



Reviewing the current situation and opinions of the hepatitis E virus among natural reservoirs and through the food chain

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ABSTRACT

Viral foodborne diseases have grown to be an important part of all foodborne illnesses that have been observed in recent years, and they are considered an increasing threat to the public's health. An increase in hepatitis E virus (HEV) cases that are not related to travel has been identified in surveillance studies carried out in developed countries in the EU. Hepatitis E genotype 3 virus was primarily associated with eating undercooked or uncooked pig meat or other wild animals, according to the research. The main reservoirs in nature are domestic pigs and wild boars. The main route of infection involves the fact that pigs infected with HEV enter the slaughterhouse as healthy animals (most often they do not have visual symptoms), and so their tissues and meat are used for human consumption. Currently, adequate heat treatment is the most effective way to prevent HEV infection from contaminating meat, liver and meat products. This virus is an ideal pathogen for full implementation of the One Health approach, where it is necessary to communicate, collaborate and coordinate in all sectors, including human health, animal health, environment, and other areas of expertise. Success in implementing the One Health approach would lead to controlling all links in this complicated chain and achieving the best health outcomes.

1. Introduction

Over the past few decades, the food business market has shifted from being locally oriented to being globally based as a result of growing urbanization and altered eating patterns. A rise in the population of middle-class people has been accompanied by an increase in the demand for meat in some parts of the world, including China, Southeast Asia, India, and Africa. As livestock production and international trade increase to meet demand, the risk of exposure to various foodborne hazards rises as well because they can spread along the global food sup-

ply chain that creates possibilities for local foodborne occurrences to travel globally (FAO, 2022). The global food supply may be vulnerable if there is a flaw in the process, as contamination can happen with pathogens from throughout the world, including those that have recently emerged (Lord *et al.*, 2022). Regardless of the fact that contamination prevention and control strategies are generally successful in reducing foodborne diseases, diverse and complex food systems, especially those located in less developed nations, pose a big challenge.

According to De Aceituno *et al.* (2013), noroviruses, a type of foodborne virus, are the prima-

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ry source of foodborne illness in developed countries. However, across the European Union (EU) and Asia, the prevalence of recently identified foodborne viruses like the hepatitis E virus (HEV) has increased (Ruggeri et al., 2013). On a worldwide basis, it is estimated that 939 million people, or 1 in 8, have had an infection caused by HEV (Li et al., 2020). In contrast to norovirus and hepatitis A virus, this virus is zoonotic and is considered as a growing issue in veterinary public health (Meng et al., 1997).

The single-stranded, positive-sense RNA genome of the small, non-enveloped icosahedral HEV is about 7.2 kb in size. Short untranslated areas and three main open reading frames (ORF1, ORF2, and ORF3) make up the RNA. HEV belongs to the Orthohepevirus genus and is a member of the Hepeviridae family (Smith et al., 2014). Furthermore, this genus is classified into four species, from Orthohepevirus A to Orthohepevirus D. The most explored, Orthohepevirus A, is further divided into 7 genotypes, and only genotypes 1–4 are capable of infecting people (Doceul et al., 2016). Genotypes 3 and 4 have been discovered in different animal species, and they are zoonotic. On the other hand, genotypes 1 and 2 most frequently infect people via water. Among people, HEV infection can result in a wide spectrum of symptoms (Lhomme et al., 2020), from asymptomatic to self-limiting icteric hepatitis and even permanent liver damage. Immunocompromised patients and those with underlying liver disease are more likely to develop serious or chronic illness after infection. Mortality is rare, happening in only about 2% of cases (Park et al., 2016).

Genotypes 3 and 4 can infect people via a number of different pathways. However, intake of HEV-contaminated animal tissues and food products is the most significant method of transmission (Park et al., 2016). HEV infection can also develop through transplantation of organs or a blood transfusion. Genotypes 3 and 4 are capable of infecting a variety of animals, but nevertheless, the primary animal reservoirs for these genotypes are the domestic pig (*Sus scrofa domesticus*) and wild boar (*Sus scrofa*) (Ricci et al., 2017; Caruso et al., 2016).

Faecal-oral transmission is the main way of transmitting HEV infection in pigs, and they are usually infected without showing any clinical symptoms, although some pigs develop mild to moderate acute self-limiting hepatitis that may progress to permanent liver damage (Meng, 2010). The virus in pigs is primarily present in the liver, where it replicates. However, it has been found that the virus can

be present in other pig tissues. Pork liver and pork liver products are the most evident cause of foodborne HEV, in accordance with several research studies. Pigs infected with HEV enter the slaughterhouse as healthy animals (they do not have visual symptoms), and so their tissues and meat, used for human consumption, can pose a high risk of foodborne HEV transmission.

