# Hepatitis E: epidemiology and disease burden

A document prepared for

Strategic Advisory Group of Experts on Immunization (SAGE)

by the

Hepatitis E Vaccine Working Group

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## Introduction

Hepatitis E virus (HEV) is the leading cause of acute viral hepatitis in the developing world. The epidemiology and clinical presentation of HEV infection vary greatly by geographic location, based primarily on differences in HEV genotypes (Teshale, 2011; Kamar 2012, Aggarwal 2012). The overall burden of disease is the highest in parts of the world where clean drinking water is scarce, as fecal contamination of drinking water is a major route of transmission (Rein 2012). In these areas, the predominant HEV genotypes are genotypes 1 and 2. By contrast, in the developed world, where disease burden is lower, zoonotic transmission, mainly through consumption of uncooked or undercooked meat, is a well-recognized mode of transmission (Kamar, 2012), and HEV genotype 3 is the predominant genotype. HEV genotype 4 causes disease mainly in China and Taiwan and mode of transmission is mainly zoonotic. A few sporadic cases of hepatitis E caused by HEV genotype 4 have been reported in Europe. Other modes of transmission of HEV infection include transmission from pregnant mothers to their fetuses, and rarely through blood transfusion (Arankalle, 1999; Robson, 1992; Boxall, 2006; Mansuy, 2009; Hewitt, 2014). Two recombinant subunit vaccines have undergone human trials, and a few others are under development (Shrestha, 2007; Zhang 2010). One of the recombinant vaccines (Hecolin®) was licensed for use in China in 2012. This has led to an interest in the use of HEV vaccines as a public health tool to reduce the burden of hepatitis E. Strategies for vaccine use would need to take into account the varying epidemiologic patterns across different regions of the world and populations vulnerable to severe disease. This paper summarizes the current knowledge of burden of disease, disease outcome, and vulnerable groups, to inform policy for vaccination.

## Hepatitis E

Hepatitis E is a disease caused by infection with hepatitis E virus (HEV), an RNA virus that exists in both enveloped and non-enveloped forms and was first recognized in the early 1980s (Balayan, 1983). The virus is member of the *Hepeviridae* family. It has at least 4 known mammalian genotypes (named 1 to 4), which belong to a single serotype. The viral genome contains three non-overlapping open reading frames (ORF 1-3). Of these, ORF2 codes for the viral capsid protein which is the target of neutralizing antibodies against HEV (Bradley DW, 1995). To date, genotypes 1 and 2 have been found only in humans, whereas genotypes 3 and 4 have also been found in several mammalian species. The virus is relatively stable in the environment (Clemente-Cesares P, 2003), and is sensitive to heat, chlorination and ultraviolet light (Albinana-Gimenez, 2006; Girones, 2014).

Clinical features of hepatitis E are indistinguishable from acute hepatitis caused by other hepatotropic viruses. The incubation period ranges from 15–60 days, with a mean of 40 days (Viswanthan R, 1957). HEV-infected persons exhibit a wide clinical spectrum, ranging from asymptomatic infection through acute icteric hepatitis to fulminant hepatitis. The ratio of symptomatic to asymptomatic infection has not been reliably determined, and may vary with viral genotype and epidemiologic setting. Acute hepatitis E usually manifests with icterus, malaise, anorexia, fever, hepatomegaly, and occasionally pruritus. Studies in non-human primates have shown a relationship between the host's immunological response and degree of liver injury with the dose of viral inoculum (Tsarev SA, 1994). Immunosuppressed persons, in particular solid organ transplant recipients on immunosuppressive drugs, fail to clear the virus leading to chronic HEV infection (lasting >6 months); such cases have mostly had HEV genotype 3 infection, except for one child who had infection with genotype 4 HEV (Kamar, 2008; Kamar 2008; Dalton, 2009; Fujiwara, 2014; Geng, 2014). The laboratory abnormalities in acute hepatitis E are similar to those in acute viral hepatitis caused by other viruses. Laboratory

diagnosis of recent HEV infection is based on detection of HEV-specific IgM (IgA in some countries) antibodies or detection of HEV RNA in clinical samples (Khudyakov, 2013). Past HEV infection is characterized by specific IgG antibodies against ORF2, which may confer protection against reinfection; however, the protective titer and the duration of their persistence are uncertain. (Table 1 and table 2 summarize select virologic and epidemiologic characteristics of HEV infection.)

Certain population sub-groups are at a higer risk for severe disease following HEV infection. These include pregnant women, persons with pre-existing liver disease and persons with immunosuppression (Kamar, 2008; Teshale, 2010; Kumar 2007, Khuroo, 1981). During HEV epidemics, fulminant hepatitis occurs with a disproportionately high rate among pregnant women (Khuroo, Ramalingaswami, 1988; Tsega, 1993). During a recent outbreak in northern Uganda, a high mortality rate was recorded among children younger than 2 years (Teshale, 2010); however, the cause of death in these children was not verified. Overall case-fatality rates from hepatitis E have ranged from 0.1% to 4%; however, case-fatality rates among pregnant women are much higher, being 10%-25%.

