Research Article

Hepatitis E Virus and Zoonosis

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Abstract | Hepatitis E virus (HEV) is an important public health problem both in developing and developed nations. HEV is a single stranded RNA non-enveloped virus belonging to the family *Hepeviridae*. Globally, HEV is known to cause approximately 20 million infections per annum with a mortality of 44,000. The virus is endemic in developing nations and the outbreaks occur mainly in the post monsoon season when the drinking water gets contaminated with sewage. However, the mode of acquisition of infection is different in developed nations with good sanitary conditions where the infection is a zoonosis. Though the virus has only one serotype, 8 genotypes have been documented. Out of these, HEV 1 and 2 have been reported from developing countries and are transmitted mainly through faeco-oral route while HEV 3 and 4 are reported from developed countries and the infection is acquired by humans due to the eating of undercooked pigs, deer and wild boar meat. Recently HEV genotypes 5 and 6 have been reported in Japanese wild boars while HEV genotypes 7 and 8 have been reported in camels from Middle-East countries. Considering the increasing globalization of food markets, the possibility exists of widespread HEV infection in new areas of the world. In the present era, there is a need to study transmission dynamics of HEV in context to humans, animals and the environment so as to develop better prevention control measures through 'One Health' concept. The clinical manifestations of HEV can vary from self-limiting acute viral hepatitis which occurs in apparently healthy individuals to acute liver failure which leads to high mortality among pregnant women. Recently, chronic infections due HEV genotypes 3 and 4 have also been documented in immunosuppressed and transplant patients where prolonged virus shedding has been documented. The conventional diagnosis is established by detection of HEV antigen or anti-HEV IgM in acute sera. However, the detection of HEV RNA is important to establish the diagnosis in immunosuppressed patients. In transplant patients, decrease in immunosuppression is usually done, however ribavirin therapy has also shown a definitive role. There is upcoming literature on the role of sofosbuvir also in these groups of patients. Since the virus has only one serotype, univalent vaccine can provide protection against all HEV genotypes. Two vaccine candidates have been evaluated in clinical trials. Among these two vaccine candidates, one has been developed by Glaxosmithkline and another HEV 239 (Hecolin) has been developed by Innovax (China) and is in use in China since 2012. Considering the expanding clinical spectrum of HEV, it is an emerging zoonotic illness and prevention is the most effective approach against HEV.

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Introduction

Hepatitis E virus (HEV) is one of the major causes of self-limiting hepatitis, especially in developing countries. Globally, it is known to cause ~ 20.1 million HEV infections, 3.4 million symptomatic cases, 70, 000 deaths, and 3000 stillbirths annually. (WHO, Hepatitis E, n.d.) Though the virus has only

one serotype, 8 genotypes have been documented. Out of these, HEV genotype 1 and 2 have been reported from developing countries and are transmitted mainly through faeco-oral route and responsible for causing water borne outbreaks. On the other hand, HEV genotype 3 and 4 are reported in a sporadic fashion from developed countries and the infection is acquired by humans due to the eating of undercooked pigs, deer and wild boar meat. Recently HEV genotypes 5 and 6 have been reported in Japanese wild boars (Smith et al., 2014) and HEV genotypes 7 and 8 have been reported in camels from Middle-East countries. (Woo et al., 2014; Sridhar et al., 2017) HEV 7 has also been isolated from a liver transplant patient, who used to consume camel meat and milk regularly (Lee et al., 2016).

The clinical manifestations of HEV can vary from self-limiting acute viral hepatitis which occurs in apparently healthy individuals to acute liver failure which leads to high mortality among pregnant women in ~20% and has the potential of vertical transmission to the fetus. (Purcell and Emerson, 2008) Recently, chronic infections due to HEV genotypes 3 and 4 have also been documented in immunosuppressed and transplant patients. (Kamar et al., 2014) This is more often encountered by genotype 3 and the zoonotic link to such cases has been hypothesized. In India, the most common circulating genotype amongst humans is genotype 1 while the animal genotype has been reported to be genotype 4. (Aggarwal et al., 2014; Gupta et al., 2018; Shukla et al., 2007) In India, the zoonotic transmission has not been reported possibly because of eating properly cooked meat. (Christou et al., 2013; Shukla et al., 2007; Yugo et al., 2014) However, considering the increasing globalization of food markets, the possibility of widespread HEV infection in new areas of the world does exist. In the present era, there is a need to study transmission dynamics of HEV in context to humans, animals and the environment so as to develop better prevention control measures through 'One Health' concept.

Breakthrough unearthing of hepatitis E

The first renowned outbreak of Hepatitis E was noted in New Delhi in 1955-56, affecting ~29,000 people. (Viswanathan, 2013) This was initially considered as an epidemic of Hepatitis A virus, but retrospective serological testing of stored sera identified a novel infectious agent as the causative agent and the identification remained cryptic until revealed by sequencing in 1993. (Krawczynski, 1993) Hepatitis E virus was first identified as the causative agent of non-A, non-B hepatitis from Kashmir, India in 1978. (Khuroo, 1991) The epidemic affected a population of ~600000, with a total of 52000 cases and mortality of ~1700. (Khuroo, 1991) Later, many such outbreaks were noted in the region. (Khuroo, 2011; Khuroo et al., 2010) The remarkable trait observed in this outbreak was the increased rate of illness in pregnant women more than in usual outbreaks. (Khuroo et al., 1981; Khuroo and Kamili, 2003a, 2003b) Consequently, a 14-year long investigation finally led to the discovery of a unique, yet unidentified non-A, non-B hepatitis virus, having a high predilection to affect pregnant females with a potential for vertical transmission to the fetus. (Khuroo et al., 1980, 2009) Subsequently, it was hypothesized that this virus doesn't lead to any chronic illness and the IgG antibodies were lost in ~50% of the population over a period of 14 years. (Khuroo et al., 1980, 1993).

Later in 1983, a similar kind of outbreak was observed in Soviet soldiers in Afghanistan. Several soldiers presented with an unexplained hepatitis and to unveil the mysterious cause, Dr. Mikhail S. Balayan himself ingested a pooled fecal extract from nine affected personnel. On day 36 of the self-infection, he developed severe hepatitis and his stool samples of day 28, 43 and 45 revealed virus-like particles (VLP) under the electron microscope. (Balayan et al., 1983) Despite these efforts, the VLPs could not be cloned owing to the low yield. Consequently, in 1990, the virus was successfully cloned in bile of experimentally infected macaques. (Reyes et al., 1990) This was followed by the whole-genome sequencing in 1991 and the development of a diagnostic enzyme linked immunoassay (Tam et al., 1991; Yarbough et al., 1991; Reyes et al., 1990).