2. Presence of HEV in domestic pigs

2.1. HEV seroprevalence

According to Meng et al. (1997), there were farms with detected HEV antibodies (Ab) in all tested adult pigs. In Europe, HEV seroprevalence has been at various levels, but all studies reported a measurable presence of HEV Ab in pigs. In France, it was discovered that out of 186 randomly selected farms, 65% of them had seropositive animals (Rose et al., 2011). The results were even more dramatic in Norway and Spain. In Norway, 90% of farms had pigs with HEV Ab (Ig-G) (Lange et al., 2016), while in Spain, 204 out of 208 farms had seropositive pigs (Casas et al., 2009). In Denmark and the Netherlands, seroprevalence at farm level was about 55% (Breum et al., 2010; Rutjes et al., 2007). In their research, Steyer et al. (2011) reported HEV seroprevalence of farms was 33.3% in Slovenia. According to the results of Asimoula et al. (2009), all tested farms in the territory of northern Greece had pigs positive for anti-HEV Ab.

On the other hand, on an individual level, HEV seroprevalence depends on the age of the examined pigs as well as the territory. Consequently, Meng et al. (1997), during their investigation, observed that the infection begins after the second month of life in piglets and that the seroprevalence is significantly higher in pigs older than 4 months. Salines et al. (2017), in their comprehensive review, presented data showing that pig seroprevalence (45 analysed studies) ranges from 8 to 93%. A large retrospective study in Spain for the period from 1985 to 1997 showed that among 2,871 examined pigs, the presence of HEV Ab was recorded in 48.45% (Casas et al., 2009). In Croatia, according to Jermisic et al. (2017), the pig seroprevalence was 32.94%. Tsachev et al. (2019) published the results of a study of HEV seroprevalence in pigs in Bulgaria, according to which the overall prevalence was 60.3% and that it varied between regions and categories of examined pigs. They concluded that the highest seroprevalence

was in the sow category (80%). In Serbia, in Vojvodina, the HEV seroprevalence was 34.6%, according to *Lupulovic et al.* (2010). Furthermore, it fluctuated between different municipalities and ranged from 16.7% to 75%.

2.2. HEV prevalence

The potential presence of viral RNA can be examined in different types of animal samples (serum, faeces, liver, meat, and intestinal organs) using the reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) method. If seroprevalence is observed at the farm level, according to the data of *Salinas et al.* (2017) and based on the comprehensive results of 25 analysed studies, it was determined that the prevalence of the virus in the animals ranges from 10% to 100%. *Fernández-Barredo et al.* (2007), in their research in Spain from 2002 to 2004, came to the conclusion that in 131 samples of faeces and serum, viral RNA was present in 76% of farms. Similar results were published in Sweden by *Widen et al.* (2011), who examined the presence of HEV in faeces samples. Furthermore, 40% of the samples from the 30 farms in Hungary that *Reuter et al.* (2009) examined were HEV positive. The results reported by *Forgách et al.* (2010) (39% of animals were the viral-RNA positive) provided additional evidence of the reliability of previous findings. In Serbia, *Petrovic et al.* (2008) published preliminary findings showing that HEV infection was found in 4 of the 5 farms investigated. They analysed samples were pig organ tissue and faeces from different locations.

When we observe HEV prevalence on an individual level, we can conclude that it fluctuates greatly. Consequently, *Salinas et al.* (2017), based on the results of a comprehensive analysis (which included 69 analysed studies), concluded that HEV prevalence in animals can range from 1% to 89%. Furthermore, the sample origin does not have an impact on the HEV prevalence; it oscillates greatly among all examined sample categories (blood, faeces and serum). Therefore, HEV prevalence in faeces samples from European nations fluctuated between 2.5 and 87.5% (*Widén et al.*, 2011; *Kantala et al.*, 2015; *Monini et al.*, 2015). Furthermore, HEV prevalence in sera samples ranged from 0.9% to 45% (*Grierson et al.*, 2015; *Ivanova et al.*, 2015). Among liver samples analysed in Europe, the HEV prevalence ranged from 0% to 75%, depending on the country (*Jori et al.*, 2016; *Lainšček et al.*, 2017; *Feurer et al.*, 2018).

On the other hand, when samples were classified according to age category, the most commonly examined categories were younger than 3 months and older than 6 months. In the category older than 6 months, HEV prevalence was significantly lower than in the younger animals. So, in Serbia, there was no detectable presence of HEV in liver samples from pigs older than 6 months (*Milojević et al.*, 2019), while in Slovenia, HEV prevalence in this age group was 0.25% according to *Lainšček et al.* (2017). *Kantala et al.* (2017) also did not establish the presence of HEV in this age category. According to available data, the prevalence in pigs older than 6 months in France was 2.8%, according to *Feurer et al.* (2018). A similar percentage of positive results was obtained in Germany (4.0%) as published by *Wenzel et al.* (2011). Differently from that, in the age category younger than 3 months, HEV prevalence is significantly higher. According to *Milojević et al.* (2019), HEV prevalence was 34% in this age group in Serbia. Similar results were published by *Forgách et al.* (2010) in Hungary, where 36% of tested samples from the < 3 month category were HEV-positive. In Italy, HEV prevalence in this age group was 30% (*Ruggeri et al.*, 2013). The high percentage of HEV-positive pigs in this age category noted in various studies confirms the hypothesis that piglets are the most vulnerable after 2 months; at this time, the period of passive immunity expires.

