Hepatitis E Virus: An emerging enigmatic and underestimated pathogen

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Abstract
Hepatitis E virus (HEV) is an RNA virus causing hepatitis E disease. The virus is of one serotype but has diverse genotypes infecting both humans and animals. Based on evidence from seroprevalence studies, about 2 billion people are estimated to have been infected with HEV globally. HEV, therefore, poses a significant public health and economic challenge worldwide. HEV was discovered in the 1980s and was traced back to the 1955 – 1956 outbreak of hepatitis that occurred in India. Subsequently, several HEV epidemics involving thousands of individuals have occurred nearly annually in different countries in Asia and Africa. Initially, the virus was thought to be only enterically transmitted, and endemic in developing countries. Due to the environmental hygiene and sanitation challenges in those parts of the world. However, recent studies have suggested otherwise with the report of autochthonous cases in industrialised countries with no history of travel to the so-called endemic countries. Thus, suggesting that HEV has a global distribution with endemicity in both developing and industrialised nations. Studies have also revealed that HEV has multiple risk factors, and modes of transmission as well as zoonotic potentials. Additionally, recent findings have shown that HEV leads to severe disease, particularly among pregnant women. In contrast to the previous narration of a strictly mild and self-limiting infection. Studies have likewise demonstrated chronic HEV infection among immunocompromised persons. Consequent to these recent discoveries, this pathogen is considered a re-emerging virus, particularly in the developed nations. However, despite the growing public health challenges of this pathogen, the burden is still underestimated. The underestimation is often attributed to poor awareness among clinicians and a lack of routine checks for the disease in the hospitals. Thus, leading to misdiagnosis and underdiagnosis. Hence, this review provides a concise overview of epidemiology, diagnosis, and prevention of hepatitis E.

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1. Introduction

Recently, viral infectious diseases have threatened global public health safety (Parvez, 2013). Major incidences of these emerging and re-emerging viral infectious diseases have a zoonotic link from arthropods, wild animals, domestic animals, and poultry (Parvez, 2013). Alas, most of the emerging viral infectious diseases are caused by RNA viruses (Nichol et al., 2000). Hepatitis E virus (HEV) is one such RNA virus causing the disease known as hepatitis E.

The global burden of hepatitis E is estimated to be about 2.3 billion based on seroprevalence studies (Guerra, 2017). Hepatitis E virus is the fifth of the known hepatitis viruses (after A, B, C & D) and the commonest cause of acute viral hepatitis worldwide (Melgaco, 2018; Teshale and Hu, 2011). One study revealed that more than 20 million people traversing nine regions of the world are estimated to have had hepatitis E in 2005 alone (Rein, 2012). With East and South Asia accounting for over 61% of all cases (Rein, 2012). In another report (by the Southeast Asia Regional Office of the World Trade Organization), symptomatic cases of this disease are put at 6.5 million with annual case mortality of 160,000 and over 2,700 cases of stillbirth in Asia alone (Hudu, 2018).

However, despite these alarming figures, hepatitis E is still grossly underestimated. There is poor awareness of the disease among physicians. Thus, routine check for the disease is rarely conducted in the hospitals in most parts of the world. Thereby leading to misdiagnosis and underdiagnosis of hepatitis E. There is also a paucity of research on the epidemiology of the disease, particularly in developing countries. This is due to the initial idea that hepatitis E is only endemic in the developing regions of the world.

Nevertheless, recent HEV research has resulted in a pattern shift in the understanding of HEV epidemiology. These studies have provided new details as well as more unresolved issues about this enigmatic pathogen. HEV is now regarded as an emerging pathogen of global public health concern (Webb and Dalton, 2019). Epidemics of HEV infection were indeed recorded only in the developing countries of Africa, Asia, and in Mexico. However, sporadic cases occur in both developing and advanced nations (Aggarwal, 2011). Though endemic in parts of Asia and Africa, recent studies have reported sporadic autochthonous infections (Lewis et al., 2010) and high seroprevalence rates in industrialised nations (Capai et al., 2019). So, hepatitis E is now believed to have evolved from an enteric self-limiting illness to a multifactorial, multi-risk and chronic disease. It is believed to have changed from a regional disease to a global disease (Harrison and DiCaprio, 2018).

2. HEV history and evolution: From discovery to the present

The journey for the discovery of HEV started with the realisation that a large outbreak of jaundice that occurred in New Delhi India between 1955 and 1956, was due to an enterically transmitted non-A non-B hepatitis. Also, in 1980, Khuroo suggested that the causative agent of an outbreak of non-A, non-B acute viral hepatitis that occurred in 1978 in the Kashmir valley of India was likely enterically transmitted (Khuroo, 1980). These discoveries thus established the basis for the existence of a new hepatitis agent different from the earlier known hepatitis viruses.

Subsequently, with the combined efforts of Balayan and colleagues in 1983 and Reyes and co-workers a decade later, came the unearthing of the virus (Balayan, 1983). Their collective effort led to the isolation of the nucleic acid clone (Reyes, 1990), molecular cloning, and sequencing of the full genome of the new virus (Tam, 1991). The discovered virus was named “Hepatitis E Virus” “E” being the next available letter of the alphabet after “D” in the sequence of English alphabets. Also, because the virus tends to cause “e”piedemic and “e”ndemic diseases (Aggarwal, 2011). After the discovery of the virus, the molecular and serological tests for the diagnosis and detection of HEV antibodies followed suite. This development opened a new window for more HEV research in different regions of the world. Although HEV was discovered in the 1980s, epidemiological evidence suggests ancient origin dating back to the 18th and 19th centuries (Teo, 2012). This evidence was further strengthened by molecular-clock analysis of the HEV genomic sequences suggesting common ancestral origin with an agent that existed between 500 and 1300 years back (Purdy and Khudyakov, 2010).

From inception, the belief was that HEV infection was exclusively human disease. Also, that the virus is only enterically transmitted with a propensity to regions where poor hygiene and inadequate sanitation have always been a challenge (Aggarwal, 2013). Thus, explaining the fact why the disease was endemic in developing countries. Whereas, the industrialised nations only have imported cases due to travel to endemic regions (Schwartz, 1999). It was also believed that HEV infection is self-limiting with only occasional severe cases leading to fulminant hepatic failure (Aggarwal, 2013).