Genomic structure of the virus

HEV is a positive-sense, single-stranded RNA virus with 7.2 kb genome. The virus is non-enveloped with a size of 27-34 nm and icosahedral capsid. The genome is capped at 5' end and polyadenylated at 3'end (Reyes et al., 1990; Tam et al., 1991) with three open reading frames (ORF) in the genome (Figure 1). Though the virus is non-enveloped, but it circulates in our circulation as a quasi-enveloped form, host-membrane derived quasi-enveloped HEV (eHEV). This quasi-envelope is thought to provide protection to the virus from neutralizing antibodies in circulation, thereby

facilitating the cell-to-cell spread. In spite of the protection provided to the virus, attachment of eHEV is less efficient than the usual non-enveloped HEV, owing to which serum is less infective than faeces. (ICTV Virus Taxonomy Profile: Hepeviridae, n.d.; Yin et al., 2016) ORF1 acts alike an mRNA-alike fragment, being directly translated from the genome and encodes for 1,693 bp protein, having the functional domains of all non-structural proteins like cysteine protease, methyltransferase, RNA helicase and polymerase. (Koonin et al., 1992) ORF2, overlapped by ORF3, is translated from subgenomic RNA rather than the genome directly, encoding for 660AA capsid protein, involved in assembly, interaction and immunogenicity of the virus. (Li et al., 1997; He et al., 2008; Kalia et al., 2009; Xing et al., 2011) There are three linear domains within ORF2: shell domain, middle and protruding domain. (Guu et al., 2009) ORF3 encodes for 113 AA protein involved in morphogenesis and virion release since it encodes viroporin. (Emerson et al., 2006; Yamada et al., 2009; Graff et al., 2006) Apart from these three orfs, ORF 4 has also been reported in genotype 1 and the synthesis is driven by internal ribosomal entry site-like sequences. (Nair et al., 2016; Graff et al., 2006) The sequence analysis of the genome has divulged the presence of cis-reactive elements, which are involved in replication and are located in intergenic region forming stem-loop like structure, which serves as promoter for replication. (Cao et al., 2010; Parvez, 2015).

The detailed evaluation of domains encoding for orf in HEV genome indicates contribution of recombination event leading to the emergence of the virus. The recombination event is thought to have occurred between structural and non-structural encoding regions between *Astroviridae* and *Alphatetraviridae*. (Kelly et al., 2016) It has been noted that the rate of amino-acid substitutions in genome of genotype 3 and 4 is much higher, consequently leading to fewer conserved regions and lesser codon bias across the genome, paving the path for ease of adaptation in multiple hosts. (Bouquet et al., 2011; Nan et al., 2017; Sridhar et al., 2017).

Diagram of HEV and its genome

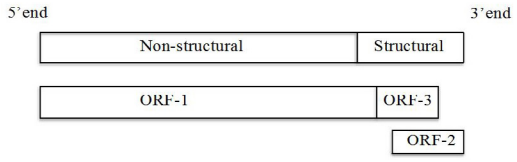

Figure 1: *HEV structure and genome.*

Taxonomy and classification of HEV

HEV belongs to genus *Hepevirus* in the family *Hepeviridae*. It was earlier classified under the same family as Hepatitis A, the family *Picornaviridae*. (Sreenivasan et al., 1984) But later it was found to be distinct genomically and was thereby, re-classified under genus *Hepevirus* and family *Caliciviridae*. (International Committee on Taxonomy of Viruses (ICTV), n.d.) Subsequently, due to its great variation in sequences, it was classified under 'Hepatitis-like virus'. Finally, after its full genome characterization, the virus is now classified in the genus *Hepevirus* in the *Hepeviridae* family (Purdy and Khudyakov, 2011) Earlier, the only member of the family was human HEV, but later based on the phylogenetic study, the closely related avian HEV, including rabbits, wild boars, rats, ferrets, bats and cut-throat trout, were also included in this family. (Smith et al., 2014) *Hepeviridae* family has been sub-classified into two genera, *Orthohepevirus* and *Piscihepevirus*. The former one includes mammalian and chicken isolates while the latter includes isolates from Cutthroat trout. The genus *Pischihepevirus* includes only one species: Pischivirus A. (Lin et al., 2014; Woo et al., 2014; Batts et al., 2011) *Orthohepevirus* is sub-divided into four species: A, B, C and D. An includes isolates from humans, rabbit, wild boar, deer, mongoose, pigs and camel (Woo et al., 2014; Sridhar et al., 2017). B includes isolates from chicken; C from rats and ferrets and D encompass isolates from bats. These four species have multiple genotypes with different subtypes within each genotype. (Lu et al., 2006) Based on pairwise amino acid sequence comparisons of available concatenated ORF1 and ORF2 sequences (excluding the ORF1 hypervariable region) of HEV variants visualized using a *p*-distance frequency distribution histogram, a *p*-distance of 0.088 appears to mark the demarcation between intra-genotypic and inter-genotypic sequence diversity, Orthohepevirus A has four groups: HEV-1 and 2 (isolates from humans), HEV-3 and 4 (humans and pigs), HEV-5 and 6 (wild boar) and HEV-7 and 8 (dromedaries). Similarly, Orthohepevirus B includes three genotypes: avian HEV-1 (Australia), avian HEV-2 (US and Canada) and avian HEV-3 (Europe and China). Orthohepevirus C includes HEV-C1 (rats) and HEV-C2 (ferrets). Orthohepevirus D has sequences only from bat. The nucleotide identity within each genotype is >80% while it varies between 73-77% between all the genotypes. (Smith et al., 2013) HEV-1 and 2 are exclusive to humans and are the genotypes

responsible for major outbreaks in Asia, Africa and Mexico. The genotypes HEV-3 and 4, found both in humans and animals, are mainly responsible for sporadic human cases, especially in developed countries. (Pérez-Gracia MT et al., 2015) Recently, variants were noted in Sweden moose and fox but till now, the full genome is not available (Smith et al., 2013; Lin et al., 2014; Bodewes et al., 2013)

To simplify the classification at genera level, a new classification system has been proposed which has four major genera: *Orthohepevirus:* including all mammalian isolates, except bats; *Chiropteran-hepevirus:* isolates from bats; *Avihepevirus:* avian isolates and *Piscihepevirus:* cutthroat virus. (Meng, 2013) Though the subtypes are not universally accepted (Smith et al., 2013; Oliveira-Filho et al., 2013), but few studies have proposed 24 sub genotypes based on full-length genome sequencing: 5 for HEV-1, 2 for HEV-2, 10 for HEV-3, 7 for HEV-4. (Lu et al., 2006; Purdy and Khudyakov, 2011) 1a, 1b and 1 c are the circulating ones in Asia, 1d and 1e in Africa (Lu et al., 2006) while 3a and 3b are more prevalent in US, Japan and 3f, 3c, 3e in Europe. (Legrand-Abravanel et al., 2009a; Bouquet et al., 2011)

