# Hepatitis E virus in pigs and environment and its public health concerns: An updated review

Tauseef Ahmad[1], Hui Jin[2], Kuldeep Dhama[3], Mohd. Yatoo[4], Ruchi Tiwari[5], Muhammad Bilal[6], Manish Dhawan[7], Talha Emran[8], and Harapan Harapan[9]

[1]Southeast University
[2]Affiliation not available
[3]Indian Veterinary Research Institute (IVRI)
[4]Sher-E-Kashmir University of Agricultural Sciences and Technology of Kashmir, Shalimar,
[5]Uttar Pradesh Pandit Deen Dayal Upadhyaya Pashu Chikitsa Vigyan Vishwavidyalaya Evam Go Anusandhan Sansthan (DUVASU)
[6]Huaiyin Institute of Technology, Huaian
[7]Punjab Agricultural University, Ludhiana
[8]BGC Trust University Bangladesh, Chittagong
[9]Universitas Syiah Kuala, Banda Aceh

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**Abstract**

Hepatitis E virus (HEV) is an important public health problem and responsible for both acute and chronic viral hepatitis. The HEV transmission usually occurs through the fecal-oral route, and public health implications of its water-borne and food-borne transmissions along with environmental contamination raise high concerns towards its zoonosis. Apart from affecting developing countries, this virus is causing a rising number of cases in the developed countries. The spread of HEV particles to the environment can pollute surface waters, which could be an HEV infection source for humans and animals. HEV has also been identified in urban sewage samples in various countries. HEV virus quite frequently infects the European community and some animal species and identification of virus in polluted animal products suggest the circulation of HEV from water to food chain. Several studies indicating high seroprevalence and circulation of HEV in pigs as well as in environmental samples warrants to investigate the role of trade in carrier pigs, elucidate HEV virulence maintenance in the environment and meat supply chain to throw light on the possible sources of infection in humans and the degree of occupational risk, and zoonosis. The purpose of this review is to discuss the HEV infections and associated risk factors with an emphasis on pigs, presence in environment, food-borne, water-borne, and zoonotic transmissions.

*REVIEW*

**Hepatitis E virus in pigs and environment and its public health concerns: An updated review**

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[1]Department of Epidemiology and Health Statistics, School of Public Health, Southeast University, Nanjing (210009), China

[2]Key Laboratory of Environmental Medicine Engineering, Ministry of Education, School of Public Health, Southeast University, Nanjing (210009), China; (E-mails: tahmad@seu.edu.cn (TA); jinhui_hld@163.com (HJ)

[3]Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly- 243 122, Uttar Pradesh, India; (E-mail: kdhama@rediffmail.com)

[4]Sher-E-Kashmir University of Agricultural Sciences and Technology of Kashmir, Shalimar, 190025 Srinagar, Jammu and Kashmir, India (Email: iqbalyatoo@gmail.com)

[5]Department of Veterinary Microbiology and Immunology, College of Veterinary Sciences, Uttar Pradesh Pandit Deen Dayal Upadhyaya Pashu Chikitsa Vigyan Vishwavidyalaya Evam Go Anusandhan Sansthan (DUVASU), Mathura–281001, India (E-mail: ruchi.vet@gmail.com)

[6]School of Life Science and Food Engineering, Huaiyin Institute of Technology, Huaian 223003, China; (Email: bilaluaf@hotmail.com)

[7]Department of Microbiology, Punjab Agricultural University, Ludhiana-141004, India (Email: dhawanmanish501@gmail.com)

[8]The Trafford Group of Colleges, Manchester-WA14 5PQ, United Kingdom

[9]Department of Pharmacy, BGC Trust University Bangladesh, Chittagong-4381, Bangladesh; (Email: talhabmb@bgctub.ac.bd)

[10]Medical Research Unit, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia; (E-mail: harapan@unsyiah.ac.id)

[11]Tropical Disease Centre, School of Medicine, Universitas Syiah Kuala, Banda Aceh, 23111, Indonesia

[12]Department of Microbiology, School of Medicine, Universitas Syiah Kuala, Banda Aceh, 23111, Indonesia

**Corresondence**

**Tauseef Ahmad**

Department of Epidemiology and Health Statistics,

School of Public Health,

Southeast University, Nanjing (210009), China

Email: tahmad@seu.edu.cn

**Kuldeep Dhama**

kdhama@rediffmail.com

https://orcid.org/0000-0001-7469-4752

**Abstract**

Hepatitis E virus (HEV) is an important public health problem and responsible for both acute and chronic viral hepatitis. The HEV transmission usually occurs through the fecal-oral route, and public health implications of its water-borne and food-borne transmissions along with environmental contamination raise high concerns towards its zoonosis. Apart from affecting developing countries, this virus is causing a rising number of cases in the developed countries. The spread of HEV particles to the environment can pollute surface waters, which could be an HEV infection source for humans and animals. HEV has also been identified in urban sewage samples in various countries. HEV virus quite frequently infects the European community and some animal species and identification of virus in polluted animal products suggest the circulation of HEV from water to food chain. Several studies indicating high seroprevalence and circulation of HEV in pigs as well as in environmental samples warrants to investigate the role of trade in carrier pigs, elucidate HEV virulence maintenance in the environment and meat supply chain to throw light on the possible sources of infection in humans and the degree of occupational risk, and zoonosis. The purpose of this review is to discuss the HEV infections and associated risk factors with an emphasis on pigs, presence in environment, food-borne, water-borne, and zoonotic transmissions.