Surprisingly, however, recent pieces of evidence suggest a major paradigm shift in the understanding of the epidemiology of HEV infection. Unlike the hepatitis A virus (HAV) that is strictly enterically transmitted, it is now known that HEV has multiple routes of transmission (Yugo and Meng, 2013). It has also been established that the virus has a wide host range and frequent
cross-species transmission (Meng, 2013). The identification of HEV – like genetic sequences from animal specimens (both domestic and wild animals) (Meng, 2010; Meng, 1997) further strengthens the above arguments. Thereby confirming strongly, the zoonotic transmission of HEV. This is not also unconnected with the global distribution of the disease thus, negating the initial belief of regional restriction.

Additionally, studies have shown that HEV can cause chronic disease with the clinical persistence of the virus in the immuno-compromised, and those on immunosuppressive treatment (Kamar, 2008). Similarly, recent studies have revealed the ability of HEV to cause severe and fatal infections mostly in pregnant women (Patra, 2007).

Also worthy of note, are the periodic epidemics, particularly in developing countries (Kim, 2014) and sporadic and autochthonous infections (Lewis et al., 2010) in the advanced regions (Clemente-Casares, 2016). Thus, these discoveries have contributed to the growing concerns about the emergence and spread of HEV.

Fig. 1. The current classification of Hepatitis E Virus, the Hepeviridae family divided into two genera; Orthohepevirus and Piscihepevirus. HEV: Hepatitis E Virus.

Table 1
The Epidemiology of the Eight identified genotypes of Orthohepevirus A.

| S/N | Genotype | Host | Region of Occurrence | Human Epidemic Disease | Human Sporadic Disease |
|-----|----------|------|----------------------|------------------------|------------------------|
| 1   | 1 (I)    | Human (only) | West Africa, North Africa & Asia | Yes | Yes |
| 2   | 2 (II)   | Human (only) | Asia, Africa & Mexico | Yes | Yes |
| 3   | 3 (III)  | Human, Swine, & several other animals | North America, South America, Europe, Asia, & Africa | No | Yes |
| 4   | 4 (IV)   | Human, Swine, & several other animals | Americas, Europe & Asia | No | Yes |
| 5   | 5 (V)    | Wild Boar (only) | Asia (Japan) | No | No |
| 6   | 6 (VI)   | Wild Boar (only) | Asia (Japan) | No | No |
| 7   | 7 (VII)  | Human & Camel | North Africa & Middle East | No | Yes |
| 8   | 8 (VIII) | Human & Camel | North Africa & Middle East | No | Yes |

Fig. 2. shows the assigned classification of the major four pathogenic HEV genotypes into 28 sub-genotypes; HEV – 1 has 6 (a – f), HEV – 2 has (a – b), HEV – 3 has 11(a – j, ra), HEV – 4 has 9 (a – i).
3. HEV Taxonomy

HEV is a highly diverse pathogen that is witnessing a constant discovery of different variants across different animals the world over. Thus, the classification of the virus has been dynamic as the diversity of its variants. Over the years HEV has undergone three taxonomic categorisations. The virus was initially classified as a member of the Caliciviridae (Koonin, 1992). Due to certain biophysical and morphological similarities of the virus to the members of the Caliciviridae family (Berke and Matson, 2000). Years after this classification, HEV was later removed from the Caliciviridae family and became unclassified (Berke and Matson, 2000). Subsequently, in 2004 the International Committee on Taxonomy of Viruses (ICTV), re- classified HEV as a solitary virus in the Hepevirus genus and a member of the Hepeviridae family (Mayo, 2005). However, in 2014 Smith and colleagues put forward the reclassification of HEV (Smith, 2014) which was later adopted in 2015 by the ICTV. The current classification divided the Hepeviridae family into two genera: Orthohepevirus and Piscihepevirus based on the analysis of the existing sequence information (Smith, 2014). The Orthohepevirus genus is further subdivided into four species (see Fig. 1) designated with the English alphabets A to D (Smith, 2014). On the other hand, the Piscihepevirus genus consists of a solitary species of cutthroat trout virus assigned as Piscihepevirus A (Smith, 2014). Orthohepevirus A comprises genotypes from humans, pigs, rabbits, wild boar, mongoose, deer, and camel (Smith, 2014). The avian isolates are the sole genotype in Orthohepevirus B (Smith, 2014). Orthohepevirus C includes isolates from rats, greater bandicoot, ferret, Asian musk shrew, and mink. While the bat isolate makes up the Orthohepevirus D (Smith, 2014).

Orthohepevirus A has eight identified genotypes named as shown in Table 1. HEV genotype 1 (HEV – 1) infects only humans and is responsible for most of the infections in the developing world. The genotype is transmitted through contaminated drinking water. HEV genotype 2 (HEV – 2) is infrequent also affects humans only and was first isolated in Mexico (Fierro, 2016), then in some parts of Africa (Villalba, 2008). HEV genotypes 3 and 4 (HEV – 3 and HEV – 4) are found in the swine population. These two genotypes (HEV – 3 & HEV – 4) have been implicated as the cause of autochthonous human infection in industrialised nations linked to zoonotic foodborne transmission. The two new genotypes discovered in Japanese wild boar are genotypes 5 and 6 (HEV – 5 and HEV – 6). Most recently discovered genotypes (Sridhar, 2017) are the 7 and 8 (HEV – 7 and HEV – 8) isolated from camels with one human (Lee, 2016) reported case. The major genotypes in the Orthohepevirus A genus, are further divided into different sub-genotypes. At present only 28 of these genotypes have so far been assigned (Fig. 2) and a large number remain unassigned (Smith, 2016). This sub-classification further reveals the level of HEV genetic diversity.

4. HEV molecular virology

The understanding of the molecular basis of HEV was enhanced following the isolation, cloning, and sequencing of the virus in the early 1990 s (Tam, 1991). This was made possible by the propagation of the virus in non-human models. HEV is a small non-enveloped virus with an approximate diameter of 27 – 34 nm. HEV is a single-stranded positive-sense RNA virus. The viral genome (see Fig. 3) is capped (methylguanine) at the 5' end and polyadenylated at the 3' end. The virus is isosahedral in shape with a genome of 7.2 Kb in length (Panda and Varma, 2013).