Treatment for acute hepatitis E is generally supportive. Chronic hepatitis E in solid organ transplant (SOT) recipients on immunosuppressive treatment has been successfully treated by withdrawal or reduction of immunosuppressive drugs, administration of ribavirin, administration of interferon or a combination of these measures (Pischke, 2013; Kamar, 2012).

## Methods

General information on the agent, disease, and disease outcome was obtained from existing literature. Data on incidence and prevalence of HEV infection and disease in the general population were obtained from a systematic review on hepatitis E and seroprevalence published by the WHO in 2010 (Aggarwal, 2010), which included data published during the period 1980 to 2007, and through a search of the literature published subsequently using methods similar to those used for that previous review to identify articles published during the period 2009-2013 (Myrian Saboui, personal communication).

Articles were first screened at a title and abstract level to determine if they were eligible for inclusion. Eligible articles included original articles, studies reporting on outcomes of interest including HEV prevalence, incidence, mortality or HEV related outbreaks, studies representative of the general population, and case reports, case-series, cohorts, cross-sectional and case-control studies. Studies focusing on high-risk populations, reviews, animal studies, environmental studies, studies not reporting any HEV outcomes of interests listed above, and articles reporting data solely on travellers were excluded. Additionaly, studies not reporting numerators and denominators for HEV outcomes were excluded. Data was extracted from studies that met the inclusion criteria. For HEV seroprevalence, we grouped countries based on geographic proximity, economic development, and known HEV genotypes associated with locally acquired disease, all of which are important determinants of the epidemiology of hepatitis E.

## Hepatitis E disease burden and epidemiologic patterns

HEV is the leading cause of enterically-transmitted viral hepatitis. Hepatitis E as sporadic disease or outbreaks have occurred in at least sixty three countries; about half of these countries have reported large outbreaks (Aggarwal, 2010). There are also countries where no sporadic disease or outbreak is reported but have reported seroprevalence of HEV which suggests that

HEV infection may be endemic. A global burden of disease study estimated that HEV genotypes 1 and 2 account for approximately 20.1 million incident HEV infections, 3.4 million cases of symptomatic disease, 70,000 deaths, and 3,000 stillbirths (Rein, 2012).

In developing countries, where HEV genotype 1 and 2 are the cause of hepatitis E, the disease mainly affects young adults (15-39 years of age); conversely, in developed countries where HEV genotype 3 is the main cause of disease, median age of hepatitis E cases is 50 years. There is significant male gender preponderance among cases in developed countries; in the developing countries, this is less marked. HEV infection in persons with pre-existing chronic liver disease causes decompensation and death more often than in previously healthy persons. Table 2 summarizes the epidemiologic and clinical characteristics of hepatitis E by HEV genotype.

In developed countries, HEV infection in persons who receive immunosuppressive treatment following solid organ transplant is associated with risk of progression to chronic hepatitis E (Kamar, 2008). However, this phenomenon has not been observed in developing countries where infections are mainly caused by HEV genotypes 1 and 2. While hepatitis E causes high mortality among pregnant women in developing countries, there have been no reports of this phenomenon from developed countries. Hepatitis E is rare among children in developed countries; however, in developing countries, hepatitis E occurs in children and, according to a single report, mortality in very young children may be high (Sharapov, 2009). A study in India found that a prolonged HEV viremia (longer than 100 days) occurs among icteric and non-icteric adolescents (Arora, 1999). During waterborne outbreaks children may develop severe hepatitis E as a result of co-infection with hepatitis A virus (Tian, 2009).

Large waterborne outbreaks of hepatitis E occur in developing countries where contamination of drinking water occurs (Labrique 1999; Gurley, 2014); large outbreaks have not been reported from developed countries. However, a few small clusters of hepatitis E associated with foodborne transmission have occurred in Europe and Japan (Matsuda, 2004).

Whereas HEV genotype 1 and 2 exclusively infect humans, genotype 3 and 4 mainly infect animals with cross-species transmission to humans. The distribution of HEV genotype 2 has been focal with the majority of cases reported from Mexico, Nigeria, Namibia and a few other West African countries (Kim 2014). Despite the ubiquity of HEV genotype 3 in the swine population, to date clinically apparent human infections with genotype 3 had occurred almost exclusively in developed countries. There is one report of hepatitis E caused by genotype 3 from South Africa (Andersson, 2013). In recent years, HEV genotype 4 has been noted to widely circulate in animals in India and China, and has recently been found in several European countries; most human cases of genotype 4 occur in China and Taiwan. Despite high prevalence of HEV genotype 4 in pigs, hepatitis E caused by HEV genotype 4 in humans has not been reported from India (Aarankalle, 2002). However, a case of hepatitis E genotype 4 has been reported in a traveller returning from India (Rolfe, 2010). Figure 1 shows the global distribution of human HEV genotypes.