**KEYWORDS** Hepatitis E virus, pigs, zoonotic transmission, water-borne, environment

**Abbreviations**

HEV: Hepatitis E virus

NHPs: Non-human primates

WHO: World Health Organization

WWTPs: Wastewater treatment plants

**HIGHLIGHTS**

- HEV is an emerging zoonotic pathogen transmitted from animals to humans.
- HEV is mainly transmitted through undercooked pig products in developed countries.

- HEV genotypes 1 and 2 cause unprecedented waterborne epidemic and endemic diseases in resource poor countries.
- Standardized methodology should be implemented for HEV detection in food and environmental samples.

## 1 INTRODUCTION

Hepatitis E virus (HEV) infection, the cause of acute viral hepatitis worldwide, poses a significant public health concern with high prevalence in low-income countries. It is long-neglected although has now also emerged as an important virus in the developed countries.[1-4] In areas with heavy seasonal rainfall, high evaporation rates, and high population density the HEV can cause outbreaks of acute hepatitis.[5-7] According to the World Health Organization (WHO), approximately 20 million cases of HEV have been reported every year globally. Of the total reported cases, an estimated 3.3 million infections are leading to asymptomatic hepatitis. In 2015, according to the WHO estimates, approximately 44,000 deaths due to HEV have been reported worldwide.[8] HEV mortality rate among pregnant women especially in the third trimester can reach up to 30%.[9-12]

HEV is a small (approximately 27–34 nm in diameter) non-enveloped single-stranded positive-sense RNA virus belonging to the family *Hepeviridae* , which consists of two genera named *Orthohepevirus* (infect birds and mammals) and *Piscihepevirus* (infect fish). The genus *Orthohepevirus* is further classified into four species known as Orthohepevirus A, B, C, and D. Furthermore, the species Orthohepevirus A includes at least eight distinct genotypes (HEV-1-8) infecting both humans and animals.[13-15] Genotype 1 and 2 are responsible for large-scale water-borne epidemics in developing countries, while genotypes 3 and 4 are responsible for small outbreaks in industrialized countries.[1,6]

The species causing HEV infection in swine belongs to the Orthohepevirus A.[14] The genotype 1 and 2 are constrained to humans; genotype 3 circulates in humans, deer, rabbits, mongooses, and swine; genotype 4 circulates in human, pig, wild boar, cattle, cow, sheep, goat, and yak; genotype 5 and 6 are found in wild boars; genotype 7 has been identified in dromedary; and genotype 8 has been isolated recently in Bactrian camels.[15-17] Figure 1 demonstrates different HEV genotypes circulate in humans and animals.

**<FIGURE 1>**

The HEV infection is prevalent in Asia and Africa.[18-19] In developing countries, the HEV infection is responsible for 20-25% of acute hepatitis cases,[18] and in the general population, the mortality ranges from 0.2 to 1%.[15] In Africa, a high prevalence of HEV infection has been documented recently in animals with HEV genotypes closer to that of humans and some animals may act as virus reservoirs suggesting the possibility of zoonotic transmission.[20] In developed countries, the HEV cases have been increased recently mainly due to the consumption of undercooked meat, and is a silent threat which need much epidemiological investigations and appropriate mitigation strategies to be adopted.[18,21-22] In the present scenario, HEV is considered as an emerging zoonotic infection in many European countries.[23]

Autochthonous HEV causes considerable clinical problems in industrialized countries, where animal species including domestic swine, wild boar, and wild deer act as reservoirs of HEV-3 and HEV-4 genotypes. Humans acquire HEV infections by consuming uncooked or undercooked meat of the infected animals, especially pig livers or sausages made from infected livers.[24] Not much data are available with regards to HEV prevalence and contamination in food as well sources of contamination, especially in developing countries, and investigations on such issues therefore would elucidate a better understanding of food-borne impact of this important virus and its maintenance.[25]

The disease is mainly transmitted via the fecal-oral route by ingestions of contaminated food and drinking water. HEV contamination of food sources and surface waters could occur through solid and liquid residues of infected animals, which act as zoonotic reservoirs. The food-borne transmission of HEV is mainly due to insufficiently uncooked pig products, although living in close contact with animals or irrigation water are the known risk factors of HEV infection in both healthy and immunocompromised patients.[26-28] The HEV may

also transmit via other routes such as zoonotic transmission, mother to child, and blood transfusion.[24,29-34] The transmission of HEV from person-to-person is infrequent.[34-36]

The importance of HEV as an important public health issue is rising, and wide distribution of HEV in humans, animals and environmental as well as associated zoonotic concerns warrants the strengthening of One Health concept to tackle HEV. [3,23,25,28-30] This review discusses the importance of HEV infections and associated risk factors, with a particular focus on pigs, zoonotic transmissions, environmental contamination, and water-borne outbreaks.