The virus has three open reading frames (ORFs) and three untranslated regions (UTR) (Tam, 1991). The three ORFs (ORF1, ORF2 & ORF3) are somewhat overlapping and discontinuous as revealed by computer-based genome annotation (Panda and Varma, 2013). The ORF1 is the longest of the three ORFs, and it is formed by the 5' distal end of the genome. Beginning after 27b of the non-coding region (UTR) and terminating at the nucleotide position 5107 thus extending 5079b nucleotides (nt) (Tam, 1991). The ORF2 begins 38 nucleotides 3' after the termination of ORF1 and extends 1980b nt. The third ORF is about 369 nucleotides long overlapping ORF1 and ORF2 (Tam, 1991).

HEV contains three viral proteins, each with its unique functions and features (Zhou, 2016). These viral proteins are encoded by the three ORFs within the viral genome. ORF1 encodes the non-structural viral polyprotein that has 1693 amino acid residues (Zhou, 2016). Starting from the N- terminal end, the non-structural protein has the functional domains as shown in Fig. 3 (Zhou, 2016). The ORF2 codes for the major structural protein (capsid protein), which has about 660 amino acid residues (Zhou, 2016). The capsid protein encapsidates (Ahmad et al., 2011) the viral RNA genome and protects the integrity of the viral genome (Zhou, 2016). It also plays a significant role in viral infection, viral assembly, and
host immunity (Zhou, 2016). Thus, serving as the basis for HEV vaccine development, epitope presentation system, and studies of the interactions of HEV with its target cells (Ahmad et al., 2011). The last ORF, the ORF3 codes for a small protein known as the minor structural protein (Panda and Varma, 2013). This protein is a phosphoprotein and consists of two domains (D1 & D2 at its N – terminus) that are highly hydrophobic (Zhou, 2016). It also has two proline – rich domains – P1 and P2. The amino acid residue of pORF3 is about 113 or 114 sequences long. The protein functions as a viral accessory protein that is required for infection but dispensable for replication (Ahmad et al., 2011).

5. Epidemiology of HEV infection

5.1. Global distribution

Hepatitis E has a global distribution with two separate epidemiological patterns of distribution based on the circulating HEV genotypes and clinical disease frequency (Aggarwal, 2011). One pattern is referred to as the ‘endemic disease’ regions. In these regions, the infection is caused by HEV – 1 (to a larger extent) and HEV – 2 (less frequent). The other pattern is termed as the region of ‘sporadic disease’. Infection in these regions is caused by HEV – 3 (more frequent) and HEV – 4 (less frequent). Developing countries are regions where HEV infection was considered endemic and linked to contaminated drinking water and poor sanitary hygiene. The so – called regions of hepatitis E endemicity include Asia (Central, South & Southeast), Africa (West, Central & North), the Indian subcontinent, Middle East, and Central America (Arbeitskreis Blut und Virus, 2009). On the other hand, industrialised nations were considered ‘sporadic disease’ regions. Infection in these regions is thought to be imported from travel to the endemic regions as the only source.

5.2. Outbreaks of hepatitis E

Epidemics of hepatitis E have been reported only in the developing countries in addition to many sporadic cases. These outbreaks affect thousands of people across these regions (Table 2). Occurring mostly during rainy (or Monsoon) seasons with resultant floods. The floods result in the contamination of drinking water sources with human faeces.

The first epidemic of hepatitis E were the 1955–1956 New Delhi outbreak that occurred in India (Viswanathan, 1957). The outbreak was retrospectively established and linked to HEV after about 30 years of its occurrence. The outbreak was reported to have caused more than 29,000 symptomatic cases (Viswanathan, 1957). After the initial outbreak, India has witnessed about 30 HEV epidemics between 1975 and 1993 (Labrique, 1999). However, the first and four other major outbreaks in India have a total reported case of approximately 135,500. Also, in China Zhuang et al., reported 9 epidemics of hepatitis E were recorded between 1982 and 1988 (Zhuang, 1991). Affecting 6 of the 30 provinces in China and is associated with both contaminated drinking water and foodborne transmission. The largest outbreak in China lasted for 20 months with 119,280 total cases. Whereas, in Bangladesh, two outbreaks were reported from 2008 to 2010 (Gurley, 2014; Harun-Or-Rashid, 2013). The number of symptomatic cases in the 2009 outbreak was estimated to be above 4500 with recorded 20 deaths (Gurley, 2014). In Nepal, between 1973 and 2006, four epidemics were recorded. Kane and colleagues in 1984, reported an outbreak of hepatitis E that occurred in Nepal between 1981 and 1982 (Kane, 1984). Following the 26th December 2004 tsunami in Indonesia, an epidemic of hepatitis E were reported between 1982 and 1988 (Zhuang, 1991). Affecting 6 of the 30 provinces in China and is associated with both contaminated drinking water and foodborne transmission. The largest outbreak in China lasted for 20 months with 119,280 total cases. Whereas, in Bangladesh, two outbreaks were reported from 2008 to 2010 (Gurley, 2014; Harun-Or-Rashid, 2013). The number of symptomatic cases in the 2009 outbreak was estimated to be above 4500 with recorded 20 deaths (Gurley, 2014). In Nepal, between 1973 and 2006, four epidemics were recorded. Kane and colleagues in 1984, reported an outbreak of hepatitis E that occurred in Nepal between 1981 and 1982 (Kane, 1984). Following the 26th December 2004 tsunami in Indonesia, an epidemic of hepatitis E were reported in Aceh. Involving only 49 symptomatic hepatitis cases of both hepatitis A and E but no death was recorded (World Health Organization, 2005). However, prior to the 2004 outbreak, Indonesia had witnessed three previous epidemics in Borneo (1987 and 1991) and Java (1998) (Sedyaningsih-Mamahit, 2002; Corwin, 1995). In 2004 in the war-turned Darfur region of South Sudan, a large outbreak of hepatitis E was reported (Pinoges, 2006). A total of 2621 cases were reported with 1.7% mortality over a 6-month duration. The outbreak was linked to inadequate and unsafe drinking water in the region. Coupled with the poor sanitary condition because of the crises. One of the single largest hepatitis E epidemics in the world was also reported in Africa. The
outbreak was in the Kitgum district of Northern Uganda (Teshale, 2010). It started in October 2007 and by June 2009, it has caused hepatitis in over 10,196 persons. A total of 160 deaths were recorded with pregnant women having the highest case fatality. Other selected countries in Africa, Asia and Central America that have also had epidemics are presented in Table 2.