Epidemiologic and clinical characteristics of hepatitis E in different parts of the world depend in a large measure on the human HEV genotype circulating in a particular region and the water, sanitation and hygiene conditions, which in turn depend on socioeconomic circumstances. The population vulnerable to severe disease also depends on the geographic location where infection is acquired, which in turn depends on HEV genotype. For this reason, this paper presents the epidemiology and burden of disease caused by human genotypes associated with waterborne transmission (genotypes 1 and 2) and zoonotic transmission (genotypes 3 and 4) separately.

## Hepatitis E caused by genotype 1 and 2

HEV genotypes 1 and 2 are the most commonly identified causative agents of hepatitis E in developing countries. HEV genotype 1 and 2 cause large waterborne outbreaks in countries where water and sanitary conditions are below acceptable standards. HEV genotype 1 mainly affects young adults including women of reproductive age, with slight male preponderance. However, once infection occurs, the outcome significantly varies by pregnancy status, stage of pregnancy, and pre-existing liver disease. Among healthy persons HEV infection results in a spectrum of illness ranging from asymptomatic infection, to anicteric illness, to icteric hepatitis. There are estimates that the symptomatic to aymptomatic ratio ranges from 1:2 to 1:10 or even more and may be dependent on age at infection. Hepatitis E occurs among children and symptomatic disease increases with increasing age. The risk of symptomatic disease in children is lower compared to persons older than 15 years of age (Verghese 2014). Although waterborne HEV outbreaks result in large number of cases over a short period of time, the majority of hepatitis E cases in developing countries are a result of sporadic transmission. The risk factor for sporadic hepatitis E is less well understood, although water contamination may play a role. There is no evidence for sexual transmission of HEV (Mirazo, 2014). HEV is transmitted from mother to her unborn fetus and results in poor fetal outcomes (Khuroo, 2003). Transfusion transmission of HEV occurs and is well documented, however, the contribution of transfusion transmitted HEV to the overall disease burden is negligible (Khurro, 2004)

Waterborne hepatitis E outbreaks have been reported from at least thirty countries from three continents; all were caused by either HEV genotype 1 or 2. Large waterborne hepatitis E outbreaks frequently occur in the Indian subcontinent (Labrique, 1999). In recent years, outbreaks have been regularly identified in camps for displaced persons (refugees) in Africa, resulting in substantial morbidity and mortality. These outbreaks are caused by HEV genotype 1. Persons living in such camps may not have adequate access to clean water and sanitary conditions, leading to a risk of exposure to a higher infectious dose. There is evidence that other modes, including person-to-person transmission, contribute to the prolonged course of outbreaks particularly in displaced populations (Teshale, 2010). There is anecdotal evidence that hepatitis E occurs in health care workers from developed countries who respond to outbreaks in such situations.

The unique characteristic of hepatitis E caused by HEV genotypes 1 and 2 is high mortality among pregnant women. While in the general population the mortality from hepatitis E ranges from 0.1 to 4%, among women in the third trimester of pregnancy, mortality can reach up to 25%. A population-based verbal autopsy study in Bangladesh found that approximately 20% of maternal deaths were associated acute jaundice illness, many of which could be hepatitis E (Gurley 2012). Another group prone to develop severe morbidity following HEV infection are those with pre-existing chronic liver disease. Persons with advanced liver disease, including cirrhosis, can develop acute hepatic failure when super-infected with HEV (Monga, 2004). Chronic infections due to HEV genotypes 1 or 2 have not been described; there are no reports in solid organ transplant recipients or in HIV-infected persons (Naik, 2013; Feldt, 2013). Data on HEV genotype 1 infection and HIV is also scarce.

## Hepatitis E caused by genotypes 3 and 4

The clinical feature of hepatitis E caused by genotypes 3 and 4 is similar to that of acute viral hepatitis caused by other hepatotropic viruses including genotype 1 and 2 HEV. However, in immunocompetent persons, acute illness is often mild and infrequent. Hepatitis E caused by genotype 3 commonly affects older persons (median age 50 years) and predominantly male

(about two-third of cases) (Nelson, 2011). HEV genotype 4 disease is prevalent in China and Taiwan, however, isolated cases have occurred in some European countries. In recent years a notable epidemiologic shift has occurred in China from genotype 1 to genotype 4; the reason remains to be explained. Hepatitis E associated with HEV genotype 3 occurs in locations where genotype 1 or 2 are not endemic. In this area genotype 1 infections occur only as a result of importation by travellers to countries where this genotype is prevalent.