## 2 HEV INFECTION IN PIGS

HEV is a zoonotic disease that can be transmitted from animals to humans. The Orthrohepevirus A affects humans, wild boar, mongoose, camel, and pigs; Orthrohepevirus B infects chickens; Orthohepevirus C causes infection in ferrets, rats, shrews, and mink, while Orthohepevirus D affects bats.[37] Studies suggested that the most important reservoir for HEV genotypes capable of infecting humans is pigs.[38] In 1997, the HEV was identified for the first time in pigs and pigs are recognized as the main reservoir of HEV genotypes 3 and 4.[39] Several studies have been conducted on pigs infected with HEV.[40-43] However, anti-HEV antibodies have been isolated from a wide range of species such as cattle, dogs, goats, deer, donkeys, sheep, and pigs.[37-38,44-45]

Exposure to animal feces and consumption of undercooked pork meat can cause HEV infection. Due to limited data in resource-deficient countries, Hoan et al.[46] evaluated whether pigs could potentially be a source of HEV infections in Vietnam. Liver samples from domestic pigs (n = 210) and individuals serum samples exposed to pork meat and pigs (n = 283) and compared with unexposed controls (n = 168). In contrast to healthy individuals, persons occupationally acquainted with pork/pigs meat showed a high seroprevalence. Twenty-six of 210 liver tissues of pig showed HEV-RNA and detected to be HEV genotype 3. Overall, the results indicate that individuals occupationally exposed to pork meat and pigs are at associated risk of HEV. Furthermore, studies showed that HEV is reportedly associated with the consumption of meat products from wild boar and pigs.[29,47-48] Therefore, in developed countries cross-species transmission is considered as the major cause of HEV infection.[49-50] Figure 2 shows the transmission of HEV through a pig.

**<FIGURE 2>**

The HEV infection in pigs normally occurs during early life, and the virus shedding peaks at about at age of 3 months. The people occupationally exposed to pigs increase the probability of the past HEV infection by almost threefold.[51] A cross-sectional study was conducted in Lao People's Democratic Republic, the prevalence of anti-HEV IgG antibody in slaughter pigs was 54.0% (136/252), in professionals exposed to pigs was 41.0% (57/139), and 18.1% (38/210) was in non-risk controls. The results showed that the individuals occupationally exposed to pigs are at higher risk of HEV infection ($p < 0.001$). Furthermore, contact with young piglets was a major risk factor as compared to contact with the older slaughter pigs ($p = 0.011$).[52] Another recent study published from 10 US states, reported that the prevalence of HEV-IgG antibody was 40% of 5,033 serum samples from market-weight pigs at 25 slaughterhouses, of which the HEV RNA was detected in 6.3%. The detected sequences belonged to HEV genotype 3, group 2 (HEV-3abchij).[53]

Studies from the European countries reported a high prevalence of HEV in pigs. In Germany, the reported anti-HEV IgG seroprevalence in pigs (at farms) was 70.7%.[54] Another study from Germany, reported the overall seroprevalence of anti-HEV IgG in serum to be 68.6% and in meat juice samples from pigs (at slaughter) as 67.6%.[55] In the Netherlands, HEV seroprevalence in pigs (at slaughter) was 70%, and 50% RNA +ve on the farm.[56] In Scotland, the overall seroprevalence of anti-HEV antibodies in slaughter-age pigs was 61·4%.[57] In Switzerland, the overall HEV seroprevalence of 12.5% was documented in wild boar, and 58.1% in domestic pigs.[58]

In Bulgaria overall, HEV seroprevalence has been noted to be 60% (95% CI 42.7-77.1) in domestic pigs and 12.5% (4/32) in wild boar with seroprevalence of the slaughter-aged pigs being 73.65% (95% Cl 58.7-87.3), higher prevalence in domestic pigs indicating the probable reason for cross-species transmission.[21] The involvement of other animal species including both domestic and wild ones risks human life also. Around

10.12% samples (95% CI: 5.44-14.8) from wild boar and 16.05% samples (95% CI: 8.06-24.04) from red deer have been positive for HEV RNA detected by real-time RT-PCR.[59] Though none of the 48 samples from Iberian pigs, was positive for HEV RNA detection but 43.75% (95% CI: 29.75-57.75) serological samples from Iberian pig were positive for anti-HEV antibodies when the 57.40% (95% CI: 48.10-66.70) from wild boar and 12.85% (95% CI: 5.01-20.69) samples from red deer were positive.[59]