5.3. HEV seroprevalence in the population

In most parts of the world, there has been serologic evidence of prior exposure to HEV in the population. Industrialised nations have lower (1%-52%) HEV seroprevalence when compared to the developing regions (4%-94%). Most of the seroprevalence studies were conducted among different groups including, the healthy general population, healthy blood donors, population with HIV, and those exposed to animals. Seroprevalence studies were also conducted in animal populations both domestic and wild (Tsachev, 2020; Jemeršic, 2017). Indicating that animals (swine in particular), play a significant role in HEV epidemiology.

Faber and colleagues conducted a study on the seroprevalence of HEV among adults in Germany. The study showed anti – HEV IgG positivity of 16.8% in the adult population (Faber, 2012). In a study in Spain conducted among the general population, the HEV seroprevalence rate was 1.6% (Dalton, 2008). However, in the developing countries of Asia and Africa, the HEV seroprevalence rate is shown to be as high as 94%. In Bangladesh, Labrique and colleagues reported a seroprevalence rate of 25.5% in a population-based study in a rural area of the country (Labrique, 2009). In Indonesia, studies have shown seroprevalence rates of between 5% (in urban areas) to 59% (rural setting) in the country (Corwin, 1999). In Nepal, the prevalence of HEV antibody is between 10 and 25% (Clayson, 1997; de Bruyn and Song, 1998). A study in India also revealed 94.1% anti – HEV IgG seroprevalence in swine handlers (Vivek and Kang, 2011). Whereas the HEV seroprevalence of 43% in China shown by a study, is low compared to some countries in Asia (Li, 2006). This may not be unconnected to the fact that a less virulent HEV – 4 is predominant in China (Li, 2006). In Africa, the seroprevalence of HEV also varies with higher rates in rural areas than in urban areas. It could be as low as 4.3% (Rezig, 2008) and 4.4% (Li, 2006) in Tunisia and Ghana, respectively. In Tanzania 6.6% (Stark, 2006), South Africa 10.7% (Tucker, 1996) and 14% in Burundi (Aubry, 1997). Others include Zambia 42% (Jacobs, 2014), Djibouti 58.5% (Coursaget, 1998), Ethiopia 45% (Tseg, 1992), Chad 48% (Coursaget, 1998) and Egypt 84.3% (Stoszek, 2006).

Studies of HEV seroprevalence in blood donors also vary across different regions. Relatively high HEV seroprevalence is reported in blood donors in some European countries. A study in Bulgaria reported a prevalence of 25.9% (Baymakova, 2021). While in Croatia and Serbia reported prevalence was 21.5% and 15% respectively (Petrović, 2014; Miletić, 2019). These figures are similar to those recorded in South Africa (42.8%), Thailand (29.7%), and India (17.7%) (Maponga, 2020; Jupattanasin, 2019; Tripathy, 2019). Nevertheless, in France, seroprevalence rates have been in the range of 3.2% to as high as 52% in different blood donor populations (Boutrouille, 2007; Mansuy, 2011). The HEV prevalence among blood donors in England, Greece, Italy, Germany, and Canada, are 16%, 9.43%, 8.7%, 6.8%, and 5.9% respectively (Dalton, 2008; Pittaras, 2014; Spada, 2018; Juhl, 2014; Fearon, 2017). While a study in the blood donor group in Switzerland, Spain, and Japan showed the respective prevalence of 4.8%, 3.9%, and 3.4% (Dalton, 2008; Kaufmann, 2011; Takeda, 2010).

5.4. Age and gender distribution of HEV infection

Studies have shown evidence of two separate age – specific patterns in the epidemiology of HEV age distribution across the world. In one pattern, the disease attack rate is higher in teenagers and young adults (age 15 – 50 years). While the attack rate is surprisingly lower in children (age < 15 years), considering that the younger age group is more prone to enteric infection. This pattern is seen in both endemic and non – endemic regions, irrespective of whether it is sporadic or epidemic. This pattern was seen in Germany where prevalence increases with age (Faber, 2012). The situation is also similar in France, United Kingdom, Spain, and the Netherlands (Horn, 2018). Also, in India (Arankalle, 1995) HEV prevalence is higher between ages 15 – 30 years and in Nepal, it is between 15 and 34 years (Clayson, 1997). This distribution pattern is also seen in many endemic African countries (Kmush, 2013). However, the second pattern of age distribution is seen in North Africa. Where children appeared to be more affected than adults with high seroprevalence rates. This has been documented in Sudan (Mudawi, 2008) and Egypt (Fix, 2000).

The disease is more common in adult males than non – pregnant women globally. The predilection of the disease to the male gender has been attributed to higher behavioural risk factors in males than females (Kmush, 2013). Though, the disease attack rate appears to be higher in pregnant women than the general population in HEV – 1 developing nations (Kmush, 2013). HEV infection in pregnant women has the possibility of increased symptomatic illness, fulminant liver failure, and death (Kumar, 2004). It may also lead to increased extrahepatic manifestations, intraterine foetal demise, premature deliveries, abortions, antepartum haemorrhage, and stillbirths (Pairol, 2007). The fatality rate in this group is on the average of 15 – 20% in contrast to lower rates seen in non – pregnant women. The fatality rate may rise as high as 30 – 100% in the presence of complications such as acute hepatic failure (Stoszek, 2006; Kumar, 2004). Interestingly, however, this pattern is dissimilar in some endemic regions. HEV runs a benign course in the endemic areas of Egypt and South India with little or no symptoms (Stoszek, 2006). Acute liver failures are not also reported in pregnant women with HEV infection in these regions (Stoszek, 2006). The reason for this discrepancy remains unclear, but studies have hypothesised possibilities of a less virulent serotype of HEV – 1 in Egypt (Kmush, 2013). It has also been postulated that host factors (immune - mediated) and viral factors (viral mutation) play significant roles in the severity of HEV infection in pregnant women seen in some regions (Navanaethan et al., 2008). Likewise, studies have also reported a relationship between HEV genome recombination in patients with viral virulence and the severity of hepatitis E (Zhang, 2016).