While the majority of hepatitis E caused by genotype 3 is mild and self-limited illness, in immunocompromised persons it can result in chronic hepatitis E (persistence of HEV infection for at least 6 months). The clinical manifestation and progression of chronic hepatitis E is variable with some cases progressing to significant fibrosis in a relatively short period of time. There is no data to show that infection with genotype 3 in pregnant women carries the same risk of high mortality as hepatitis E caused by genotype 1 or 2. Hepatitis E in persons with pre-existing liver disease is not common in developed countries, however, there is a report of severe liver failure as a result of HEV infection of an undiagnosed case of cirrhosis (Crossan, 2014).

There is limited data on the clinical presentation of disease caused by HEV genotype 4. It is believed that hepatitis E caused by genotype 4 closely resembles, but is milder than disease caused by HEV genotypes 1 or 2. Hepatitis E with genotype 4 has occurred in Germany (Wichmann O, 2008), northern France (Tesse S, 2012) and southern France (Colson, 2012) as well as Italy (Garbuglia et al., 2013). Chronic hepatitis E following HEV genotype 4 infection is uncommon, however, there is a recent report of chronic infection in a child with acute lymphoblastic leukaemia (Geng 2014).

In the 1980s hepatitis E in developed countries was associated with travel to countries where HEV genotype 1 infections are endemic. Authochthonous hepatitis E, caused by genotype 3 HEV, has been increasingly reported in developed countries over the last decade (Kamar, 2005; Dalton, 2007; Amon 2007; Tohme 2010). Hepatitis E genotype 3 disease occurs as sporadic cases except for a few small clusters reported as a result of consumption of undercooked game meat and in one instance consumption of shellfish on a cruise ship (Said, 2009). Transfusion transmitted hepatitis E is documented in a recent retrospective study which also found that one in 2848 blood units collected in southeast England had HEV RNA (Hewitt, 2014). The demographic characteristics of acute cases remains striking with the majority of infections occuring in older males. Disease often occurs among solid organ transplant (SOT) recipients (Dalton, 2008; Kamar, 2008). One study found that the incidence of hepatitis E among immunosuppressed SOT recipients in southern France is 3.2 per 100 person-years of follow-up (Abravnel, 2011).

The unique characteristic of HEV genotype 3 infection is chronicity in persons who receive immunosuppressive therapy following SOT and persons with severe immunodeficiency from other causes. In one small study, about two thirds of SOT patients with acute hepatitis E progressed to chronic hepatitis E. The course of chronic hepatitis E is variable and the differential diagnosis can be complex including: subacute rejection of transplanted organ, autoimmune hepatitis, and CLD of unknown etiology. The diagnosis of acute and chronic hepatitis E in immunosuppressed persons may be challenging due to the inability of such persons to mount an immune response. The mortality from chronic hepatitis E can be high. Small case series have shown that treatment, with reduction of the dose of immunosuppression therapy and/or ribavirin, can result in a high rate of sustained virologic response. Although HIV infected patients are at high risk for HEV infection, the number of acute infections is low and very few chronic cases have been reported (Robbins, 2014; Fujiwara, 2014). There is scarcity of data

regarding hepatitis E genotype 3 infections and disease in children, pregnant women, persons with pre-existing liver disease, and otherwise healthy persons.

## Sero-epidemiology of HEV infection

Surveillance for hepatitis E disease is very limited and information on disease occurrence and distribution are available only from a few European countries, and most of the data from other parts of the world are limited to reports of outbreaks and case series. By contrast, much more information is available on the seroprevalence of antibodies to HEV, a marker of previous exposure to HEV. However, the interpretation of seroprevalence data is immensely challenging for several reasons.These challenges include the lack of comparability of results from the different assays, high seroprevalence in populations where disease is rare or never reported, the presence of multiple genotypes with different disease patterns and inability of serological tests to distinguish between genotypes, and lack of data for reliable mathematical modelling to determine disease burden from seroprevalence. Furthermore, the majority of seroprevalence studies do not involve a representative sample of any population making it difficult to infer prevalence and trends to the population.

Poor laboratory assay performance is the major challenge in interpreting seroprevalence study results. Many studies have shown poor concordance between commercial IgG HEV assays; some reports showed significant batch to batch variability of IgG anti HEV assays (Abravenel, 2013; Drobeniuc, 2010). The lack of a gold standard test to determine the performance of IgG assays is another challenge. Recent studies comparing the diagnostic accuracy of assays commonly used in Europe and the US for the detection of antibodies against HEV have yielded a significant discrepancy in performance (Drobenuic, 2010; Abravanel, 2013).