Prevalence of HEV in diverse animal species

Apart from genotype 1 and 2, which are unique to humans, other genotypes are present in different animal species viz. pigs, rabbits (HEV-3 and 4), wild boar (HEV-5 and 6), dromedaries (HEV-7 and 8) (*Orthohepevirus A*), chicken (*Orthohepevirus B)*, rats and ferrets (*Orthohepevirus C)*, bats (*Orthohepevirus D)*, cut throat trout (*Piscihepevirus*). HEV-3 is mainly seen in Americas, Asia, Europe, Oceania and Africa. (Baez et al., 2017) However, HEV-4 has a restricted geographic spread, mainly to Japan and China. Recently, few swine strains were noted positive in Europe also. (Hakze-van der Honing et al., 2011; Monne et al., 2015). It was in late 90's when HEV genome was identified for the first time in swine in Nepal. 6% of fecal and serum samples of pigs tested positive for HEV while HEV-specific antibodies were detected in 33% of the swine samples. (Clayson et al., 1995) Later, in 1997 when Meng et al devised the term 'swine HEV' for the virus, that was similar to human HEV with few distinct characteristics (Meng et al., 1997). The same authors in 1999 showed the high seroprevalence (80-100%) of anti-HEV IgG antibodies in pigs older than 3-4 months. This high seroprevalence was present in both endemic (China and Thailand) as well as non-endemic countries (Korea and Canada). (Meng et al., 1999) Since then, many studies have been conducted to know the sero-status amongst different species of animals, the most common being swine (Pavio et al., 2017; Yugo et al., 2013), wild boar (Pavio et al., 2017), deer (Sonoda et al., 2004), rabbit (Lhomme et al., 2013; Johne et al., 2014), mongoose (Li et al., 2019; Nakamura et al., 2006) Studies in US have reported seroprevalence of 2.9% in wild swine, 41.2% in farmed swine, 0.6% in rats, 0.9% in dogs, 15% in cattle, 4.6% in bison. (Dong et al., 2007) Antibodies amongst goat (Sanford et al., 2013) and rabbit upto the level of 50% (Birke et al., 2014) have recently been identified in US. While in Korea, 8.1% seropositivity was noted amongst cats with no antibodies noted in cattle and dogs. (Song et al., 2014) Surveillance study from China has shown 6.28% in cats and 21.12% in dogs (Liang et al., 2014). Another study revealed the seroprevalence up to the level of 57% amongst rabbits in China (Zhao et al., 2009). The similar findings have been observed from other countries as well (Lhomme et al., 2013). (Arankalle et al. (2001) has shown the seroprevalence up to the rate of 4.4-6.9% in cattle, 54.6-74.4% in pigs, 22.7% in dogs, 2.1-21.5% in rodents. (Kulkarni and Arankalle (2008) conducted a study to determine the risk of swine HEV to humans and they collected liver of pigs and found 0.83% prevalence in retail markets of Pune, India. Recently, transmission of HEV-C1 has been confirmed in a study in Hong-Kong, establishing the first case of this novel zoonosis (Sridhar et al., 2020).

Apart from these strains of HEV from animals, novel avian HEV has also been isolated. It has been seen to affect chicken leading to hepatitis-splenomegaly syndrome with viral shedding in bile. (Haqshenas et al., 2001) 30-70% of chicken was found to be seropositive for HEV in US. (Huang et al., 2010) These strains showed 56-61% homology with human isolates. Similar findings have also been observed in Korea (Kwon et al., 2012). Rat HEV has also been observed to be seroprevalent in 13-90% of rats. (Yugo et al., 2014) Similar HEV strains have also been found isolated in mink and ferrets (Raj et al., 2012; Krog et al., 2013). Bats have also been noted to harbor HEV but the prevalence is extremely low (0.18%) with negligible potential for transmission to humans (Drexler et al., 2012).

Transmission dynamics between humans and animal species

To investigate the zoonotic potential and transmission

dynamics, many experiments have been performed in varied animal models. In one such experiment, the sera from the infected swine were found to cross-react with human sera. To verify this, rhesus monkeys and chimpanzee were infected with the strains from infected swine and their serum and fecal samples were tested weekly for sixteen weeks. Evidence in the form of seroconversion, viremia, elevated liver enzymes and fecal shedding was noted. For further confirmation, the specific pathogen free pigs were reciprocally infected with human US-2 strain. Four pigs were infected in pairs with one uninoculated pig serving as the control in each pair. Seroconversion and viral shedding was noted in the infected animals with no elevation in liver enzymes. All the animals appeared normal clinically. These experiments proved the cross-reactivity between different species and that the humans are at an increased risk of infection from other related species (Meng et al., 1998). In another such experiment, rabbit HEV was inoculated into human lung cancer and hepatocellular cell lines (A549 and PLC/PRF/5 respectively) and a very efficient replication was noted in these cell lines. (Jirintai et al., 2012) Similarly, when cynomolgus macaques were infected, they developed clinical disease and seroconversion along with viral shedding was also recorded. Hepatic as well as non-hepatic replication for the same was observed (Liu et al., 2013). This replication in human cell lines and non-human primates prove that HEV can have zoonotic transmission.

In order to know the transmission potential of avian virus, it was inoculated into rhesus monkey but it did not result in clinical disease or seroconversion. This concluded that unlike swine or rabbit HEV, this avian HEV lacks the transmission potential to humans (Huang et al., 2010). However, a similar experiment revealed the successful transmission of avian HEV to turkeys (Sun et al., 2004). Failure of transmission to humans was noted in experiments conducted with rat (Li and Wakita, 2019) and goat strains (Sanford et al., 2013). Apart from these, transmission potential of strains isolated from wild boar and dromedaries is still cryptic. A successful transmission from animals to humans does not occur with all animal species possibly due to the species barrier or factors like adaptability and ecological exposure. Few authors have even proposed the relation of inter-species transmission with non-structural protein, encoded by ORF-1 (Feagins et al., 2011; Cordoba et al., 2011). However, ~100% nucleotide identity between swine and human strains (Bouquet et al., 2011), ease of transmission of human strains to swine and vice-versa, show that there is no substantial need for adaptability of this virus for transmission. On the contrary, the absence of transmission of HEV genotype 1 to swine does upsurge the question for species barrier or some clandestine factors.

Various experiments have also been performed to elucidate the effect of HEV on pregnancy and vertical transmission of the virus. In one such experiment, twelve gilts were intravenously infected with HEV. The gilts showed seroconversion, however there was no evidence of vertical transmission as the fetuses were uninfected and did not show any seroconversion. But transmission of anti-HEV antibodies via colostrum was noted but they soon re-converted back to seronegative status after 71 days (Kasorndorkbua et al., 2003). On the contrary, when similar kind of experiments were tried in rabbits, the results were unusual. In this study, six pregnant and six non-pregnant rabbits were infected with HEV and consequently, two of the infected six rabbits, miscarried and the rest three died, owing to liver necrosis. HEV replication was also seen in the placenta, confirming the passage of anti-HEV antibodies. This confirms the vertical transmission of HEV in animals (Xia et al., 2015) and suggests that rabbit may be a better model for studying HEV kinetics as the results of vertical transmission were similar to humans.