Constant contact and consumption of pig and pig products increase risk and hence warrants proper inspection and surveillance.[59-60] Raw viscera more likely harbors HEV than pork, and ground pork and pig liver could act as a potential source of this virus.[60-61] In one study HEV RNA has been detected in liver, kidney, and blood samples with positivity of 6.1% (7/114), 3.1% (4/129), and 1.2% (2/170) respectively, and viral loads ranged from $10^{2.4}$to$10^{4.4}$ (2.4Log-4.4Log) genome equivalents per gram whereas none has been detected in pork indicating a higher transmission risk related to consuming pig organs.[61] Similarly, HEV has been detected in 99 pork and 63 wild boar sausages and salami sold in Southern Italy few belonging to the HEV-3 genotype.[62] However the mere presence of HEV in samples may rarely matter than the infectivity of HEV and there should be a robust system for measurement of HEV infectivity in food samples with cell culture-based systems having promising prospects.[63]

Though detection of HEV RNA in pigs and retail pork livers have been found comparable to that noted in the USA and Europe however the incidence of sporadic locally acquired hepatitis E in Canada, is believed to be low relative to other non-endemic countries thus posing a relatively low risk in vulnerable Canadian population.[64] Anti-HEV antibodies have been detected in 77.6% to 90.6% of serum samples from backyard pigs by indirect enzyme-linked immunosorbent assay in southern Brazil showing a herd seroprevalence of 83.7% to 91.7%.[65] HEV RNA has been detected in 0.8% (6/713) of samples falling in three different genotypes 3 subtypes related to human HEV strains indicating backyard pigs as a reservoir of HEV and thus need to control infection and spillover from backyard farms.[65]

HEV-RNA has been detected in 10 of the total 90 (11.1%) meat products, 7 of 37 (18.9%) liver sausages, and 3 of 53 (5.7%) raw meat sausages in Switzerland.[66] Virus loads of up to 5.54 $\log_{10}$ HEV genome copies per gram have been estimated. These belong to HEV genotype 3. This study indicates the presence of HEV on ready-to-eat meat products on the Swiss retail market and hence necessity for developing efficient diagnostic methods for easy detection.[66] Boxman et al. [67] have also detected and quantified hepatitis E virus RNA in ready-to-eat raw pork sausages in the Netherlands and have found 46 of 316 samples positive for HEV RNA. The average viral load in positive tested products has been found to be 2.76 to 4.5 $\log_{10}$ genome copies per 5 g. This study provides the basis for risk assessment and risk management with respect to pork and pork product consumption and raw pork sausages as a risk factor for hepatitis E virus infection in the Netherlands.[67]

Various ingredients related to pigs and piggeries are considered as a potential risk for transmission of HEV. Hepatitis E virus (Genotype 3) has been noted in slurry samples from swine farming activities in Italy.[68] Of the 24 samples, 18 samples (75%) have been found positive for HEV RNA and characterized as genotype 3.[68] On quantitative Real-Time PCR assay two swine slurry samples that were found positive, contained 600 and 1000 UI per mL of sewage.[68] Hence improving swine farming operations safety and increasing operators' awareness of the zoonotic potential of swine waste can minimize risk for HEV. HEV RNA has been found in fresh meat markets with 0.23 % in the market samples and 3.93 % in the slaughterhouse samples in Bangkok.[69] Fecal and bile samples were commonly found positive compared to liver, pork, and intestine samples hence posing a risk of zoonosis. Domestic pigs, wild boars, pig farmworkers, and hunters in Estonia have demonstrated the presence of HEV hence the requirement of attention for direct contact persons or handlers.[70] Not only direct contact but also environmental contaminations are responsible for not only the transmission of HEV in pigs but also in humans.[71]

In one study average latent period has been noted to be 6.9 days (5.8; 7.9) in inoculated animals, an average infectious period of 9.7 days (8.2; 11.2), however the quantity of virus existing in the environment was found to play a vital role in the transmission process.[71] It has also been shown that porcine blood which is used as an ingredient in meat productions may serve as a vehicle for HEV transmission.[72] HEV RNA has been detected

in 33/36 batches of (non-heated) liquid products and in 7/24 spray-dried powder products.[72] Contamination levels through variable but were found to be highest in liquid whole blood, plasma, and fibrinogen reaching levels of $2.2\times10^2$ to $2.8\times10^2$ HEV genome copies per 0.2g respectively.[72]

A study from Finland, reported 11.9% of domestic pigs to be HEV RNA positive. The occurrence of HEV was found high in fattening pigs (14.8%) and the lowest in weaning pigs (12.5%).[73]The mean seroprevalence was 87.0% in swine at a slaughterhouse in Italy, 64.6% pigs were positive for HEV RNA in at least one sample, and the HEV genome was detected in bile samples, feces, and liver, 51.1%, 33.3%, and 20.8%, respectively.[74] In another study from 4 abattoirs in Italy, 21 (3.6%) out of 585 pigs were tested positive for HEV RNA in either feces or liver by real-time RT-PCR, ELISA tests revealed a high seroprevalence (76.8%) of HEV antibodies pointing out frequent exposure to virus, and circulation of HEV-3c and a novel unclassified subtype was noticed by phylogenetic analyses.[75] A study from Denmark reported faecal samples of 49.5% Danish pig population to be positive for HEV RNA.[76] In a study published from France, the farm-level HEV seroprevalence was 65%, and 31% in the slaughter-aged pigs. Furthermore, 4% of livers were recorded as HEV RNA positive.[77]