5.5. Mode of transmission and risk factors for HEV infection

The reservoir of infection, mode of transmission, and risk factors of HEV have two patterns with some areas of overlap (Khuroo et al., 2016; Ruggeri, 2013). Dependent largely on the predominant genotype and regional distribution. It has already been established as mentioned previously, that HEV – 1 and HEV – 2 are predominant in Africa and Asia (Khuroo et al., 2016; Ruggeri, 2013). While HEV – 3 and HEV – 4 are seen largely in the developed world (Khuroo et al., 2016; Ruggeri, 2013).

There are multiple confirmed routes of HEV transmission (Fig. 4) yet more are still speculated (Mesquita, 2016; Kokkinos, 2017). The foremost mode of HEV transmission is through the faecal – oral route (Kmush et al., 2015). This is secondary to the faecal contamination of drinking water (Kmush et al., 2015). This is particularly true for HEV – 1 and HEV – 2 infections in the endemic areas or for the imported cases in developed regions (Khuroo et al., 2016). Though it also applies to water contamination by undomesticated pigs and water runoff from swine farms in industrialised nations (Khuroo et al., 2016; Yugo and Meng, 2015). Corroborating this fact is the detection of HEV RNA in various water
sources, especially during outbreaks of hepatitis E (Baez, 2017; Givens, 2016).

In the advanced countries where HEV – 3 and HEV – 4 are predominant genotypes, the mode of transmission is believed to be zoonotic (Lewis et al., 2010). The genomic and amino acid sequence similarities of human HEV isolates from autochthonous cases to the swine HEV isolates, supports the evidence of zoonotic transmission in this region (Lewis et al., 2010; Aggarwal, 2013). Also, the ability of human HEV – 3 and HEV – 4 to successfully infect experimental pigs, (Aggarwal, 2013) contributes to the indication of zoonotic origin. Zoonotic transmission thus is largely foodborne through the consumption of meat products or undercooked meat from infected animals (Lewis et al., 2010).

Parenteral transmission of HEV is also a possibility. There have been reports of nosocomial HEV infections following whole blood transfusion and transfusion of blood products (Gallian, 2019). Other sources of parenteral transmission include organ transplant (Denner, 2019), intravenous drug abuse (Kuznetsova, 2018), and haemodialysis (Eini et al., 2015). Direct contact either person-to-person (intra – familial) or contact with infected animals such as pigs (Denner, 2019) also plays a role in HEV transmission. In some outbreaks in Africa, HEV transmission has been attributed to person-to-person contact (Teshale, 2010). Especially among displaced populations in refugee camps (Organization, 2014). Additionally, household members of patients with acute hepatitis E experience increased secondary attack rates compared to those without (Kmush et al., 2015). Another mode of HEV transmission is the vertical transmission. Mother-to-infant transmission of HEV (during the third trimester of gestation) has been reported in numerous studies (El Sayed Zaki et al., 2014; Gupta and Agarwala, 2018).

Furthermore, there are many risk factors of HEV infection, and some may be specific to different HEV genotypes or regions. Increasing age is a significant risk factor for HEV infection in regions of HEV – 1 and HEV – 2 endemcity. (Clayson, 1997; Arankalle, 1995; Kmush, 2013). For the industrialised nations with HEV- 3 and HEV – 4 predominance, 15 – 25-year group are more at risk of infection with prevalence peaking at 40 – 60 years (Faber, 2012; Horn, 2018; Kmush et al., 2015). Male gender is also a risk factor for seroprevalence and clinical infection as against non – pregnant women (Sridhar et al., 2015). The increased risk in males cut across all ages as evidenced by numerous studies (Kmush et al., 2015). Though the reason for this predilection for the male gender is still poorly understood, studies have attributed it to social conventions and increased exposure to HEV (Kumar, 2013). Pregnancy, immunosuppression, and pre – existing chronic liver disease are also factors, that increase the risk of severe HEV infection (Kamar, 2014). Irrespective of age or gender, disease severity tends
to be higher in the immunocompromised and those with existing chronic liver disease (Parvez, 2013).

Environmental factors also play a role as a primary risk factor for HEV infection (Kamar, 2014; Howard, 2010). Rainy season or monsoon season affects the incidence of hepatitis E as seen in the developing countries (Labrique, 1999). Most of the major epidemics of hepatitis E are associated with rainy or monsoon seasons (Drabick, 1997). Floods that occur during these seasons contaminate drinking water with inadequately disposed sewage. Thus, increasing the chances of HEV transmission. Other environmental factors include poor water treatment and excessively dry conditions. The concentration of HEV in water bodies used for domestic activities tends to increase during excessive dry seasons (Corwin, 1995; Isaaclson, 2000; Skidmore, 1999). Similarly, those living in rural areas, urban slums, internally displaced person camps, and refugee camps are at risk of HEV infection. Also, the prisoners, cross-border population, migrants, nomads, and ethnic minorities are at increased risk of HEV seroprevalence and infection (Organization, 2014). The link between these groups and HEV risk is due to poor sanitation, inadequate safe drinking water, and lack of health education. However, for developed countries, recent travel to endemic regions and consumption of unsafe water is a contributory factor for infection (Piper-Jenks et al., 2000).

Another important risk factor for HEV infection is the consumption of undercooked or raw animal meat (Meng, 2011). This is particularly so for organ meat such as liver in developed countries and non-endemic Asian countries where HEV – 3 and HEV – 4 are prevalent (Kmush et al., 2015). Studies have found HEV – 3 and HEV – 4 circulating in swine, deer, and other animals in these regions (Mizu, 2005). A study in Japan reported HEV – 3 and HEV – 4 contained in about 2% of commercial pig liver packages sold in Japanese provision stores (Yazaki, 2003). Also, pig liver sausages have been linked to human HEV disease in France and the United States (Colson, 2010; Feagins, 2007). Additionally, certain occupational exposures are contributors to increased HEV seroprevalence, particularly for HEV – 3 and HEV – 4 infections. Swine farmers, swine veterinarians, pig slaughterers, meat inspectors, gamekeepers, forest workers, sewage workers, and wood cutters, all have higher seroprevalences than the general population (Kmush et al., 2015).

Equally, those receiving a blood transfusion, organ transplant patients, haemodialysis patients, injection drug use, and ‘O’ blood groups are predisposed to HEV IgG seropositivity compared to the general population (Mast, 1997; Nelson, 2014).