The protective efficacy and the long-term persistence of IgG antibodies against HEV following natural infection has not been clearly determined. In Kashmir, researchers conducted serological follow up of 320 persons who were known to have hepatitis E during the 1978 HEV outbreak. In 50% of the cases there was detectable IgG anti-HEV 14 years after infection (Khuroo, 2010). In another short term follow-up study, researchers found that 100% of persons maintained evidence of past infection 3 years later (Chadha, 1999). However, the implication of the persistence of antibodies is not clear. The fact that the prevalence of anti-HEV in the population does not reach the very high levels observed with hepatitis A and that attack rates are higher among young to middle aged adults suggests that infections may not confer lifetime protection or infections usually occur later in life. This intriguing finding is complicated by the recurrence of outbreaks in countries where past epidemics in the population would have resulted in immunity to prevent future outbreaks. The duration of anti-HEV IgG and the protective efficacy of naturally acquired antibodies are important because of the implications for long term vaccine efficacy. In spite of all these challenges, seroprevalence data provides a general picture as to whether HEV infection is endemic in a country, if population has a disproportionately high rate of infection (e.g., persons with animal contact), and for estimation of population level susceptibility to HEV infection.

### Seroprevalence in developing countries

There are several studies that have examined the prevalence of antibodies against HEV in different population groups. However, the sero-epidemiology of hepatitis E in developing countries is not uniform and often does not follow the pattern of clinical disease. Many studies have consistently observed that the prevalence of antibodies against HEV is much lower than the

prevalence of anti-HAV. In a study in Pune, India, researchers found that the prevalence of anti-HAV increased rapidly and reached a peak of around 90% by age 10 years. However, the prevalence of anti-HEV remained low until age 15 years at which point it slightly increased and peaked at around only 50% (Arankalle, 1995). There is no clear explanation for the relatively low prevalence of anti-HEV but it may be due to loss of serological evidence following natural infection (Mathur, 2001). On the contrary, serological data from Egypt have shown that anti-HEV could reach 100% with a very high prevalence even at a very young age (Fix, 2000). Table 1 summarizes salient features of HEV infections and recent seroprevalence estimates.

## Seroprevalence in developed countries

The discordance between seroprevalence and incidence of hepatitis E is even more dramatic in developed countries. Despite the high seroprevalence in many European countries and the US, the occurrence of disease is generally low. As demonstrated by many studies, the anti-HEV prevalence in the general population is high and a number of studies have shown that the anti-HEV prevalence among persons with close work contacts with pigs is even higher. The HEV seroprevalence in most study populations is higer among older persons, generally increasing with age, but not different by gender (Drobeniuc, Wenzel, 2014; Faber, 2012; Christensen, 2008; Mast, 2000; Meng , 2002; Kuniholm, 2009; Teshale 2014). In the US, in a nationally representative sample tested using the same assay, the HEV seroprevalence declined significantly during the period 1988-94 to 2009-10 from 21% to 10% (Teshale 2014). There is no clear explanation for this observed decline but a similar trend had been documented in Germany and Denmark (Teshale, 2014, Christensen, 2008, Wenzel 2014). Table 1 summarizes salient features of HEV infection and recent seroprevalence estimates.

### Special populations

Hepatitis E manifests with variable severity both in areas where the prevalent cause of disease is genotype 1, 2, and 4 or genotype 3. Infection with HEV genotype 1 is associated with fulminant hepatitis and death in pregnant women and persons with pre-existing CLD. The extent to which such severe disease occurs with genotype 2 and 4 is not very well known. Due to the nature of the living conditions including over crowding and poor hygiene, displaced persons and refugees experience the highest attack rate whenever outbreaks occur. However, such outbreaks are not observed in regions where disease is mainly caused by genotype 3 virus; in this region HEV causes severe disease including chronic hepatitis E in immunocompromised persons. Travellers from developed countries to developing countries also belong to this special population group because of the increased risk of exposure to the virus due to environmental factors.

## Pregnant women

HEV infection in pregnant women is typically severe during the third trimester of pregnancy (Kumar, 2004; Khuroo, 2003). Mortality rates among pregnant women in the third trimester range from 10%-25%. To date, the exact mechanism for the disproportionately high mortality among pregnant women is unknown (Naveneethan, 2008). The causes of death include fulminant liver failure and obstetric complications including excessive bleeding (Hussaini, 1997; Tsega, 1993). This HEV-associated high mortality occurs in countries where disease is commonly caused by HEV genotype 1. Similar high mortality in pregnant women has not been reported from western countries. A case of genotype 3 hepatitis E was reported in a 26 weeks pregnant woman from Germany who did not develop fulminant hepatitis and had a normal foetal outcome (Tabatabi, 2014). HEV genotype 1 infection during pregnancy is associated with poor foetal outcomes including abortion, premature delivery, and stillbirths.