Studies from other countries also reported a high prevalence of HEV in the pig population.[21,51,56] A study published from China reported the overall seroprevalence of anti-HEV antibodies was 64.7% in swine.[78] Furthermore, the prevalence of HEV was high in swine farmers than that of the general population. However, peoples living in the urban area showed a high prevalence of HEV infection.[78] A systematic review and meta-analysis conducted recently, based on studies published within the last decade (2010 to 2019) indicated that HEV infection is very common among swine population in China, and suggested that reducing the mixed feeding of different stages could decrease HEV infection in pigs and consequently prevent from the risks of transmission of zoonotic HEV infection from pigs to humans.[79]

A study conducted to analyze the serological prevalence and molecular characterization of HEV in imported pigs in Singapore for the past two decades (2000-2019) from live pig and post-slaughter samples demonstrated the presence of HEV in pigs being used for consumption by humans.[80] This study suggested the importance of regular monitoring of the prevalent HEV strains and evaluation of the genetic diversity of HEVs in the imported pigs to confirm the potential association of the role of pigs for transmission of HEV to humans.[80]

In one study conducted in Japan, of the 160 serum samples collected from pigs and tested for the presence of HEV antibodies (IgG & IgM) showed that 116 (72.5%) were found IgG positive and IgM negative, while 38 (23.8%) were positive for both IgG and IgM.[81] A recent study showed that those individuals who had exposure to pigs/pork meat when compared with unexposed individuals had high chances of HEV infection.[46] Anti-HEV IgG seroprevalence was 66% in slaughterhouse staff, 51% in pig-farmers, and 38% in pork meat vendors (P =0.00073).[46] In a study from Abruzzo, Italy, reportedly hyperendemic region having highest HEV seroprevalence in humans, out of 233 blood samples collected from different local pig slaughterhouses between 87.3% and 100% of serum samples were found positive for anti-HEV antibodies (IgG), such high seroprevalence in pigs indicates that HEV is highly circulating in this region.[82] Previously published studies showed that the pigs are successively infected with HEV on farms, and the prevalence rate increases with age.[26,83-84]

## 3 HEV ANIMAL MODELS

*In vivo* studies on HEV infection have long been hindered due to many issues such as the lack of a small animal model. Recently, to study the HEV infection human liver chimeric mice were used.[85] For some HEV strains, the cell culture system has been established such as genotype 3, genotype 4, and genotype 1, among these genotypes the genotype 1 replicate poorly *in vitro*system. The best animal models to study HEV infection are pigs and non-human primates (NHPs) such as African green monkeys, chimpanzees, cynomolgus monkey, owl monkeys, squirrel monkeys, rhesus macaques, vervets, tamarins, but some issues like finance and research ethics restrict the use of these models in research. Therefore, much attention has been paid to the development of small animal models to study the HEV infection properly, examine cross-species transmission, elucidate virus and host interaction, testing the potential and efficacy of HEV vaccines,

and analyze adverse outcomes.[86]

From pregnant mice tissues (liver, spleen, kidney, colon, uterus, and placenta), the establishment of the HEV infection was confirmed by detection of HEV RNA. The results showed that the HEV infection was successfully established with a high rate of miscarriage (7/8, 87.5%) in the middle of pregnancy. To study the HEV infection in pregnant women, this animal model can be used to study the HEV adverse outcomes, pathogenesis, and host response. This model may be useful for future anti-HEV drug development.[87]

## 4 HEV IN ENVIRONMENTAL SAMPLES

The persistence and transmission of HEV in the environment are still poorly studied.[88] Genotypes 1 and 2 are mainly found in regions with limited resources and poor sanitation resulting in the contamination of water supplies and food.[1,16-17] In India, the HEV outbreaks were caused by highly polluted water between 1978 and 2013.[24] However, the role of water in the transmission of zoonotic cases of HEV has only been suspected, but the detection of genotype 3 in shellfish and seemingly shellfish-related outbreaks have recently raised the question and discussions on this issue of public health concern among researchers and scientists.[89-90] The above statement is supported by some studies from developed countries; seems to show higher HEV seroprevalence in people exposed to water or in shellfish consumers.[91-92]

Besides the evidence of HEV infection in humans via ingestion of seafood (shellfish, mussels), captive dolphins, which generally feed on fish, have been reported to be positive for HEV by serology (anti-HEV Ig), HEV RNA testing and findings of liver disorders with virus strains identified as genotype 3, which raises concerns of environmental contamination of food or wastewater as source of HEV.[93]