Transmission to humans

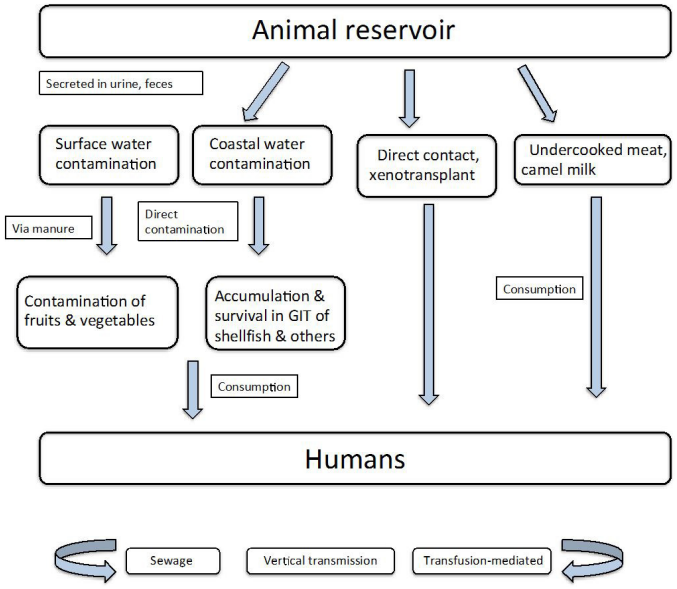

Figure 2: *Transmission dynamics of HEV.*

The major mode of HEV transmission is feco-oral route. Other vehicles for transmission include the contaminated water, food and sewage. (Figure 2)

HEV is also recognized as an occupational hazard for professionals dealing with swine and sewage. Many cases and outbreaks have been reported due to these sources (Rutjes et al., 2009; Bouwknegt et al., 2008; Bansal et al., 2017).

Transmission via sewage

Since the most common route of transmission of HEV is feco-oral, poor hygiene, inadequate sewage disposal and treatment can lead to infections among humans. Fecal shedding of virus from infected animals; eventually leading to the contamination of sewage, water and food makes it a vicious cycle, in absence of proper treatment of the source. The virus has also been isolated from the urine of infected swine and this abridges the contamination of water, sewage and food (Kasorndorkbua et al., 2003). The sewage contaminating the river waters and the use of this water for routine activities has led to many outbreaks in developing countries (Ceylan et al., 2003; Corwin et al., 1999; Sedyaningsih-Mamahit et al., 2002; Toole et al., 2006; Aggarwal, 2013). The genotype isolated from these waters has been found to be similar to those isolated from humans (HEV-1 and 2) and animals (HEV-3 and 4). (Vaidya et al., 2003; Clemente-Casares et al., 2003; Ippagunta et al., 2007; Pina et al., 2000; Jothikumar et al., 2006; Rutjes et al., 2009). Many natural calamities like floods and other catastrophes have also led to HEV outbreaks (Kumar et al., 2013; Rab et al., 1997; Ceylan et al., 2003; Corwin et al., 1999).

Transmission via contaminated water

Cross-contamination of water with HEV shed in feces of infected animals is a potential source of infection to other animals as well as humans. (Rodríguez-Lázaro et al., 2012; Jiménez-Clavero et al., 2005) HEV genotype 3 has been detected in many agricultural fields and the same strain has been isolated from the local animal species over there. In Canada, HEV-3 was isolated from strawberry fields and it had 99% sequence identity with local swine genotype (Brassard et al., 2012; Leblanc et al., 2007). Similarly, in Slovenia, HEV-3 has been isolated from surface waters as well as local pig farms. (Steyer et al., 2011) The manure used from the same fields may act as a potential source of infection to non-endemic areas leading to autochthonous cases. (Brassard et al., 2012; Ijaz et al., 2005; Rutjes et al., 2009) India too is an agricultural country, still hyperendemic for Hepatitis E due to contamination of fields via manure and slurry from the infected animals. Further transmission also occurs via run-off from swine farms leading to contamination of surface and coastal waters, continuing the cycle of cross-contamination of fields, fruits and vegetables (Khuroo, 2011).

Apart from the contamination of the surface waters, contamination of the coastal water leads to accumulation of HEV in gastrointestinal tract of shellfish, mussels, oysters and cockles. Owing to the ability of HEV to survive in acidic, alkaline, frozen or hot environment for years together, HEV can easily be transmitted to humans by consuming raw, uncooked, steamed or slightly cooked food (Emerson et al., 2006; Namsai et al., 2007). HEV has also been isolated from mussels and shellfish in Scotland, Finland, Spain, Greece, Korea and Japan (Crossan et al., 2012; Zhao et al., 2009; Diez-Valcarce et al., 2012; Kamar et al., 2014; Li et al., 2007). Out of these, shellfish consumption has the highest association. Cases have been reported from France, Italy and England (Ijaz et al., 2005; Cacopardo et al., 1997; Renou et al., 2008). One such huge outbreak was reported from Europe after consumption of shellfish on a cruise (Said et al., 2009).

Foodborne transmission

Since Hepatitis E virus infects various hepatic and extra-hepatic organs like gastrointestinal tract, mesenteric lymph nodes and also the spleen of the animals; consumption of improperly cooked meat can lead to human infection. It has been experimentally noted that HEV gets concentrated in kidney, salivary glands, tonsils, stomach, and muscles on intravenous administration (Williams et al., 2001; Billam et al., 2008; Bouwknegt et al., 2009). Three cases of HEV infection after consumption of meat have been reported from Japan. The cause of all three cases was traced back to meal from a common barbeque restaurant (Miyashita et al., 2012). Afterwards, many other cases after the consumption of undercooked pork have been reported from Japan (Miyashita et al., 2012). When the epidemiological link was established, it was observed that pig liver tested from the local market also tested positive for the same (Miyashita et al., 2012). Many experiments have shown that the isolate retains its infectivity even when re-inoculated back into pigs after infecting humans (Feagins et al., 2011).

Apart from pork, the meat of wild boar has also been linked to human cases in Japan, Korea and Germany (Wichmann et al., 2008; Sonoda et al., 2004; Li et

al., 2005). Cases of HEV infection after consumption of figatellu sausage, a raw pig liver fish, have been reported from France. On further investigation, the sequence obtained from human patients was identical to the sequence of fish from grocery shop (Christou et al., 2013; Colson et al., 2010). Cases of HEV have also been associated with the consumption of deer meat (Tomiyama et al., 2009) and later on, the HEV antibodies were also found to be higher in this population (Tei et al., 2003).

In order to confirm whether the infection of meat occurs during slaughter or is present beforehand itself, the meat juices and serum samples were also tested in Bravaria, Germany and they turned out to be positive for the presence of anti-HEV IgG antibodies (67.6% and 68.6% respectively). (Wacheck et al., 2012) A similar kind of testing food production chains has been undertaken in UK and Spain and similar results were obtained (Di Bartolo et al., 2007, 2012).