## Persons with chronic liver disease

Persons with pre-existing chronic liver disease represent another group in developing countries prone to develop severe morbidity following HEV infection. Persons with advanced liver disease, including cirrhosis, can develop acute hepatic failure when super-infected with HEV (Monga, 2004). The same phenomenon has been observed with hepatitis A super-infection of persons with chronic liver disease and was the basis for administration of hepatitis A vaccination to persons with chronic liver disease (MMWR, 1999). The data from developed countries is limited; there is a report of severe liver failure as a result of HEV infection of an undiagnosed case of cirrhosis (Crossan, 2014). Hepatitis E was found to be the culprit in a number of studies where drug induced liver injury was erroneously diagnosed (Dalton, 2007; Davern, 2011). The burden of HEV-induced acute liver failure in patients with pre-existing chronic liver disease is unknown.

## Persons with immunosuppression

The unique characteristics of HEV genotype 3 infection is chronicity (persistence of HEV infection for at least 6 months) in persons who receive immunosuppressive therapy following SOT or persons with severe immunodeficiency from other causes. In solid organ transplant recipients, acute hepatitis E can progress to chronicity in up to 60% of infected patients. (Kamar, 2011). Risk factors independently associated with chronic infection include heavy immunosuppression, reflected by a shorter time from transplantation to infection, lower CD2, CD3, CD4 and total lymphocyte counts as well as being on a tacrolimus versus a cyclosporine regimen (Halleux, 2012). In one small study, about two third of SOT patients with acute hepatitis E progressed to chronic hepatitis E (Krain, 2013). Solid organ transplant recipients are advised to avoid raw or undercooked pork and seafood to prevent HEV infection. A few small case series have shown that treatment with reduction of dose of immunosuppression therapy and/or ribavirin can result in a high rate of sustained virologic response. Although HIV infected patients are at risk for HEV infection, the number of acute infections is low and very few chronic cases were found thus far (Robbins, 2014; Fujiwara, 2014). A study of kidney transplant recipients that looked for chronic hepatitis E in India did not reveal chronic infection (Naik, 2013).

## International travelers

Prior to the documentation of authochthonous cases of hepatitis E in developed countries, hepatitis E was mainly a disease imported back by international travelers. The first serologically confirmed travel-associated cases of hepatitis E in the US were reported as early as 1985 (DeCock, 1985). Surveillance data from England and Wales showed that travel related hepatitis E contributes to 28% of reported cases. In most countries there is no reporting of hepatitis E whether it is authochthonous or travel associated. It is therefore difficult to determine the magnitude of imported hepatitis E in western countries and the risk of infection among international travelers. As the number of authochthonous hepatitis E increased, the attention shifted from travel associated genotype 1 or 2 disease to genotype 3 disease which is believed to be zoonotically transmitted in such countries. The epidemiologic and clinical characteristic of travel associated hepatitis E cases in developed countries is different from authochthonous cases. Hepatitis E has occurred among international health workers providing assistance during hepatitis E outbreaks.

## Internally-displaced populations

Recent large outbreaks have occurred among displaced persons in Sudan, Chad, and Uganda (Kim, 2014; Teshale, 2010; MMWR, 2013; CID, 2004). The first such outbreak documented in Africa occurred among Angolan refugees in Namibia in 1983. A recent outbreak in South Sudan shares similar epidemiologic characteristics with other HEV outbreaks in such settings. Similar to a 2007 outbreak in northern Uganda, the Sudanese outbreak started during the rainy season with high attack rates (7.4%) among camp residents and high mortality among pregnant women (10.4%) (MMWR, 2013). A serosurvey conducted during this outbreak showed that more than half of residents had no evidence of recent or past HEV infection, suggesting that these persons remained uninfected and were still susceptible to HEV infection 3 months after the implementation of control measures. Like the Ugandan outbreak, the South Sudanese outbreak took a protracted course of well over a year, demonstrating that prevention and control efforts in such outbreaks is challenging.

Table 1: Salient features of HEV infection prevalence and hepatitis E by geographic region.