To date, the waterborne HEV-3 transmitting remains to be explicated. A current study in Germany recognized that work-related contact with wastewater can be associated with autochthonous hepatitis E, indicating the possible role of water in transmitting HEV-3.[94] Animal and human hosts of HEV-3 might pollute wastewater matrices by the secretion of faeces in developed countries. The spread of HEV particles to the environment can pollute surface waters, which could possibly be an HEV infection source for humans and animals.[88]

HEV has been identified in urban sewage samples in various countries in Spain, Italy, and the Netherlands.[95-97] Recently, in European countries a number of studies have been carried out for HEV detection in urban sewages.[98-106]

Beyer and colleagues determined the occurrence of HEV in water sources in urban areas of Germany. Wastewater samples were found positive by RT-qPCR for genotypes HEV-3c and 3f, where HEV-3c was identified among the most dominant genotype. Approximately, 75% of samples from the urban river showed the detection of HEV RNA.[107]

In another study, HEV prevalence was monitored in effluent and influent water in drinking and wastewater treatment plants (WWTPs). The performance of various methods was assessed for concentrating HEV in effluent and influent water from both treatment plants. The prevalence of HEV in inflowing water samples varies based on the WWTPS and RT-qPCR analysis, while no HEV was identified in effluent water.[108] A large-scale study of 9 years (2011-2019) was executed into urban sewage in Italy for gaining a deep insight into the HEV epidemiology. In this investigation, 1374 sewage samples were collected from 48 different WWTPs, which are situated in 20 distinct regions of Italy. The RT-qPCR analysis quantified the HEV RNA detection in 74 urban sewage samples. Among these, 56 and 18 samples showed the detection of G3 and G1, respectively. G3 strains were detected throughout the investigation period, whereas the detection of G1 strains occurred only in 2011-2012 samples. The findings illustrate substantial viral circulation in the Italian people with a prevalence of G3 strains.[106]

In a 5-year integrated environmental and human HEV surveillance study, 169 cases were confirmed with HEV with an annual occurrence of 0.72 cases/1,000,000. Among 65 HEV RNA-positive samples, 66%, 32%, and 1% were detected to be genotype HEV3, HEV1, and HEV4, respectively.[105] For the first time, HEV circulation was demonstrated in the northwest of Argentina to indicate the presence of the virus in water

samples from the Arias–Arenales River in Salta city. HEV circulation was detected by nested PCR, IgM and IgG, and ELISA. Results revealed the detection of HEV-RNA in 1.6% of the tested samples, belonging to HEV genotype 3. Three samples showed the presence of IgM, while the IgG anti-HEV prevalence was recorded to be 9%.[109]

Heldt and colleagues collected 250 water and 68 sediment samples from the Sinos River tributaries, along with 50 pork products samples sold in the Sinos River, Brazil, and investigated for the detection and characterization of HEV genome by RT-PCR and nucleotide sequencing. Among the tested samples, HEV genotype 3 was identified in 36% of food samples, whereas no water or sediment evidence of the circulation of HEV. The outcome indicates polluted pork products as a possible route for HEV infection and necessitates a careful assessment of swine herds and food safety.[110]

Numerous evidence and research information demonstrate that HEV is widespread in both industrialized and developing countries representing a devastating threat to public health worldwide.[30]Animal-based HEVs are appeared to trigger HEV infections in the developed nations that require the development of vaccines for preventing the spread of HEV infection to humans.[111]Clemente-Casares and colleagues reviewed the European countries-based environmental, animal, and human data collected since the 90s.[22] Based on the serological data, it was inferred that the HEV virus quite frequently infects the European community, and some animal species, i.e., deer, wild boars, and pigs are host reservoirs. Identification of virus in polluted pork products and mussels indicate the circulation of HEV strains from water to food chain. In water, the HEV in natural conditions may be inactivated by temperature and sunlight (UV). The virus may be removed by the physical treatment of water or disinfection methods.[88] The HEV cases caused by genotype 1 can be controlled and prevented by improving the personal hygiene practices, and proper sanitation in developing countries.[24]

## 5 HEV IN WATER AND WATER-BORNE OUTBREAKS

Genotypes 1 and 2 are mainly reported in Asia including Afghanistan, India, Bangladesh, China, Nepal, and Pakistan, and some African countries such as Chad, the Central African Republic, Mexico, Nigeria, and Sudan.[112] Genotype 1 and possibly 2 caused several water-borne outbreaks in many parts of the world.[3,24,113] Qualitative analysis of drinking and sewage water samples by using RT-PCR from Faisalabad, Pakistan, showed the presence of HEV genotype 1 strain.[114] Another study from Italy reported a high prevalence of HEV in water samples with the presence of HEV genotype 1 and 3 in sewage water samples in which 11 out of 19 WWTPs were positive for HEV RNA.[96]

In Spain, the HEV genome was detected from slaughterhouse sewage mainly from pigs and showed 92-94% nucleotide similarity with strain detected from the human.[115] A high positivity rate of 20/46 (43.5%) of HEV was reported in sewage samples from Barcelona, Spain.[116] Another study from Spain showed the presence of both genotypes 1 and 3 in samples from WWTPs.[117] In Spain, the HEV genotype 1 and 3 were detected from sewage and biosolid samples from urban sewage treatments.[118] In Colombia of the total sixty environmental samples, the HEV genome was detected in 23.3% (7/30) of drinking water plants/creek and in 16.7% (5/30) of sewage samples.[119] Several HEV outbreaks have been reported in some countries in particular in developing countries. The recent HEV outbreaks associated with water contamination are presented in Table 1.