In India, the most common circulating genotype amongst humans is genotype 1 and the genotype present in animals is 4 (Shukla et al., 2007). Though the cases of zoonotic infection have not been reported from India but the reasons can be either ways (Christou et al., 2013; Shukla et al., 2007). It can be attributed either to the genotype difference or to the cultural and cooking habits of Indians (Christou et al., 2013; Yugo et al., 2014).

Occupational exposure and risk

The people working in close proximity with swine and sewage are at a higher risk of getting infected than the general population as has been shown from studies in Spain, Italy, Rome and Sweden (Olsen et al., 2006; Baylis et al., 2013; Dalton et al., 2011). The seroprevalence has been noted to be ~5.4 times higher in swine workers than the general population in Spain (Galiana et al., 2008). Based on the Bayesian model. Bouwknegt et al. (2009) have reported the IgG positivity to be ~ 11% in swine workers, 6% in non-swine veterinarians and 2% in the general population. Occupational exposure in forestry, hospitals and swine workers has been noted to have more odds foe seropositivity. The same rise in odds has been noted for hunting and meat consumption in a recent meta-analysis. (Wilhelm et al., 2020).

Parenteral transmission

Though this mode of transmission isn't very well-known but many studies across the globe have reported the transmission via blood and blood products. This is due to the subclinical and asymptomatic infections in blood donors. Since there are no screening recommendations for the same, the transmission is more than expected. The first report dates back to 2000 when viremia was noted in 1.5% of blood donors (3/200) in Pune, India (Arankalle et al., 2000). Though the transmission could not be proved by molecular techniques, but this study suggested the possibility due to blood transfusion especially in HEV endemic areas. Subsequently, another study demonstrated the higher rate of HEV infections in individuals with multiple transfusions than control population. The authors reported three cases of post-transfusion HEV in 22 susceptible patients. The epidemiological link for these three cases was found to be viremic but asymptomatic blood donors (Khuroo et al., 2004). Thereafter, many studies have demonstrated the presence of viremia in asymptomatic blood donors in China (0.031%) (Ma et al., 2015), Japan (0.13%) (Gotanda et al., 2007), Germany (0.15%) (Juhl et al., 2014) and England (0.035%) (Hewitt et al., 2014). On the contrary, studies conducted in US failed to demonstrate any such cases (Xu et al., 2013). Apart from blood transfusion, HEV can also be transmitted via organ transplant from HEV-positive patient. The same has been noted in a 73-years old male patient who developed HEV infection after liver transplant from a donor with occult HEV infection. The authors used phylogenetics to prove that occult HEV infection of donor was transmitted via graft to HEV seronegative transplant recipient (Schlosser et al., 2012). However, since the post-transfusion and post-transplant transmission of HEV is rare, routine screening for the same is not warranted.

Transmission via xenotransplant

Since, HEV is commonly encountered in swine and other animals, there is a potential risk of transmission via transplant. Pigs are a choice for transplant since they are easy to breed and share common anatomic as well as metabolic similarity with humans. The chances of transmission exist after hepatic as well as extra-hepatic organ transplant like heart valves, pancreas etc. (Meng, 2003; Halbur et al., 2001) Though xenotransplant is not common but in developing countries and in absence of suitable door, the risk of transmission via xenotransplant does exist. Pharmaceuticals of animal origin like pancreatin,

heparin, proactant alfa (surfactant used in preterms) can also transmit HEV, if not properly tested for the same (Mesquita et al., 2017). One such case was noted in the year 2011 in a 42 years old female in Truro, UK, who developed infection four weeks after laproscopic appendicectomy. During her hospitalization, she was given porcine-derived subcutaneous heparin injections as prophylaxis for thromboembolic disease. Though the batches of heparin tested, after the diagnosis, were negative for HEV but the low level of viral contamination and false negativity due to Poisson's effect could not be ruled out (Crossan et al., 2013). In such a scenario, screening tests in the form of RT-PCR may be preferred to demonstrate the viral replication in blood during the window period.

Globalization and HEV as zoonosis

HEV is also amongst those infectious diseases that have seen a rising trend with increase in travel, food and animal trade. Globalization has led to emergence and re-emergence of many infectious diseases including viral, bacterial, parasitic and fungal diseases. HEV was earlier proposed to be a disease prevalent in developing countries only (Aggarwal, 2011), but with the increase in travel and trade, many cases have been reported from developed regions as well, many of which could be epidemiologically linked to travel from endemic regions (Tassopoulos et al., 1994).

Apart from the spread of infection to developed regions, globalization is also playing a major role in zoonotic spread of the disease. Genotypes linked to zoonotic spread are 3 and 4 and these are mainly encountered in developed regions (Pavio et al., 2015). On the contrary, the common circulating genotypes in most of the developing countries including India are 1 and 2. However due to increase in globalization, the zoonotic spread of HEV is on a rise.

One-health approach for HEV

The comprehensive approach to understanding the molecular epidemiology, prevention, mitigation and control of HEV via human, animal, food or environmental origin is a "One-health approach". This involves collaboration from different disciplines and sectors of the community, involving physicians, veterinarians, food industry, water safety department, government and administrative sectors. The foremost step in this direction has already been initiated in the form of HEV net. This network was convened in April 2017 as database for partaking all the sequences with supplementary metadata from human, food, animal and environment sources. Till date, more than 1,615 HEV sequences have been submitted by members from different quarters viz public health (89%), blood safety, veterinary (5%), food (6%) and environment (0.3%). The supplementary metadata mainly includes gender (93%), date of birth (92%) and date of sampling (100%); region of sampling (37%) and clinical details (hospitalization 27%, symptoms 20% or mortality 8%). (Mulder et al., 2019) HEV net helps to identify the circulating genotypes in different regions of the world, using molecular typing to understand the relationship between different strains of HEV, to study the complex transmission dynamics of the virus along with giving an in-depth insight into the pathogenesis and virological analysis of HEV evolution (Mulder et al., 2019).

Clinical presentation of HEV

HEV is mainly a self-limiting illness, lasting for few weeks. The incubation period varies from 2-6 weeks. The patient presents with non-specific symptoms like fever, malaise, anorexia followed by abdominal pain, nausea, vomiting and jaundice. Jaundice is noted in ~40% of the patients. (Labrique et al., 2010).

In pregnant females, HEV infection can be severe leading to acute liver failure, it can also be fatal for the mother and the fetus leading to abortion. HEV in patients with chronic liver disease has also been found to be severe. A higher mortality of up to 30% due to HEV has been reported in patients with chronic liver disease. Cases of superimposed HEV infections in HBV-positive patients have been reported. Anti –HEV IgG antibodies have been seen in 45% of chronic HBV patients while IgM seroprevalences was noted to be 11.6% (Hoan et al., 2015). A higher mortality has been in reported in such cases (Lai et al., 2018) as both the infections increase the severity of each other (Aslam et al., 2018), especially in cirrhotic patients (Chen et al., 2016).

The presentation of HEV is almost similar in developing as well as developed countries. The main difference is in clustering of cases in developing nations whereas only sporadic cases, especially amongst middle-aged and elderly males, are seen in developed countries. Jaundice is more common and is seen in ~75% of patients. Neurological sequalae are also more commonly noticed in developed countries. (Dalton et al., 2007).

