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Hepatitis E Virus in Human: The Current Status in Europe

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Abstract

Background: An increasing number of human hepatitis E virus (HEV) infections have been described in the last decade in Europe. In this review, we described the serological data concerning the general population and particular group of patients (i.e immunocompromised patients, pig farmers in different European countries). HEV genotype distribution and anti-HEV therapies are described in the second part of the review.

Results: HEV antibody prevalence ranged from 1.3% (blood donors in Italy) to 21.5% (blood donors in Serbia). Only one paper described a seroprevalence of 52% found in blood donors of Toulouse; in this study an assay WANTAI (Wantai Biological Pharmacy, PE2-assay; Beiying, China) with high sensitivity was used. A study carried out in the Netherlands showed that pig veterinarians had a higher anti-HEV IgG prevalence than non-pig veterinarians (11% vs 6%), confirming that pigs represent an important source of HEV infection. Genotypes 3c, 3e, 3f are the main genotypes diffused in Europe, however, sporadic cases of autochthonous genotype 4 have been described in several countries (Spain, France, and Italy). Several cases of fulminant hepatitis E, all related to genotype 3, have been described.

Conclusion: The data reported in this review suggests that hepatitis E virus a wide spread infection, even in industrialized countries. The serum prevalence varies greatly, depending on the geographic areas considered and the population studied. Moreover, the seroprevalence may be due to the diagnostic assay used for the detection of antibodies.

Keywords: HEV; Genotype; Antibodies

Introduction

A recent study estimated that the global burden of HEV infection is 3.4 million symptomatic cases of hepatitis E each year, with 70,000 deaths and 3000 stillbirths [1]. This virus represents more than 50% of acute hepatitis in India, about 25% of acute hepatitis infection in Africa, and 15-20% in Eastern-Oriental countries [2]. In these countries the greatest HEV outbreak happened in the last 50 years. In industrialized countries the scenario is different. Several sporadic cases of hepatitis E infection has been described in United States, Australia, United kingdom (UK) and other European countries [3]. In a study carried out in France by the "Centre national de reference des enterotransmissible hepatitis" (CNR) the number of HEV autochthonous cases rose 5 times from 2002 to 2007 [3]. In this review we would like to provide an overview of human HEV diffusion in Europe, so we omit the HEV infection in the other mammals. We also will not describe the avian HEV, since this virus differs genetically from mammalian HEV strains, and it has never been recovered in human or in other mammals. In the first part of the review we describe the serological data concerning HEV in European countries, while in the second part we describe HEV chronic infection in immune depressed patients and the therapies used in their care.

HEV genotype 1 is the cause of severe clinical fulminant hepatic failure in pregnant women and is associated with high mortality, particularly in the third trimester and in obstetric complications such as eclampsia or hemorrhage [4,5].

Discovery of HEV

Hepatitis E virus represents a major cause of enterically transmitted hepatitis worldwild. This virus was discovered by immune electron microscopy in 1983 by Balayan [6]. Balayan was charged to investigate a non-A, non-B hepatitis outbreak occurred in a Soviet military camp located in Afghanistan. To assess if the causative agent of this outbreak could be transmitted from human to human Dr. Balayan himself ingested pooled stool extracts of 9 patients from Afghan epidemic hepatitis. He developed typical symptoms of acute hepatitis 36 days after stool extract ingestion. 27-30 nm spherical viral particles were identified in stool samples collected on day 28, 43, 44, 45 after inoculation. This was the first description of the virions. Shortly thereafter this virus was identified in serum derived from patients involved in a large epidemic of water-borne hepatitis in New Delhi (India) during 1955-1956, initially defined as non-A non-B epidemic hepatitis [7]. Subsequently even the stored sera from an outbreak occurring in Kashmir from 1978 to 1979 years resulted HEV positive. The virus was named E virus because of its enteric route of transmission and its ability to cause epidemics.

The HEV virus

HEV is a single-stranded, positive-sense RNA molecule of approximately 7.3kb in size and capped. He belongs to the genus *Hepevirus*, the only member of the family Hepeviridae [8]. Two main species of the virus are recognized: mammalian HEV, a virus that causes acute hepatitis in human beings (genotypes 1 and 2) and which could have many mammalian species as reservoir especially pigs, wild

boars, deer, rabbit (genotypes 3 and 4) as well as other mammals (rabbit, cow, bat). The other is an avian HEV (genotype 5), which causes severe liver and spleen disease in chickens, and is known to infect other birds such as Turkey [9]. Its capside is icosahedral in 27-34 nm in diameter and does not possess an envelope.

The viral genome includes 2 short non-coding at 5'UTR and 3'UTR with a poly(A) tail [10]. They contain cis-acting elements which have important roles in HEV replication and transcription [11].