5.6. Reservoirs of HEV

Humans and other mammalian hosts have been implicated as reservoirs for the virus. Subclinical and sporadic human cases of hepatitis E serve as HEV reservoirs. This is particularly stronger in developing countries where HEV – 1 and HEV – 2 are predominant but could also be true for HEV – 3 and HEV – 4. This assertion is strengthened by the possibility of prolonged viraemia, and faecal viral shedding seen in some of these patients. Thereby, maintaining virus transmission in the population in-between outbreaks (Clayson, 1997).

Correspondingly, the zoonotic potentials of HEV have been demonstrated in numerous recently published studies (Kmush et al., 2015). Anti–HEV antibodies and HEV RNA have been detected in serum samples and faeces of domestic as well as wild animals (Clayson, 1996). These animals include domestic swine, sheep, cows, goats, camels, donkeys, deer, rodents, chickens, mongoose, mules, and cats (Clayson, 1996; Lu et al., 2006). Studies from China, Japan USA, New Zealand, and Taiwan have shown human HEV isolates to be phylogenetically related to swine HEV in these regions (Kmush et al., 2015).

6. HEV pathogenesis and clinical presentation

The pathogenesis of hepatitis E is poorly understood and is largely based on the data from a few human cell culture systems and animal models (Aggarwal and Goel, 2018). The incubation period after viral entry into the host usually through the gastrointestinal tract is 14 days to about 10 weeks (Favlov, 1992). Following entry, the virus gets to the liver through the portal vein after crossing the intestinal mucosa. However, it is still unclear whether viral replication occurs in the intestine before getting to the liver. Within three weeks of the incubation period, hepatocyte replication begins and coincides with the appearance of clinical symptoms as a result of the hepatocyte injury. However, viraemia, which often coincides with faecal HEV excretion appears few days before the onset of clinical symptoms and persists for 14 – 21 days thereafter (Aggarwal, 2000). Viral faecal excretion may persist for about 16 weeks (as shown in experimental animals) with a longer detection window than viremia (Zhang, 2012). While viraemia is declining, the appearance of anti – HEV antibodies, liver injury, and rise in serum transaminase levels occur simultaneously. This is highly suggestive of the possibility of the destruction of HEV-infected cells by host immunity. Thus, the liver cell lyses or hepatocyte injury is unlikely to be due to the direct effect of viral replication. Since it has been shown in cell culture studies that HEV lacks a cytopathic effect (Takahashi, 2008; Tanaka, 2007).

Shortly after the onset of symptoms, the host begins the production of anti – HEV antibodies (Aggarwal, 2000). The first antibody to appear is the immunoglobulin (Ig) M lasting for an average of 5 months (range 4 – 6 months) (Aggarwal, 2000). The appearance of IgG antibodies may coincide with that of IgM or soon after the appearance of IgM. The IgG antibodies last longer than the IgM though the titre also wanes away with time. Still, the exact duration remains unclear. In 1993, Khuroo and colleagues in a study revealed that anti – HEV IgG was detected in patients 14 years after infection with the virus (Khuroo, 1993). The antibodies thus give natural protection against HEV by neutralising both homogeneous and heterogeneous (all genotypes) isolates of the virus. Zhang and co–workers demonstrated the protective ability of anti – HEV antibodies in experimental animals (Zhang, 2012). However, this protection is not permanent since the antibodies disappear with time (Aggarwal and Goel, 2018). So, the possibility of reinfection cannot be negated (Zhang, 2014).

There are two distinct clinical manifestation patterns of the disease with HEV – 1 & HEV – 2 infections differing from HEV – 3 & HEV – 4 infection (Aggarwal, 2011). HEV genotypes 1 and 2 infections are largely subclinical and may ultimately present as acute viral hepatitis (Aggarwal and Goel, 2018). While HEV – 3 and HEV – 4 often lead to persistent or chronic disease (Aggarwal, 2011; Kamar and Pischke, 2018). Though a small percentage of infected individuals may be asymptomatic (anicteric hepatitis). In anicteric hepatitis, there might be a mild liver injury with transient elevation of serum liver enzymes and bilirubin (Kamar and Pischke, 2018). This group usually goes unnoticed or is accidentally detected during routine or unrelated laboratory checks (Aggarwal and Goel, 2018).

The clinical presentation of hepatitis E happens in three phases (Table 3): the prodromal, icteric, and convalescent phases consecutively (Aggarwal and Goel, 2018). The initial prodrome lasts 1 – 10 days and is characterised with non-specific flu – like symptoms (Aggarwal, 2011; Kamar and Pischke, 2018). These symptoms include low-grade fever, anorexia, intense nausea or occasional vomiting, myalgia, and malaise. The laboratory findings are those of increasing levels of serum liver enzymes. While serum bilirubin may be normal or slightly elevated. This phase is followed by the icteric phase and may last for 14 – 28 days (Aggarwal and Goel,
2018). The characteristic of this phase is the appearance of jaundice. Here, appetite begins to improve and other prodromal symptoms also start declining (Aggarwal, 2011). The liver is enlarged and tender with or without splenomegaly. From the high levels of the prodromal phase, the liver enzymes begin to decline while serum bilirubin remains high (Kamar and Pischke, 2018). After the icteric phase, the patient starts recovering with improving symptoms and the disappearance of jaundice. This stage of the disease is known as the convalescence phase. Also, liver enzymes return to normal (Aggarwal and Goel, 2018).

However, the icteric phase may be prolonged for weeks or months in some cases. With cholestatic symptoms of clay stool, dark urine, deep jaundice, and intense pruritus. Other symptoms may include poor sleep, impaired work performance, and poor quality of life (Goel and Aggarwal, 2016). This prolonged cholestasis may be accompanied by the persistence of mild non-specific symptoms (Kamar and Pischke, 2018).

Acute icteric hepatitis syndrome is usually self-limiting with spontaneous and complete recovery. Though it may progress to acute liver failure (ALF) with increased severity of disease and mortality. Acute hepatic failure often follows the icteric phase and the patient presents with features of liver failure (Goel and Aggarwal, 2016). ALF is associated with rapid and huge destruction of hepatocytes thus, impairing the synthetic and detoxification ability of the liver (Aggarwal and Goel, 2018). ALF is characterised by cerebral oedema, increased intracranial pressure, altered sensorium (hepatic encephalopathy), haemorrhage or its evidence in several body sites, shrunk liver, and ascites. Biochemical changes of hypoalbuminaemia and prolonged prothrombin time are also seen.