3. Presence of HEV in wild boars and deer

Aside from domestic pigs, wild boars and deer are considered to be natural reservoirs of this virus. Therefore, plenty of studies have examined the presence of HEV in various tissues of these wild animals. In Hungary, the presence of HEV was detected in 11% of the wild boar, 22% of roe deer and 10% of deer (*Forgách et al.*, 2010). *Jemeršić et al.* (2017), in their comprehensive study, revealed that the total seroprevalence among wild boars in the territory of Croatia was 31.1%, while among different regions it ranged from 7.7% to 50.6%. HEV RNA was detected in 11.33% of wild boars younger than one year old. During the 2013–2015 hunting seasons, 50 samples of wild boar origin were collected in Romania. They were tested for the presence of HEV RNA and the results showed that nine samples (18%) were positive (*Porea et al.*, 2017). In contrast, in Slovenia, the seroprevalence in 288 examined sera was 30.2%, while RNA originating from HEV was detected in only one sample (*Žele et al.*,

2016). As a result of all these studies, it is concluded that wild boars and deer can contribute to a significant transmission pathway for this virus, particularly in areas where game meat consumption is high.

4. Presence of HEV in food

Various studies have confirmed that food is the main route of HEV infection for people in developed countries. Thus, one of the first recorded and proven cases among people suffering from acute hepatitis was in Japan (Yazaki et al., 2003). The infections were caused by consuming the raw liver of domestic animals, as well as the meat of wild pigs. After that, cases of human HEV disease were recorded and confirmed after consuming thermally insufficiently treated food originating from domestic, wild pigs and deer. In France, Renou et al. (2014) confirmed that the hepatitis in sick people was caused by HEV and that the source of the infection was the traditional Corsican figatelli sausages. Furthermore, more human cases of acute hepatitis caused by HEV have been reported in France, and they have been linked to the consumption of the same sausage, but the source has not been completely confirmed (Pavio et al., 2014). According to Said et al. (2013), sausage and ham purchased from supermarkets were the sources in the development of HEV infections in Great Britain. Similar to this, HEV was identified in one patient in Hungary and was associated with the previous eating of sausage (Reuter et al., 2009). On the other hand, eating wild boar meat has been linked to autochthonous human HEV infections in Germany (Wichmann et al., 2008). Researchers in Spain confirmed cases of hepatitis in people infected by consuming cooked pork (piglet meat) or wild boar meat (Riveiro-Barciela et al., 2015; Riveiro-Juarez et al., 2017). Further analyses showed a very high percentage similarity of the analysed RNA sequences originating from HEV isolated from food and from sick patients (from 99.7% to 100%).

Examinations have focused on the possible presence at retail of HEV in consumer products. The presence of HEV in these products, especial-

ly ready-to-eat products, might represent a high risk for consumers (vulnerable categories are the most threatened). In Serbia, Milojevic et al. (2021) discovered a HEV prevalence of 5% in pig liver samples from retail establishments. Similar occurrences were reported in Germany and Netherlands where respective HEV prevalences were 4% and 6.5% (Bouwknegt et al., 2007; Wenzel et al., 2011). On the other hand, the HEV prevalence in ready-to-eat sausage was 14.6% in the Netherlands, according to Boxman et al. (2020). According to Pallerla et al. (2020), in Germany, 10% of the tested samples (liver products and pork meat products) were positive for HEV presence, while in Switzerland the prevalence of HEV was 18.9% in the sausages containing liver tissue (Moor et al., 2018). Di Bartolo et al. (2015) collected samples of sausages containing liver tissue and examined the potential presence of HEV from grocery stores in Italy. The prevalence of HEV in fresh sausages containing liver tissue was 22.2%, while in dried sausages it was 4.3%. All the studies confirmed that food could present a very important source of HEV. Further research should establish the exact infectious dose of HEV, with the ultimate goal of obtaining definitive answers for risk analysis of HEV infection through contaminated food.

5. Conclusion

HEV and its transmission via food has been established as a growing hazard to people's health. However, since the infection shares general symptoms with other diseases (fatigue, nausea, vomiting, diarrhoea and stomach cramps), symptoms alone do not allow for fast and proper causative agent identification in most cases. The ingestion of raw or uncooked liver or meat products containing liver has been identified as the main route in the transmission HEV. Adequate heat treatment of food is the most effective way to prevent HEV infection from contaminating meat, liver and meat products. Successful implementation of the One Health approach would lead to controlling all links in this complicated chain and achieving the best health outcomes.

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