The coding region consists of three discontinuous and partially open reading frame (ORF1-3).

ORF-1 encodes non-structural proteins involved in replication and processing, including an RNA helicase, an RNA-dependent RNA polymerase, a methiltransferase, and a cystein protease [4]. It is well characterized in Burmese strains and it extends approximately 5 kb from 5' end. ORF-2 consists of approximately 1,980 nt and encodes for capsid protein. It occupies the 3' end of coding region. ORF-3 is the smallest ORF with a maximal coding capacity of 372 nt and overlaps ORF1 by one nucleotide at the 5' and with a 3' end that overlaps ORF2 by 331 nt. ORF3 encodes a small immunogenic protein with a maximum length of 123 aminoacids. The ORF3 functions are uncertain. It has been claimed the ORF3 protein is not necessary for replication and virus assembly, while it probably does have a role in the cellular environment regulation [12].

HEV Genotypes

Four different genotypes have been described to infect human beings. A fifth (genotype 5) has been detected only in birds and it has low genetic identity with other genotypes (<50%). Genotype 1 HEV has been isolated from a human case for the first time in 1980 by Balayan [6]. This genotype is endemic in Africa and Asia, but it is frequently isolated from hepatitis E cases among travellers to these regions from non-endemic areas. The strains belong to this genotype have a>90% sequence homology. This genotype was the cause of a large epidemic waterborne hepatitis occurring in New Delhi, India in 1955 [7]. Five subtypes 1 (a,b,c,d,e) have been recognized with different prevalence in different geographical areas. Genotype 1a is the most frequent subtype 1. It is diffused in many geographical areas of Asia (Nepal, Pakistan, Bangladesh, Vietnam, India). Subtype 1b has been predominantly identified in China, and it is diffused in China, in Pakistan [13], Bangladesh [14], but also in Caribbean countries such as Haiti [15], and Cuba [16]. Subtype 1c is prevalently detected in China [17] and in India [18], but some cases are described also in Kyrgyzstan [19]. Subtypes 1d and 1e have been exclusively described in Africa [20,21]. Only a Spanish patient with HEV infection harbored genotype 1e indicating moreover that this case represented an imported infection given that the patient had visited Ethiopia a few weeks before the symptom appearance [22].

The strains belonging to genotype 2 are exclusively human strains. We know two subtypes: subtype 2a, isolated in Mexico and considered the prototype strain [23] and subtype 2b diffused in several African countries [24] mainly diffused in Nigeria and Chad. These isolates have nucleotide homology of only 75% with genotypes 1 isolates [25,21].

Genotype 3 was first identified in human cases of locally acquired hepatitis E in the USA [26,27]. Genotype 3 is diffused worldwide. In Europe it represents the most frequently detected genotype.

The subtype 3a has been described in the United States [28], in Japan [29], Korea [30] and Holland [31]. Genotype 3b has been isolated in Japan, China, and Canada, while subtype 3c is mainly described in France [32,33], Germany [34], Holland [31] and Italy [35]. Genotype 3d is diffused in Taiwan and United States [36]. Subtype 3e is considered an autochthonous European strain. It is frequently described in the United Kingdom [37] Holland [31], Italy [38,39], Greece [40] and in Spain [41]. In addition, strains from wild boars were isolated in Japan and Thailand [42,43]. Genotype 3f has been described in most of the European countries (Spain, France, United Kingdom, Greece, the Netherlands, Italy) [35], but also in Japan [25], in Thailand [44] and New Caledonia [45]. In Kirgyzstan 3g subtypes have been isolated [46]. Subtype 3h has been described in Italy [47,48], Uruguay [49] and new Zealand [50]. Subtype 3i has been described in Latin America [49,51,52] but also in Europe: Austria [53], Italy [39], France [54]. Subtype 3j has been described on different continents: Canada [55], Australia and Mexico [56].

Genotype 4 is prevalently diffused in China, Taiwan, Vietnam, and Japan, where we could find subtype 4a, 4b, 4c, 4d. However subtype 4b had been described in Belgium (pig isolate), subtype 4d is mainly diffused in China, but also found in Italy both in human and swine [57,58]. Subtype 4c has been described in India, 4f in Japan and Vietnam and an imported case had been described in Germany [59]. The subtype 4g has been described only in China [60]. Genotype 3 and 4 strains have been isolated in several animals such as pigs, cows, wild boars, and deer, all representing the main reservoirs of HEV genotype 3-4 viruses.

Four means of transmission are reported

- Fecal-oral transmission due principally to drinking water supply (1-2 genotype),
- Food borne transmission (3-4 genotype),
- Transfusion of infected blood products,
- Vertical transmission (1-4 genotype). Not relevant is person-to-person transmission.

