (Huang *et al.,* 2016), in serum from 0% (Fu *et al.,* 2010) to 3% (Wong *et al.,* 2022), and in faeces from 8.8% (Hu *et al.,* 2010) to 37.1% (Huang *et al.,* 2016).

Despite the numerous studies conducted in various European countries, no evidence of HEV presence in cattle has been provided. In Spain, 1170 serum samples from different animal species, including cattle, were analysed with no positive results (Peralta *et al.,* 2009). Similar findings were reported in Hungary, where HEV RNA was not detected in cattle (Forgách *et al.,* 2010), as well as from Germany (Baechlein & Becher, 2017) and Belgium (Vercouter *et al.,* 2018). In 2018, a study in Turkey analysed cow milk and detected HEV RNA in 14 out of 48 samples (29.16%). The genetic analysis revealed the presence of

Table 1. Serological and molecular prevalence of HEV in cattle and buffaloes

Country	Year	Seroprevalence/ Molecular prevalence	Source
China	2002	6.3%	Wang *et al.,* 2002
	2009	18.7%	Yu *et al.,* 2009
	2010	0.8%	Geng *et al.,* 2010
	2010	8.8%* (faeces);	Hu *et al.,* 2010
	2016	37.1%** (faeces); 100%** (milk)	Huang *et al.,* 2016
	2016	0%* (milk)	Khuroo *et al.,* 2016
	2010	0%* (serum)	Fu *et al.,* 2010
	2020	4.72%; 7.5* (milk)	Wei *et al.,* 2020
	2022	3%* (serum)	Wong *et al.,* 2022
Spain	2009	0%	Peralta *et al.,* 2009
Hungary	2010	0%*** (faeces)	Forgách *et al.,* 2010
Germany	2017	0%** (milk)	Baechlein & Becher, 2017
Belgium	2018	0%** (milk and faeces)	Vercouter *et al.,* 2018
Turkey	2018	29.16%** (milk)	Demirci *et al.,* 2019
Bulgaria	2023	7.7%	Tsachev *et al.,* 2023
Nigeria	2014	0%	Junaid & Agina, 2014
Burkina Faso	2019	26.4%	Ouoba *et al.,* 2019
USA	2019	68.4%	Yugo *et al.,* 2019
Laos	2018	0%*** (faeces)	Tritz *et al.,* 2018

* RT-nPCR, ** qRT-PCR, *** RT-PCR.

HEV gt1 (Demirci *et al.,* 2019), further supporting the role of cattle as a potential source of human infection.

In 2023, the first similar study in Bulgaria identified antibodies against HEV in cattle (Tsachev *et al.,* 2023). The study analysed 180 serum samples from different regions of the country and identified 14 seropositive samples (7.7%) by means of ELISA test.

The prevalence of HEV among cattle varies significantly across continents. In Africa, seroprevalence ranges from 0% in Nigeria (Junaid & Agina, 2014) to 26.4% in Burkina Faso (Ouoba *et al.,* 2019). In the United States, a study involving 983 serum samples from cattle showed that 20.4% of the animals were seropositive, with the highest seroprevalence (68.4%) recorded in a herd in Georgia (Yugo *et al.,* 2019).

In 2018, a study in Laos tested blood samples from humans and blood and rectal swab samples from different ruminant species. Of the five serum samples from buffaloes, one tested positive for antibodies. None of the 205 rectal swabs were HEV RNA-positive (Tritz *et al.,* 2018). Two years later, a research team in southern China investigated HEV prevalence in buffaloes where from tested 106 blood samples and 40 milk samples, 5 serum samples (4.72%) and 3 milk samples (7.5%) were reported HEV RNA-positive (Wei *et al.,* 2020).

All available information concerning the prevalence of HEV in cattle and buffaloes is summarised in Table 1.

PREVALENCE OF HEPATITIS E VIRUS IN SHEEP

The susceptibility of sheep, particularly lambs, to hepatitis E virus was experimentally demonstrated as early as 1994 (Usmanov *et al.,* 1994). In this study, lambs were infected with a faecal suspension containing HEV isolated from an infected patient, resulting in clinical manifestations similar to those observed in primates. Furthermore, the study demonstrated that lambs are also susceptible to HEV strains isolated from pigs, suggesting the possibility of interspecies transmission.

The first report of natural HEV exposure in sheep in China dates back to 2009 (Yu *et al.,* 2009), where serological and molecular analyses revealed the presence of HEV antigen in 9 out of 1302 samples (0.7%), and HEV RNA in 2 out of 1302 samples (0.15%), respectively. However, the lack of genotyping of the positive samples limits the ability to perform a more comprehensive analysis of the circulating strains. The subsequent molecular confirmation of HEV infection in sheep using molecular-genetic methods was also documented in China in 2010 (Wang & Ma, 2010). In this study, 54 faecal samples collected from a sheep farm were analysed, of which 6 (11.1%) tested positive for HEV RNA. The methodology included nested PCR, and analysis of the *ORF2* gene revealed a high level of nucleotide identity (84.67–95.36%) with swine and human HEV genotype 4 strains.