6.1. Chronic HEV infection

HEV infection can also cause chronic hepatitis. Chronic hepatitis E is defined as persistent HEV replication demonstrable by detecting HEV RNA in serum or stool three to six months following the original infection (Kamar, 2008). Though most of the HEV – 3 and HEV – 4 infections (more than two – third) are either asymptomatic or mildly symptomatic, it is usually a rapidly progressive disease (Narayanan, 2019). HEV – 3 and HEV – 4 infections may also present with extrahepatic involvement coexisting with or without liver affection (Kamar, 2011). However in recent times, studies have increasingly linked HEV – 3 and HEV – 4 as the causative agents for chronic HEV infection particularly in the developed world (Dalton, 2008). Chronic HEV is believed to be exclusive to immunosuppressed and immunocompromised patients. The immunosuppressed patients are those on immunosuppressive agents due to either solid organ transplant (SOT) (Kamar, 2008; Kamar, 2011) or those on chemotherapy for haematological malignancies (Mallet, et al., 2016; Tavitian, 2010). Chronic HEV has also been reported in immunocompromised patients with human immunodeficiency virus (HIV) infection (Singh, 2013). However, more cases of chronic HEV have been reported for SOT patients than for those with haematological malignancies.

Determinants of HEV chronicity have been associated with many factors. These factors are categorised into two broad groups; the virus and host factors (Narayanan, 2019). HEV – 3 that is the major cause of chronicity is less virulent and is zoonotic in contrast to HEV – 1 and HEV – 2 that are human viruses and are more virulent (Dalton, 2008). The zoonotic nature of HEV – 3 thus, makes the human host less adaptive to the virus. It was therefore postulated that these two factors (low virulence & poor host adaptability) lead to the inability of the host immunity to clear the infection (Narayanan, 2019). Which then progresses to chronicity following acute infection. However, the host factor has to do with the host immunity that plays a significant role in clearing HEV infection. In immunocompromised patients the host is unable to mount enough immunity on the virus thus, progressing to chronicity (Narayanan, 2019).

7. Definitive laboratory diagnosis of HEV infection

Numerous methods are available for detecting HEV both direct and indirect. These methods include immune electron microscopy (IEM), fluorescent antibody blocking assay, Enzyme Immunoassay (EIA), immunoblot (IB), immunochromatography, and reverse transcription polymerase chain reaction (RT-PCR) (Arbeitskreis Blut und Virus, 2009; Khudyakov and Kamili, 2011).

IEM has been one of the early assays used in the detection of HEV infection. It is used to detect HEV particles in serum and stool samples. It is a form of a direct method using the antigen – antibody reaction. The antibodies are labelled with heavy metals (e.g. gold) for detecting viral proteins (antigen) and visualised employing transmission electron microscopy. This technique though highly specific is technically challenging. It is expensive, requires specialised equipment, laborious optimisation, high antibody titre, and a huge amount of antigen. These disadvantages have limited the use of IEM in current HEV diagnosis (Arbeitskreis Blut und Virus, 2009).

Another early indirect technique employed for detecting HEV is the fluorescence antibody-blocking assay. This assay is a semi – quantitative test for detecting anti – HEV antibodies. The technique is equally specific but less sensitive, too rigorous for routine diagnosis, and expensive (Tassopoulos, 1994; Scheld et al., 2010).

Enzyme – linked immunosorbent (or enzyme immune) assays, are currently the most common assays use in the detection of anti – HEV antibodies of IgM and IgG class. Commercially developed EIAs, as well as those developed by research laboratories, are abundantly available. These EIAs have been used in various studies with varying degrees of specificity, sensitivity, and reliability across the globe. The specificity and sensitivity of these different assays range from about 40 to more than 90% for different genotypes and geographic locations (Al-Abesi, 2018). These available EIAs are developed using either recombinant proteins or synthetic epitopes for anti – HEV antibody detection (Li, 2000).
Another method for HEV diagnosis is IIB otherwise known as Western blotting (WB). IIB is used as a confirmatory test to validate HEV ELISA by determining the rate of false negative and false positive results (Mazalovska, 2017). There are several IIB assays both commercial and in-house, for detecting HEV immunoglobulins (IgG and IgM) (Khudyakov and Kamili, 2011). These IIB assays are developed using different HEV proteins for HEV IgG or IgM detection (Khudyakov and Kamili, 2011). These IIB assays used for HEV detection are highly sensitive and specific (Khudyakov and Kamili, 2011). However, the technique is cumbersome thus not used for routine diagnosis of HEV.

For detecting HEV RNA, RT – PCR, and loop – mediated isothermal amplification methods are used. Consensus primers have been developed for the amplification of specific regions on the HEV genome. RT – PCR assay is highly specific and sensitive in detecting HEV RNA in clinical samples (both serum & stool) as well as in contaminated environmental water and sewage. RT – PCR can also be used in confirmatory test assessment for the degree of protection during immunisation studies in experimental animals. Equally, RT – PCR is applied in strand – specific HEV RNA detection. To determine the negative – stranded HEV RNA replicative intermediate in the liver of infected animals. Another use of this assay is in experimental HEV infection transmission studies. By determining the infectivity titre of the inoculum to be used in the study. The conventional RT – PCR is the most frequently used for HEV RNA detection. To enhance the sensitivity and specificity of RT – PCR assay in HEV diagnosis, other types of RT – PCR can be used. These RT – PCR types include nested RT – PCR, real – time RT – PCR, and multiplex RT – PCR. Also, RT – PCR when conducted together with anti – HEV IgM ELISA, may enhance the effectiveness of diagnosing acute HEV infection (Arbeitskreis Blut and Virus, 2009; Organization, 2014; Khudyakov and Kamili, 2011; Germer, 2017).