Chronic infection

Recently, chronic infection due to HEV, persistence of HEV RNA in serum or stool for more than six months, has been noted amongst immunocompromised individuals, especially in solid-organ transplant patients. The risk factors include HIV, solid-organ transplant, leukemia, immunosuppressants like tacrolimus, but not cyclosporine and steroids. The interesting feature is that the genotype implicated in such cases is mainly genotype 3 (Kamar et al., 2010). A zoonotic mode of transmission has been proposed for the same. Subclinical infection due to HEV has also been reported to a range of ~20.8% in healthy population in an outbreak setting to ~46.7% in healthy pregnant females. (Majumdar et al., 2015; Gad et al., 2011).

Extra-hepatic presentations of HEV

CNS manifestations: HEV can lead to neurological sequalae like Guillain-Barré syndrome (Chalupa and Holub, 2010; Cronin et al., 2011; Despierres et al., 2011; Kamani et al., 2005), neuralgic amyotrophy (van Eijk et al., 2014; Rianthavorn et al., 2010), acute transverse myelitis (Mandal and Chopra, 2006), Bell's palsy (Jha et al., 2012) and acute meningoencephalitis (Kejariwal et al., 2001). Kamar et al. (2015, 2010) have successfully showed presence of HEV RNA in CSF in all four immunocompromised patients with neurological sequalae. The neurological injury posed by HEV has been attributed to the origin of neurotropic variants and compartmentalization of quasispecies (Kamar et al., 2010).

Renal: Renal impairment in the form of membranous and membrano-proliferative glomerulonephritis is a well-known complication of HEV. Though the underlying pathogenesis is still unknown, but this can be associated with cryoglobulinemia observed in all such patients. (Kamar et al., 2012) Thrombocytopenia, aplastic anemia and pancreatitis have also been noted after HEV infection (Fourquet et al., 2010; Bhagat et al., 2008; Deniel et al., 2011; Colson et al., 2008).

Though no association between the HEV genotype and severity of disease is established, but HEV-4 has been found to be more severe leading to increased elevation in liver enzymes (Mizuo et al., 2005; Jeblaoui et al., 2013). However, more studies are required to verify any such association.

HEV infection in pregnancy

It's a well-known fact that HEV is the only hepatotropic virus that leads to a high mortality amongst pregnant females. Mortality in mother is as high as 25% and may occur due to antepartum hemorrhage, eclampsia or acute liver failure, which is more during the third trimester (Labrique et al., 2012). Vertical transmission of HEV leads to either stillbirth or morbidity in infants (Khuroo et al., 1995). The severity of infection in pregnancy increases with each passing trimester (Horvatits et al., 2019). The risk of fetal loss is maximum in the first trimester (Jilani et al., 2007). This might be attributed to hormonal and immunological factors. Few studies have associated the severity of infection with decreased countenance of progesterone receptors (Bose et al., 2011). Other studies have noted the potential role of estrogen receptors as biomarkers for determining the outcome of HEV in pregnancy (Singh et al., 2019). A noteworthy point is that only HEV-1 and 2 have more predilections to affect pregnant females. Though reports of infection with HEV-3 have also been noted but the association is very rare (Andersson et al., 2008; Thoden et al., 2008; Navaneethan et al., 2008). Contrary to the belief that HEV is associated with pregnancy all over the world, Egypt has reported no increased severity of HEV among pregnant females, in spite of HEV genotype 1 being the circulating genotype there. This can be attributed to different Major Histocompatibility Complex (MHC) profile of the population, existence of less virulent quasispecies and the increased exposure of individuals in early childhood only thereby decreasing the severity of adulthood infection (Mishra et al., 2013; Navaneethan et al., 2008; Gad et al., 2011).

The overall mortality in HEV infection is around 1% in immune-competent patients, 20% in pregnancy and around 30% in patients with chronic liver disease.

The exact pathogenesis in pregnancy is still cryptic but many studies have shown the role of TH-2 response that predominates in pregnancy, elevated levels of TNF-alpha, more cytotoxic cell response and suppression of NF-KB pathway (Salam et al., 2013; Prabhu et al., 2011; Bose et al., 2011; Prusty et al., 2007; Jilani et al., 2007).

Diagnosis of HEV

HEV can be detected in blood, dried blood spots (Singh et al., 2014), saliva (Rivero-Juarez et al., 2018), vomitus, stool and liver biopsy samples (Ratho et al., 2019). The diagnosis of HEV can be either direct or

indirect. The indirect method is based on detecting anti-HEV antibodies and the direct method detects RNA in serum or other body fluids or via demonstration of virus in cell lines or animal models. The decision to opt for these tests should be based on the viral kinetics and the time of presentation of the patient. Figure 3 shows the viral kinetics of HEV and the diagnosis of HEV are summarized in Figure 4.

Viral kinetics of HEV

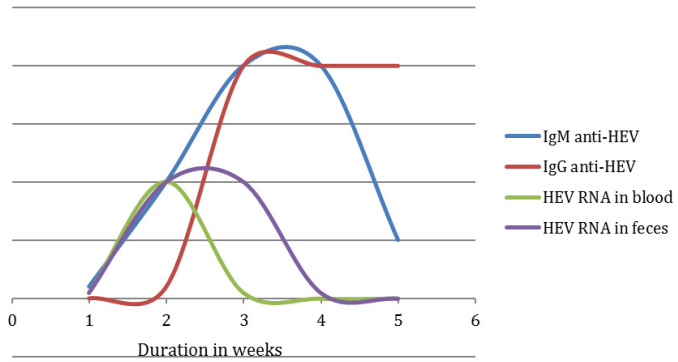

Figure 3: *Viral kinetics of HEV.*

HEV RNA: Viremia is detected by measuring HEV RNA in blood. The viremia and fecal shedding usually starts 3 weeks after infection and 1 week prior to the onset of symptoms. It peaks in the incubation period and gradually starts to decrease, becoming undetectable 3 weeks after infection. However, HEV RNA can still be detected in feces up to 5 weeks of infection by RT-PCR or LAMP. The significant viral load varies from 2.1 to 8.3-log copies/ml in immunocompetent individual to 2.7 to 7.8-log copies/ml in immunocompromised individuals. The monitoring of HEV RNA is indispensable in chronic HEV infection and to see the effect of treatment. If HEV RNA persists for more than 3 months, spontaneous recovery is very unlikely (Kamar et al., 2013). Also the detection of HEV RNA is useful if the infection occurs in immunocompromised individuals where the HEV IgM antibody response may not develop (Majumdar et al., 2013).

For detection of HEV in food, many tests have been proposed but only one is marketed till date, HepatitisE@CeeramTools™, that detects HEV RNA quantitatively in food as well as environmental samples. (Di Bartolo et al., 2012).