The prevalence of HEV among sheep has been studied in various countries, with the highest seroprevalence reported in India. In a study comprising 58 serum samples collected from slaughterhouses and assayed using two different ELISA kits, positive results were found in 100% and 77.5% of samples, respectively. However, the authors were unable to confirm the specificity of the detected antibodies through an inhibition assay (Shukla *et al.,* 2007). Besides China and India, HEV presence in sheep has also been confirmed in other Asian countries. A study in Jordan reported a seroprevalence of 12.7% among farm animals (Obaidat & Roess, 2020). In 2023, a team of researchers in Mongolia analysed 200 faecal samples from sheep, detecting HEV RNA in 4 samples (2%) using RT-PCR (Batmagnai *et al.,* 2023). The genetic analysis of the *ORF2* sequence confirmed the isolates as belonging to genotype 4.

In Africa, the seroprevalence in sheep shows considerable variation. In Egypt, it was estimated at 4.4% (El-Tras *et al.,* 2013), while in Nigeria, two independent studies reported prevalence rates ranging from 10.5% (Junaid & Agina, 2014) to 31.8% (Shuaibu *et al.,* 2017). In Burkina Faso, the reported seroprevalence was 12% (Ouoba *et al.,* 2019).

In North and South America, studies on HEV in sheep are limited. In one Brazilian study, no positive samples were reported (Vitral *et al.,* 2005).

HEV prevalence among sheep in Europe varies widely, reaching up to 24.4%. In the Czech Republic, HEV RNA was detected in 1.4% of milk samples from sheep (Dziedzinska *et al.,* 2020). In Turkey, the proportion of positive samples was significantly higher, reaching 12.4% (Demirci *et al.,* 2019). In Italy, molecular studies identified HEV RNA in 10.4% of faecal samples (Sarchese *et al.,* 2019), while serological analysis detected HEV antibodies in 21.6% of 134 tested sheep sera (Palombieri *et al.,* 2020). In Spain, two serological screenings reported seroprevalence rates of 1.9% (Peralta *et al.,* 2009) and 2.1% (Caballero-Gomez *et al.,* 2022). The highest HEV seroprevalence in sheep in Europe was recorded in Bul-

Table 2. Serological and molecular prevalence of HEV in sheep

Country	Year	Seroprevalence/ Molecular prevalence	Source
China	2009	0.7%; 0.15%*** (serum)	Yu *et al.,* 2009
	2010	11.1%* (faeces)	Wang & Ma, 2010
India	2007	100%; 77.5%	Shukla *et al.,* 2007
Jordan	2020	12.7%	Obaidat & Roess, 2020
Mongolia	2023	2%*** (faeces)	Batmagnai *et al.,* 2023
Egypt	2013	4.4%	El-Tras *et al.,* 2013
Nigeria	2014	10.5%	Junaid & Agina, 2014
	2017	31.8%	Shuaibu *et al.,* 2017
Burkina Faso	2019	12%	Ouoba *et al.,* 2019
Brazil	2005	0%	Vitral *et al.,* 2005
Czech Republic	2020	1.4%** (milk)	Dziedzinska *et al.,* 2020
Turkey	2019	12.4%** (milk)	Demirci *et al.,* 2019
Italy	2019	10.4%* (faeces)	Sarchese *et al.,* 2019
	2020	21.6%	Palombieri *et al.,* 2020
Spain	2009	1.9%	Peralta *et al.,* 2009
	2022	2.1%	Caballero-Gomez *et al.,* 2022
Bulgaria	2023	32.2%	Tsachev *et al.,* 2023

* RT-nPCR, ** qRT-PCR, *** RT-PCR.

garia, where 29 out of 90 tested serum samples (32.2%) were positive for HEV antibodies (Tsachev *et al.,* 2023).

All available data on the prevalence of HEV in sheep are summarised and presented in Table 2.

PREVALENCE OF HEPATITIS E VIRUS IN GOATS

The summarised available information concerning the distribution of HEV in goats is presented in Table 3.

The first direct evidence of hepatitis E virus circulation in goats was presented by Di Martino *et al.* (2016). In their study, based on screening of faecal samples from goats collected from six farms in Teramo province, Italy, HEV RNA was identified in 9.2% of the samples, providing data on the natural presence of the virus in this animal species (Di Martino *et al.,* 2016).