**<TABLE 1>**

## 6 PREVENTION

Considering the importance and wide circulation of HEV in humans and animals, global public health priority needs to be given for enhancing monitoring and surveillance as well as adopting adequate mitigation strategies for prevention and control of HEV and associated zoonotic significance with the virus.[138] HEV 239, Hecolin® vaccine (Xiamen Innovax Biotech, China) is available in private market in China and WHO is yet to approve it for use in endemic settings and disease outbreaks worldwide. In HEV outbreaks, the two important preventive approaches comprise the provision of drinking clean water and improving the sanitary disposal of human waste. Implementing these approaches in a timely manner in regions where the HEV

epidemic occurs is a challenging issue.[139]

In many parts of the world, the anti-HEV antibodies (IgM and IgG) seroprevalence has been recorded both in humans and animals and as well as from the environmental samples. Several factors contribute to the increasing HEV infection rate, including low socioeconomic status, poor hygiene, low access to clean water, lack of proper sanitation, and unavailability of a hepatitis E vaccine commercially especially in the high endemic regions (Figure 3). Global availability of the effective vaccine to tackle future HEV disease outbreaks, larger analysis of magnitude of the worldwide burden, improving diagnostics and epidemiological methodologies, improving standards of water quality, hygiene and sanitation in endemic regions along with implementation of one health approach are need for effective prevention and control of HEV. Awareness with regards to the prevalence and spatial distribution of HEV in livestock animals, especially in the pigs and strengthening of HEV testing in boars, along with controlling environmental contamination of the virus could play vital role in implementing appropriate prevention and control strategies to avoid transmission of HEV infection from animals to humans.

<FIGURE 3>

## 7 CONCLUSION AND FUTURE PROSPECTS

In the past, the HEV was considered an infection of resources-limited countries only. But after the discovery of new genotypes, different animal reservoirs, the cross-species transmission had changed the understanding of HEV worldwide and become a significant public health problem. In recent years, the cases of HEV have been increased in developed countries, which are mainly transmitted due to the consumption of uncooked food. However, other modes of transmission including visceral organs, sewage, fecal matter, discharges from the piggery, and persons working there cannot be ignored for this zoonotic disease.

Genotype 1 & 2 are responsible for large outbreaks in low-income countries, while genotype 3 & 4 are mainly responsible for sporadic cases in the developed countries. Exposure to animal feces and consumption of undercooked pork meat can cause HEV infection. HEV is linked with the consumption of meat products from wild boars and pigs. Therefore, the cross-species transmission is conceived the leading cause of HEV infection in the developed countries.

Identification of virus in polluted pork products and mussels indicate the circulation of HEV strains from water to food chain, and thus necessitate a careful assessment of swine herds and food safety. Though waterborne HEV-3 transmission remains uncertain, the occupational contact with wastewater might be associated with autochthonous hepatitis E, indicating the possible role of water in transmitting HEV-3. Animal and human hosts of HEV-3 might pollute wastewater matrices by the secreting faeces. HEV has also been identified in urban sewage samples in various countries. HEV with a prevalence of G3 strains has been monitored in effluent and influent water in drinking and WWTPs.

A better understanding of the viral dynamics and disease process can be elucidated by developing models that are amicable to natural host or disease pathology to support future research and minimize risks. Special attention should be paid to vulnerable and high-risk groups including pregnant women. In the absence of specific knowledge and lack of interventions, general preventive measures can be helpful. Safety measures and disease awareness are of worth importance while traveling to HEV endemic areas. There is a dire need for effective treatment and commercially available vaccines to prevent and control HEV infection with particular emphasis on low-income countries as well as adopting the concept of one health approach.

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## DATA SHARING AND ACCESSIBILITY

Data sharing is not applicable to this review.

## CONFLICT OF INTEREST

All the authors declare that there are no conflicts of interest.

## AUTHOR CONTRIBUTIONS

Tauseef Ahmad: Conceptualization, study design, data collection and preparation of first draft. All the authors potentially contributed into this review paper. The authors have read and approved to publish of this version of the manuscript.