Cell lines for HEV: HEV is one of the most difficult viruses to cultivate in conventional cell lines. Many newer cell lines, involving the generation of cDNA clones and repeated passaging of primary culture has met with some success. It has been noted that HEV can be successfully cultivated in human fetal lung diploid fibroblast cell lines, hepatoma cell lines and lung cancer cell lines (Meister et al., 2019). Development of efficient cell culture system for HEV may pave way for the development of newer antivirals.

Antigen detection: Lately, it has been found that HEV antigen detection can be used as an early marker especially in first 3 days of infection when antibody response has not been mounted. It is also more beneficial in immunosuppressed individuals, who don't mount or mount a very weak antibody response. (Majumdar et al., 2013) Antigen detection can be used as alternative to HEV RNA testing, especially in early phase of infection, immunocompromised patients and in settings where PCR facilities are not available (Majumdar et al., 2013; Soothill et al., 2018; Mishra et al., 2016). Singh et al, in an Indian study have shown that HEV antigen was a better marker than HEV RNA detection for the early diagnosis of illness (Majumdar et al., 2013).

Antibody detection: Anti-HEV IgM is a marker of acute infection and presence of HEV IgG reveals past infection. Anti-HEV IgG is also used for estimating the seroprevalence of HEV in a geographical area. Anti-HEV IgG antibody titre can also be used to discern if the person is protected from the infection, after past acquisition or vaccination. In a study, the protective antibody concentration has been estimated to be 2.5U/ml (Innis et al., 2002; Legrand-Abravanel et al., 2009b).

Anti-HEV IgM level starts rising within first week of illness, reaches its peak level at the time of clinical presentation, remain at detectable levels for 8 weeks and then, decrease gradually. IgM antibodies fall below the detectable limit after 32 weeks post-infection. Few studies have shown that anti-HEV IgM antibodies can persist up to five months also (Dawson et al., 1992).

IgG antibodies rise 2-3 weeks post-infection, reach their peak levels after 4 weeks of presentation and are maintained up to 1 year (Huang et al., 2010). Studies have even noted the persistence of IgG antibodies up to 14 years at low levels (Khuroo et al., 1993). IgG avidity has also been used to differentiate acute and chronic infections, taking cut-off as 60% (Majumdar

et al., 2015). Many commercial kits are available for the identification of IgM/ IgG antibodies, based on ORF2/ORF3 peptides or recombinant antigens, with a good sensitivity and specificity (Meng et al., 2002). There is no genotype specific serological diagnosis due to a common antibody response against all the genotypes (Engle et al., 2002). RT-PCR is considered as the gold-standard diagnostic modality (Abravanel et al., 2013). Apart from molecular tests and ELISA, point-of-care tests are also available for the diagnosis of HEV (Chen et al., 2005). Rapid kits like Adaltis (Italy) and Wantai (China) are also available for the diagnosis of HEV. (Legrand-Abravanel et al., 2009b; Abravanel et al., 2013). However, immune status of the patient should be considered while analyzing the IgM assays due to poorer antibody response generation in immunocompromised population, as was noted in a co-infection of HEV in a patient with resolving leptospirosis (Singh et al., 2012). The diagnosis of swine and avian HEV is mainly based on molecular methods (Vollmer et al., 2012). The molecular diagnosis amid the coronavirus disease-19 era should be scaled up in the light of advanced laboratory set-up for diagnosis of emerging and re-emerging diseases. This molecular and expertise set-up can be exploited for the rapid and accurate diagnosis of Hepatitis E.

Flow chart for diagnosis of HEV

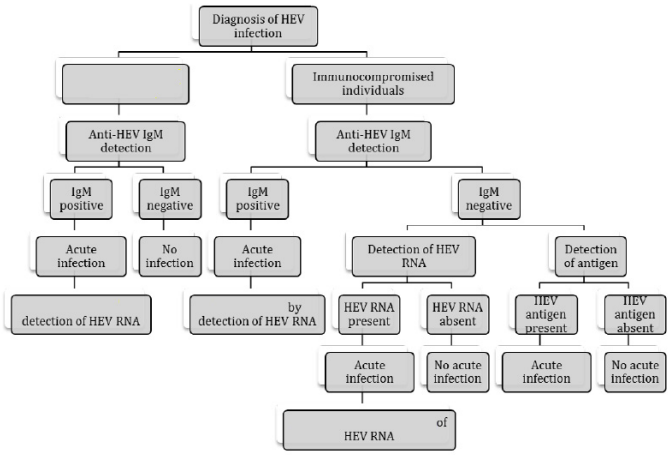

Figure 4: *Diagnosis of HEV infection.*

Treatment

No specific antiviral therapy is recommended for acute HEV. Supportive care is the mainstay of management. Therapy generally involves measures like vitamins for adequate nutrition, albumin and plasma for supporting treatment, ursodeoxycholic acid and S-adenosylmethionine and symptomatic treatment for cutaneous pruritus. In case of chronic hepatitis and in patients with liver dysfunction, ribavirin, which has been shown to clear virus in 80% of patients (Kinast et al., 2019; Rivero-Juarez et al., 2019), can be used as a substitute for liver transplantation, which is the definitive treatment. (Hui et al., 2016) Prior to ribavirin, pegylated interferons have been used as the agent of choice for chronic HEV.A recent study has shown that the combination therapy of ribavirin and mycophenolic acid (MPA) is more effective than either agent alone (Wang et al., 2014). Similarly, apart from MOA, safer directly acting antiviral, sofosbuvir, has been noted to have inhibitory effect on HEV also. Though the efficacy of sofosbuvir is less against HEV as compared to Hepatitis C but a synergistic action is seen with ribavirin. The same cannot be proved *in -vivo* in animal models due to the high esterase activity in serum and gastrointestinal tract of rodents. Thereby, the clinical efficacy of sofosbuvir against HEV can be validated in human subjects only, who are immunocompromised and fail to attain clearance with ribavirin alone (Dao Thi et al., 2016).

Prevention of HEV

Since the chief mode of transmission is feco-oral, mainstay of prevention is maintenance of personal hygiene, proper sanitation, adequate food and water safety. Vaccination of both animals and humans against HEV is also one of the preventive strategies. Surveillance is required at all levels of farming, rearing of animals, food production chain, marketing of animal products, adequate food and water safety and stringent hygiene measures. Apart from these, screening of blood and blood products is also need of the hour to prevent the blood-borne transmission but till date, no standard protocol exists for the same due to less sensitive screening tests (Pfaender et al., 2016).

Vaccine

Due to the paucity of any specific targeted therapy against HEV, prevention is the cornerstone. In view of the rising burden of chronic HEV infection and morbidity and mortality in pregnant females, there is an urgent need to introduce a vaccine in routine immunization programmes.

Vaccine development

Though eight genotypes of HEV are currently prevalent, but they all belong to one serotype and share common cross-reactive epitopes, making vaccine development easy. Despite this fact, the vaccines against HEV are still under-development owing to its failure to grow profusely in cell lines. Therefore, vaccine designing

is possible only by using recombinant technology or nucleic-acid based strategies. The two vaccines that have undergone clinical trials in humans against HEV are *E. coli* derived and Baculovirus derived vaccine. These are effective in expressing HEV viral proteins, which have been truncated due to hydrophobicity and insolubility of full-length proteins.