| *Region* | *Country or sub-region* | *Salient features* |
|---|---|---|
| North America, Europe, Japan, Australia | USA, Canada | Mainly genotype 3 disease<br>Seroprevalence ~ 15-25%<br>No outbreaks<br>Chronic infection among immunosuppressed |
| | Europe | Mainly genotype 3 disease<br>Seroprevalence 4-52%<br>Sporadic disease more common<br>Frequent progression to chronic hepatitis E in organ transplant (OT) recipients<br>Mortality in OT recipients 4-9%<br>Overall disease burden is low |
| | Japan | Mainly genotype 3 disease<br>Seroprevalence 2-20%<br>Few food-borne outbreaks |
| Latin America and the Caribbean | Mexico, Brazil, Venezuela, Uraguay, Cuba | All genotypes except genotype 4 cause disease<br>Seroprevalence 1%-16%<br>First recorded HEV genotype 2 outbreak in Mexico |
| Northern Africa and Middle East | Egypt, Libya, Morocco, Iraq, Iran | Mainly genotype 1 disease<br>Seroprevalence 1%-58%<br>Infrequent disease among pregnant women<br>Outbreaks reported in Egypt, Libya, Iraq, Morocco |
| Sub-Saharan Africa | Uganda, South Sudan, Kenya | Predominantly genotype 1<br>Waterborne outbreaks common<br>Outbreaks among displaced persons<br>High mortality among pregnant women |
| South Asia | India, Pakistan, Bangladesh, Nepal, Bhutan, Sri Lanka, | Genotype 1 disease<br>Seroprevalence 10-40%<br>High mortality among pregnant women and |

| | | |
|---|---|---|
| | Afghanistan | persons with liver disease<br>High stillbirth in hepatitis E (35-90%)<br>Waterborne outbreaks common<br>No chronic infection reported |
| Central and Eastern Asia and Caucasus | | Predominantly genotype 1 disease<br>Seroprevalence 0.6-40%<br>Occasional outbreaks |
| South-eastern Asia and Oceania | Southeast Asia, New Caledonia | Genotype 1, 3, and 4 disease<br>Seroprevalence 0-12%<br>Waterborne outbreak reported from Indonesia, Myanmar and Vietnam<br>Genotype 3 disease |

**Figure 1. The global distribution of HEV genotypes. (**The figure is reproduced with the permission of the Deutsches Ärzteblatt International (Pischke et al., 2014)

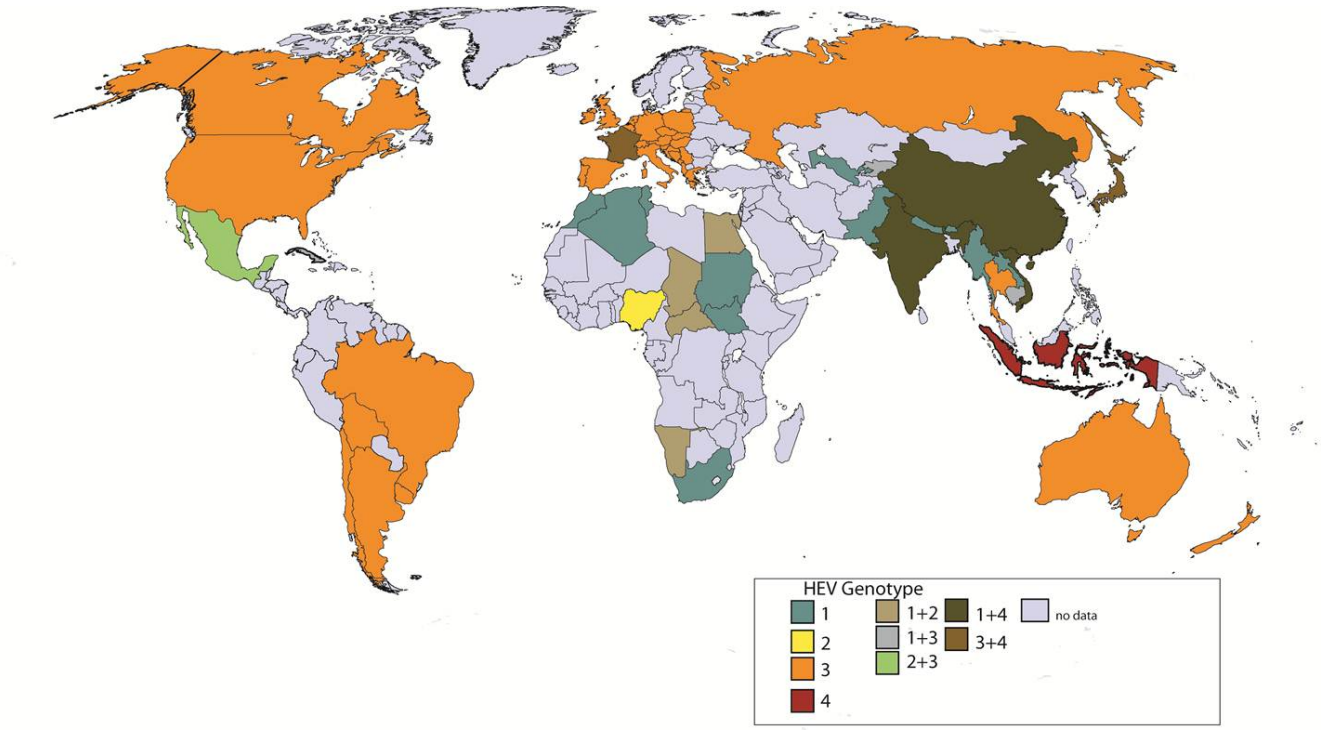

Table 2: Select characteristics of human (genotype 1 and 2) and zoonotic (genotype 3 and 4) HEV