8. Treatment of acute HEV infection

Hepatitis E virus infection treatment depends on the outcome of the infection. For acute viral hepatitis in immunocompetent individuals, viral clearance is usually spontaneous. Thus, this group of patients may require only supportive and symptomatic treatment. However, in the case of severe HEV infection in immunocompetent persons, treatment with ribavirin at 1200 mg/day for 21 days is recommended (Gerolami, 2011; Shrestha et al., 2017). Although, for acute liver failure by HEV infection in pregnancy, the major form of treatment is supportive intensive care (Shrestha et al., 2017). Since ribavirin has a teratogenic effect thus contraindicated in pregnancy. Nevertheless, there have been suggestions for weighing the risk – benefit ratio of ribavirin use in pregnancy (Kamar, 2012). Considering the fetomaternal adverse effect of untreated severe HEV in pregnancy. It is also recommended that patients with acute HEV infection awaiting transplant or undergoing haemodialysis should be treated. A short course (10 days to 3 months) of ribavirin (at 200 mg – 1000 mg/day) should be given before the transplant (Péron, 2011). While pegylated interferon-alpha (at 135 µg/week) for three months is used for the haemodialysis patients.

9. Treatment of chronic HEV infection

The goal of treatment in SOT patients with chronic hepatitis E is viral clearance. Thus, the initial step for treating this group of patients is lowering the dosage of immunosuppressive drugs (Kamar, 2016). This step may lead to about 30% of the patients achieving viral clearance (Bouts et al., 2015). However, if viral clearance is not achieved with dosage reduction of immunosuppressive drugs or reduction impossible, antiviral drugs can be used. The first line of antiviral therapy is the use of ribavirin as monotherapy. Several clinical studies have shown a continued virological response in patients with a 3 – 6-months course of ribavirin monotherapy (Lhomme, 2019; Pischke, 2013). Also, in vitro studies have revealed the ability of ribavirin to inhibit the growth of HEV (Nishiyama, 2019).

However, ribavirin is capable of inducing mutation (G1634R mutation) in the viral polymerase (RdRp domain of pORF1) (Todd, 2016). Thereby resulting in treatment failure in chronic hepatitis E patients on ribavirin monotherapy. So, in the event of treatment failure, pegylated interferon-alpha (α) can be used as a second-line drug for the treatment of chronic hepatitis E in SOT patients (Netzler, 2019). Pegylated interferon α is also recommended for treating chronic hepatitis E in patients with haematological malignancies and HIV (Netzler, 2019). Both in vitro and in vivo studies have shown a promising effect of interferon in the treatment of chronic hepatitis E. Up to 100% of sustained virological response can be achieved within six months of treatment with interferon (Kamar, 2016). Nevertheless, treatment can be extended up to 12 months in case of non-response (Kamar, 2016). Also, combination therapy of interferon and ribavirin can be used for treating chronic HEV infection (Nishiyama, 2019; Netzler, 2019). However, interferon is known to have substantial adverse effects and graft rejection in transplant recipients. Though patients with liver transplants have been successfully treated with interferon, the same cannot be said of those with kidney, heart, and other solid organ transplants. Another promising antiviral for treating chronic HEV infection is sofosbuvir. In vitro studies have shown the efficacy of sofosbuvir in inhibiting HEV RNA replication either as monotherapy or in combination with ribavirin (Dao Thi, 2016). Sofosbuvir therapy though promising, but sustained viral clearance has not been achieved in some studies (Van Wezel, 2019). Thus, more studies are required to establish the potential benefit of sofosbuvir in the treatment of chronic HEV infection.

10. Prevention of HEV infection

Preventive measures should be the way forward in confronting the menace of HEV infection. Prevention can be achieved through the provision of good basic hygiene. Strategies should include the provision of adequate clean drinking water, by adopting quality standards for public water supply. Also, good environmental sanitation, a proper disposal system for animal and human faeces, and personal hygiene will assist in prevention. Additionally, health education on environmental sanitation and personal hygiene will help prevent HEV infection. Similarly, surveillance aimed at early outbreak identification may assist in reducing the impact of epidemics. The above strategies are particularly important in the prevention of HEV infection in developing countries. While in developed nations adoption of safe eating habits will go a long way in preventing HEV infection. Eating contaminated beverages, raw or undercooked animal products should be discouraged. The heating of animal products (e.g. pork) to 71 °C for 20 min should be encouraged. Boiling will assist in inactivating HEV RNA in contaminated food products (Barnaud, 2012). Another important preventive measure is the inclusion of HEV in the blood screening policy at donation centres to avoid transmission through blood transfusion.

11. HEV vaccine

Good basic hygiene although effective in the prevention of hepatitis E, is not all-encompassing. Since it does not suffice for other
souces of transmission beyond waterborne and foodborne routes. Thus, the safest and most effective means of HEV prevention and control should be thorough vaccination. Of the numerous vaccine candidates, two were outstanding and underwent human clinical trials (Zhang et al., 2016). A baculovirus – expressed 56 KDa protein and an E. coli – expressed HEV 239 protein. The 56 KDa protein though yet to be licenced, has gone through both phase I and II human clinical trials. On the other hand, the HEV 239 vaccine has its efficacy evaluated in phase III double – blind, a randomised clinical survey conducted in China (Zhu, 2010). The vaccine has the following advantages 1) cross – protection against other HEV genotypes. 2) Potential for rapid control vaccination during epidemics. Hence, the vaccine was licenced for use in China in 2012 under the brand name Hecolin®. However, the vaccine is yet to be approved by any other country aside China. This has to do with concerns about the safety of the vaccine in pregnant women, chronic liver disease patients and other population outside China. Therefore, there is a need for more studies to address these concerns for the global acceptance of Hecolin®. Also, there is a need for more research aimed at developing novel vaccine candidates against HEV infection.

12. Conclusion

Hepatitis E virus as a pathogen has evolved since its discovery. The pathogen is now known for causing a disease that is globally distributed with an increased public health challenge. The risk factors for HEV infection have also increased due to its multiple means of transmission. Of interest are zoonotic transmission, blood-borne transmission, and to a lesser extent vertical transmission. As a result, more populations are at risk of HEV infection now than ever. Thus, the prevalence of the disease is rising across the globe although the disease is still considered to be underestimated due to a lack of awareness and unstandardised diagnostic methods. Nevertheless, appropriate awareness, early diagnosis, good treatment options, improved vaccination, and preventive measures will help curtail the spread of the disease.

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Data sharing does not apply to this article as no data were used to support this study.

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Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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