Vaccine candidates

HEV genome has three open-reading frames: ORF1, 2 and 3. ORF1 encodes for non-structural proteins, making it an unsuitable target, as it does not mount any humoral immune response. ORF3 overlaps ORF 1 and 2 and encodes for a small protein of cryptic purpose. Though this protein is highly antigenic, but the antibodies to it are non-neutralizing. Lastly, ORF2 encodes for capsid protein, which is highly antigenic and mounts significant humoral immune response with neutralizing antibodies. Therefore, ORF2 has been the major focus for vaccine development with recombinant technology.

E. coli derived viral proteins of 23kDa (aa 394-606) and 30 kDa (aa 368-606) have been prepared by the Wantai Biological pharmaceutical Co in China. The protective efficacy of HEV 239 *E. coli* vaccine (Hecolin) was noted to be 75% in high dose and 100% in low dose. This was licensed in China since December 2011 for individuals >16 years, individuals involved in animal husbandry, students, women of childbearing age, food handlers, members of the armed forces and travelers. (WHO, The Weekly Epidemiological Record (WER), n.d.).

The Baculovirus expressed viral proteins of 62 kDa; 56 kDa and 53 kDa (genotype 1) was evaluated *in-vitro* and *in-vivo* (GlaxoSmithKline). The 56 kDa protein exhibited superior results and its protective efficacy was found to be 100% in two doses and 75% in single dose regimen. The vaccine provided protection against all genotypes (Shrestha et al., 2007). Though these vaccines are available, but none of these have been licensed in any country other than China. The need of other reliable, more effective vaccine is still on; one such vaccine candidate is glycoproteins of HEV.

Vaccination in animals

Presently, no vaccine is licensed for use in animals worldwide, other than HEV-239 which has shown some promising results. Other vaccine approaches have been tested by Backer et al using a modeling approach. Three effects were tested in the form of transmission rate, animal susceptibility and curtailing the infectious period. It was noted that when vaccination wasn't insufficient for elimination, it shortened the mean infectious period leading to lesser infectious animals at the age of slaughter and the reverse happened with reduced transmission rate. Vaccination at a later age can be used as an alternative strategy in a state of reduced susceptibility of animals (Backer et al., 2012). Another study by Satou et al. (2007) concluded that decreasing the force of infection at an early age might increase the risk of human transmission by elevating the age of infection and virus secretion. In such scenario, the counter measures will be required to be implemented more strictly (Satou and Nishiura, 2007; Salines et al., 2017) Moreover, the evaluation of effect of concomitant pathogens, interference with passive immunity, rearing practices and cost-benefit analysis is required before licensing any vaccine for use.

Control of risk factors at farm

Since swine and animals are the major reservoirs of HEV, maintenance of hygiene measures and good farming practices is the need of the hour. Co-infections of the swine and other animals should be dealt with caution since these can suppress the symptoms, leading to chronic infection of HEV and eventually raise the risk of organs harbouring the virus at time of slaughter (Walachowski et al., 2014; Salines et al., 2015).

A proper pyramidal structural organization of pig farms is mandatory to reduce the transmission between different farms and the production network directly during transport or indirectly via vectors (Dorjee et al., 2013). Study by Fortier et al showed presence of HEV in and around the pig production network, slaughterhouse yards, buildings and even in transport trucks (Nantel-Fortier et al., 2016).

Surveillance of farms, animals and animal products

HEV monitoring of food production chain is required at all levels of chain, starting from the rearing in farms, at slaughterhouse, at processing cabins till marketing of animal products. A French model has been formulated for the same that suggests stringent steps, which when implemented concurrently, can reduce the transmission of HEV via animal products to a minimum. These include qualification of HEV-free farms, real-time qualification of HEV-free batches at slaughterhouses and qualification of HEV-free liver

homogenates and other products. Opinion of ANSES concerning the "Request to assess the risks related to contamination of delicatessen meats products derived from raw pork liver with hepatitis E virus (HEV).

The National Viral Hepatitis Control Program (NVHCP)

This program was launched by Government of India on 8th July, 2018 (World Hepatitis Day) with the aim to achieve a significant level of reduction in infected population, to reduce the morbidity and mortality associated with the disease. July 8 is celebrated as the World Hepatitis Day in honor of Sir Bloomberg, on his birth date, who discovered Hepatitis B virus along with diagnostic test and vaccine for the same. The WHD organization started in 2011 and every year, it involves WHO, all governments and the civil society partners to organize and work for a newer theme. The theme for WHD, 2019 is 'invest in eliminating hepatitis' (WHO, Hepatitis E). The NVHCP is not an integrated initiative for prevention and control of Hepatitis B and C, but it also shields Hepatitis A and E. It's a comprehensive approach to reduce the risk, morbidity and mortality of Hepatitis A, B, C, D and E by means of prevention, timely diagnosis, appropriate management and improving the treatment outcomes. NVHCP is a part of integrated Sustainable Developmental Goals 3.3 that plans to control viral hepatitis by 2030.

Swach Bharat Abhiyan

Apart from NVHCP, one of the other pivotal programs launched by government is 'Swach Bharat Abhiyan'. It's a nation-wide campaign implemented by GOI on 2nd October, 2014 for years 2014-2019, to ensure adequate hygiene and sanitation. The same is to be attained by elimination of open defecation practices, manual scavenging and incorporation of scientific techniques for segregation and management of municipal waste. The most important component of any program remains the awareness amongst general public, specifically in context of feco-oral borne diseases, including Hepatitis A and E. People should be made aware of the risk factors, vehicles of transmission, prevention and management for the infection. Surveillance must be undertaken to ensure the same.

Adequate food and water supply

For proper water supply, the Water supply Department and Food safety and standards authority of India (FSSAI) should formulate strict safety plans based on risk stratification and multi-barrier approach. HEV is resistant to temperatures between 45-70°C and complete inactivation cannot be achieved below this temperature. The virus remains stable in water and blood. For inactivation of HEV, heating at temperature >70°C for 20 minutes (Barnaud et al., 2012), strict chlorination of water bodies with 1-2 mg/litre of free residual chlorine (Girones et al., 2014), ultraviolet treatment is required. The contribution of Government is also required at multiple levels to ensure food and water safety, implementation of vaccines and to ensure adequate sanitation. Apart from preventing the spread via feco-oral transmission, the zoonotic transmission can be prevented by imposing strict regulations in food and import industry. In view of the rising multi-national trade and commerce, the countries should impose stringent guidelines to ensure the food safety and import-export of animal and animal products.

Authors Contribution

MPS and KG were involved in conceptualization. PG and KG reviewed the literature and drafted the manuscript. MPS approved the final draft.

Conflict of interest

The authors have declared no conflict of interest.

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