| Characteristics | Genotype 1 | Genotype 2 | Genotype 3 | Genotype 4 |
|---|---|---|---|---|
| Distribution of virus: humans | Asia, Africa and the Middle East | Mexico, West Africa | North America, Europe, Latin America, Japan | China, Taiwan, South-East Asia |
| Distribution of virus: animals | Not identified | Not identified | Widespread, reported in all continents | China, Taiwan, India, with a few recent reports from Europe and North America |
| Inter-species transmission | Only human-to-human; no inter-species transmission | Only human-to-human; no inter-species transmission | Animal-to-human (pigs, wild boar and deer) | Animal to human (pigs, wild boar) |
| Water-borne transmission | Yes, frequent (from human feces) | Yes, frequent (from human feces) | No | No |
| Food-borne transmission | Not recognized | Not recognized | Yes (from contaminated animal meat) | Yes (from contaminated animal meat) |
| Zoonotic transmission | No | No | Yes | Yes |
| Occurrence of epidemics | Yes | Yes, but fewer, focal and small-scale | No, except for a few small food-borne (pig meat) outbreaks | Not reported |
| Relation of attack rate with age | Most common in young adults (15-44 years) | Most common in young adults (15-44 years) | Mostly middle age and older (>50 years) | Limited data |
| Mortality among pregnant women | High | Not reported | Not reported | Not reported |
| Chronicity in immune-compromised persons | No | No | Yes | Yes |

## Conclusion

Every year an estimated 20 million HEV infections occur globally resulting in more than 3 million cases and 70,000 deaths (Rein, 2012). Most cases occur in developing countries where occasional large scale outbreaks also occur. Hepatitis E case fatality is highest among pregnant women, which can be as high as 20% when disease occurs in the third trimester of pregnancy (WHO). Hepatitis E is also known to disproportionately affect certain population groups (persons with pre-existing chronic liver disease, immunosuppressed persons, and refugees) for which targeted prevention may be required. International travellers and healthcare workers in outbreak settings may be at a higher risk of exposure to infection if they do not follow the appropriate precautions to prevent foodborne or waterborne transmission. There is anecdotal evidence of the occurrences of hepatitis E among international health care workers during HEV outbreaks, however, there is no evidence that health care workers are at increased risk of HEV infection as long as they adhere to standard waterborne infection prevention measures.

Data regarding burden of hepatitis E is limited owing to lack of hepatitis E surveillance in most countries; estimates of annual infections and cases are based on a modelling study (Rein, 2012). Most studies of burden are based on seroprevalence surveys of populations or specific groups without information about disease. The lack of knowledge of the protective immunity of natural infection undermines the findings of the seroprevalence study. There is no acceptable estimate of the symptomatic to asymptomatic ratio of hepatitis E in a population. Therefore, the seroprevalence estimates can barely shed light on the possible incidence of disease in that community. The diagnosis of acute hepatitis E or past infection with HEV is challenging due to the lack of well validated sensitive and specific assays (Drobeniuc, 2010). The lack of valid laboratory assays also affects interpretation of seroprevalence studies and head to head comparison of such results. The lack of surveillance data remains an important obstacle to prevention of hepatitis E worldwide. Efforts toward collection of data in particular in the area of HEV transmission and propagation in in outbreak setting, disease incidence and burden, understanding characteristics of vulnerable populations, and in the area of vaccine safety, immunogenicity and efficacy in vulnerable populations should be a priority. However, even with these limitations, some conclusions can be made about groups at highest risk for disease or death.

Hepatitis E (a vaccine preventable disease) is also emerging as a leading cause of acute viral hepatitis, maternal death and wastage of pregnancy. The burden of the infrequent, but serious authochthonous hepatitis E in Europe, is substantial with disease affecting persons on immunosuppressive treatment for organ transplant and resulting in chronic infection with death in up to 10% of affected patients (Kamar, 2012). Hepatitis E outbreaks are frequent in Asia and Africa and result in high morbidity and mortality particularly when occurring in displaced persons camps (Teshale, 2010; MMWR, 2013). Current understanding of HEV transmission indicates that effective prevention and control depend on ensuring a safe drinking water supply, adequate sanitation, and proper personal and environmental hygiene. However, in settings where hepatitis E outbreaks occur, it is difficult to mount adequate prevention measures in a timely manner mainly due to rapid transmission of HEV and the long incubation period.

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