## ORCID

*Tauseef Ahmad*

http://orcid.org/0000-0001-8793-273X

*Hui Jin*

https://orcid.org/0000-0002-5441-1652

*Kuldeep Dhama*

https://orcid.org/0000-0001-7469-4752

*Mohd. Iqbal Yatoo*

https://orcid.org/0000-0002-4501-7354

*Ruchi Tiwari*

http://orcid.org/0000-0001-7763-5547

*Muhammad Bilal*

https://orcid.org/0000-0001-5388-3183

*Manish Dhawan*

https://orcid.org/0000-0002-7783-7138

*Talha Bin Emran*

https://orcid.org/0000-0003-3188-2272

*Harapan Harapan*

https://orcid.org/0000-0001-7630-8413

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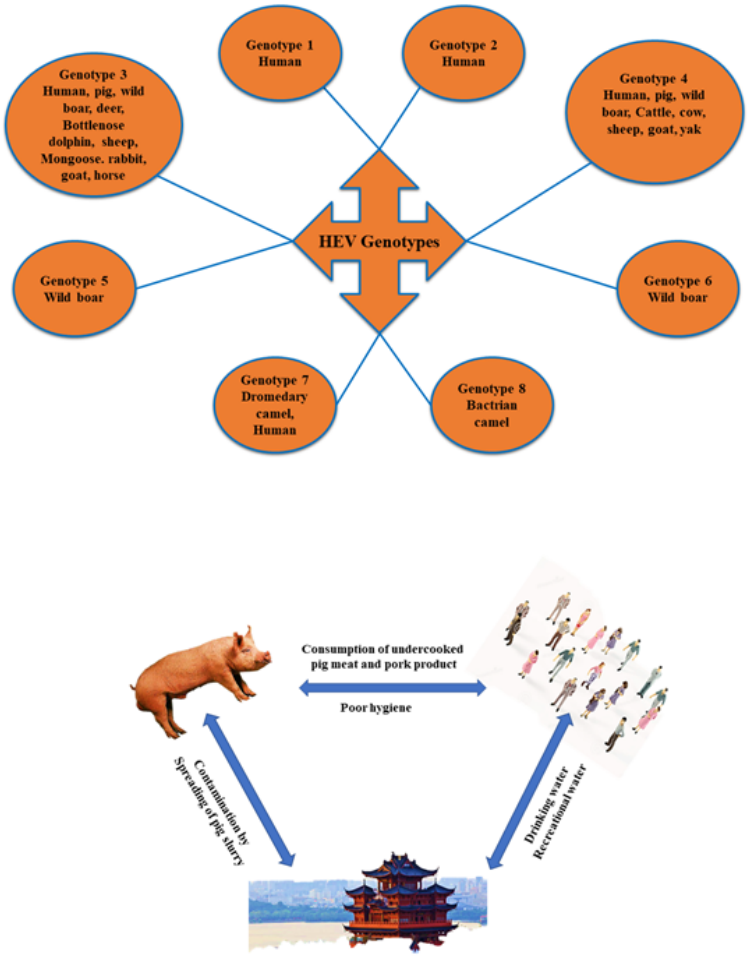
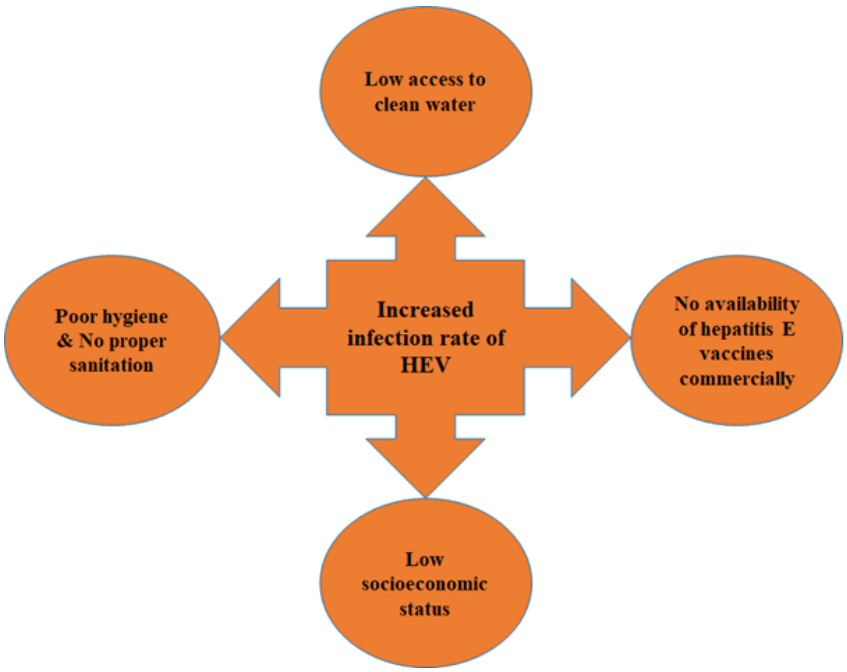
**Figure Legends**

**FIGURE 1** Orthohepevirus A genotypes and hosts

**FIGURE 2** Transmission of HEV through the pig

**FIGURE 3** Factors responsible for high HEV infection rate



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