Additional evidence for the presence of HEV RNA in goats has been also reported in other countries. In 2017, a study published in China reported data from the analysis of milk, faecal, and serum samples from goats in Yunnan city – a region where raw sheep and goat milk is traditionally consumed. The results showed that the prevalence of HEV RNA in faecal samples ranged from 60% to 74%. Furthermore, viral RNA was identified in all milk samples collected from the infected animals. Sequencing analysis revealed high genetic relatedness to human and animal HEV genotype 4, subtype h, isolated in the same region (Long *et al.,* 2017). Shortly thereafter, a study in Egypt

Table 3. Serological and molecular prevalence of HEV in goats

Country	Year	Seroprevalence/ Molecular prevalence	Source
Italy	2016	9.2%*** (faeces)	Di Martino *et al.,* 2016
China	2008	24%; 0%*** (serum)	Zhang *et al.,* 2008
	2010	7.50%	Fu *et al.,* 2010
	2017	60%* (faeces); 74%* (faeces) 100%* (milk)	Long *et al.,* 2017
Egypt	2020	0.7%** (milk)	El-Mokhtar *et al.,* 2020
Germany	2017	0%** (milk)	Baechlein & Becher, 2017
Turkey	2019	18.46%** (milk)	Demirci *et al.,* 2019
Czech Republic	2020	1.4%** (milk)	Dziedzinska *et al.,* 2020
Laos	2018	0%*** (faeces)	Tritz *et al.,* 2018
Italy	2020	11.4%; 0%** (serum)	Palombieri *et al.,* 2020
Spain	2022	13.8%; 0%*** (serum)	Caballero-Gomez *et al.,* 2022
Spain	2009	0.6%	Peralta *et al.,* 2009
Portugal	2024	2.2%	Santos-Silva *et al.,* 2024
Bulgaria	2023	24.4%	Tsachev *et al.,* 2023
Nigeria	2014	10.5%	Junaid & Agina, 2014
	2018	0%	Antia *et al.,* 2018
Egypt	2013	9.4%	El-Tras *et al.,* 2013
Burkina Faso	2019	28.4%	Ouoba et al., 2019
India	2001	0%	Arankalle *et al.,* 2001
	2007	100%	Shukla *et al.,* 2007

* RT-nPCR, ** qRT-PCR, *** RT-PCR

found viral RNA in 2 (0.7%) of 280 milk samples from goats tested (El-Mokhtar *et al.,* 2020).

Data on the presence of HEV RNA in goat milk and dairy products in Europe are limited. In Germany, a study involving 400 dairy herds found no evidence of HEV infection in milk (Baechlein & Becher, 2017). In Turkey, an investigation of raw milk from various animal species revealed HEV RNA in 18.46% of goat milk samples analysed (Demirci *et al.,* 2019). A year later, a study in the Czech Republic detected the virus in 1.4% of raw goat and sheep milk samples tested (Dziedzinska *et al.,* 2020). Attempts for molecular detection of HEV RNA have been reported from Italy (Palombieri *et al.,* 2020) and Spain (Caballero-Gomez *et al.,* 2022), but the results were negative. However, relatively high overall seroprevalence was reported from both countries – 11.4% in Italy (Palombieri *et al.,* 2020) and 13.8% in Spain (Caballero-Gomez *et al.,* 2022). Another serological study in Spain found 0.6% seropositivity for HEV antibodies among tested goats (Peralta *et al.,* 2009). In 2024, a serological study of HEV in small ruminants was conducted in Portugal (Santos-Silva *et al.,* 2024) demonstrating a seroprevalence of 2.2% in goats. The highest seroprevalence in Europe was recorded in Bulgaria – 24.4% (Tsachev *et al.,* 2023), where 22 out of 90 analysed serum samples tested positive for antibodies against HEV.

In other continents, the seroprevalence varies widely. Africa is a region with particularly diverse results, with most studies conducted in Nigeria. There, seroprevalence ranges from 0% to 55% according to different studies (Junaid & Agina, 2014; Antia *et al.,* 2018). In Egypt, the seroprevalence in goats is estimated at 9.4% (El-Tras *et al.,* 2013), while in Burkina Faso it attains 28.4% (Ouoba *et al.,* 2019).

Asia has the highest number of studies. In India, two independent studies showed opposing results – one found no positive samples (Arankalle *et al.,* 2001), while the other reported 100% seropositivity (Shukla *et al.,* 2007). Studies conducted in China revealed varying seroprevalence rates – 7.5% (Fu *et al.,* 2010) and 24% (Zhang *et al.,* 2008).

CONCLUSION

This review highlights the growing interest in hepatitis E virus as a potential zoonotic threat with a wide range of susceptible animal species. Although pigs and wild boars are recognised as the main reservoirs of the virus, results from numerous epidemiological studies indicate that ruminants are also susceptible to infection. However, there is limited conclusive evidence that ruminants play an effective role in transmitting the infection to humans. Further studies are needed in this regard, especially in light of the alarming widespread circulation of HEV among both large and small ruminants, as well as in humans.

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