In endemic areas drinking contaminated water is the mains of transmission; instead the sporadic cases of HEV infection are related to contaminated food consumption.

Clinical Features

Illness caused by HEV is difficult to distinguish from hepatitis A virus (HAV) but patients with HEV tend to be older and are more likely to be men than those observed in hepatitis A cases [61]. Acute HEV infection was defined as a resolution within the first 6 months after diagnosis. Chronic HEV infection was defined as the persistence of HEV-RNA detection for longer than 6 months which might lead to cirrhosis (in these patients) [62]. The initial symptoms of acute hepatitis E are typically unspecific and include: flu-like myalgia, arthralgia, weakness and emesis. Some patients present fever, vomiting, nausea, anorexia, abdominal pain and jaundice accompanied by elevated bilirubin and liver transaminase, alkaline phosphatase and glutamyl transferase activities.

In most instances, acute HEV 3 and HEV 4 is a self-limiting illness and the patient recovers without sequel; however case fatality rates in the general population can vary from 0.1 to 3% [4]. Symptomatic infection may be misdiagnosed. For example, HEV can be mistaken for drug-induced liver injury. A study in UK showed that 6 (13%) of 47 patients with "criterion-referenced" drug-induced liver injury had been incorrectly diagnosed, and in fact actually had acute HEV 3 infection

[63]. Furthermore, most HEV infections are asymptomatic considering its high seroprevalence in some developed countries, such as the UK, Germany and France and relative rarity of clinically diagnosed infections. This is supported by data from an outbreak of 33 cases of HEV genotype 3 on a cruise group which 67% of patients were asymptomatic [64].

As with other viral hepatitis, extra-hepatic manifestations can occur and the spectrum of clinical disorders is still emerging. In fact neurological disorders have been found to be associated with locally acquired acute and chronic HEV infection in patients two hospitals in the UK and France [65,66]. Among 126 patients observed in hospital with acute HEV hepatitis between 2004-2009, 5.5% developed neurological complications [65]. Furthermore, Guillain-Barrè syndrome is frequently reported. Tse et al. described a case report with Guillan-Barrè syndrome associated with acute hepatitis E infection [67].

Chronic infections are observed among transplant patients. Many factors are associated with failure of immune-suppressed transplant recipients to clear HEV after acute infection. These factors include the degree of immune-suppression, the time between the last episode of acute rejection and HEV infection, time since transplantation, low leukocyte level, low total-lymphocyte count, and low T-cell count [68].

Seroprevalence in the General Population and Risk Groups for HEV Infection

In developed countries, hepatitis E virus (HEV) cases usually occur sporadically and related to genotype 3 and it is generally described in men more frequently than in women and in younger patients [59,69-75] and in travellers [76,77]. In Europe acute HEV infection is diagnosed in 5-15% of patients with acute hepatitis for whom hepatitis A, B and C had been ruled out [63,78,79]. Most patients with acute E hepatitis virus are travellers in endemic areas, or they are undergone transfusions, they are commonly consumers of pig meat or they drink contaminated water. During last decade seroprevalence of anti-HEV immunoglobulin G (IgG) is increasing in European countries and shows significant variability among different geographical areas. The main studies have been carried out on the general population and on blood donors and the high prevalence of HEV-RNA positive infection and of anti-HEV antibody prevalence in blood donors between 1-52% suggests that HEV is responsible for several cases of subclinical HEV infection in Europe [80-84].

In a seroprevalence study carried out by Norder antibodies against hepatitis E (anti-HEV) were found in 248 Swedish and Danish subjects between 1993-2007, 163 harboured only IgG (109/163 were males) and 85 tested positive for immunoglobulin M (IgM) and IgG together (57/85 were males); the mean age were 43.5 and 31.5 years, respectively. HEV-RNA was found in 65 patients [85]. In second seroprevalence study, carried out in Sweden, revealed that HEV IgG prevalence was 13% (15/115) and 9.3% (10/108) in pig farmers and control subjects respectively [86].

In South-West England a study included 500 blood donors to trace the evolution the HEV antibodies prevalence infections between 2000 and 2006 the anti-HEV IgG prevalence was 16% [87]. Recently HEV seroprevalence IgG and IgM were determined also in 1559 Scottish blood donors and 4.7% (73/1559) were IgG positive, none tested positive for IgM [88].

In Finland, in a study carried out on 97 patients with diagnosed acute unexplained non-A, non-C hepatitis between 2000 and 2008, of all serum samples, 27.6% were positive for anti-HEV antibodies; 11/97 (11.3%) were found positive for anti-HEV IgG only, indicating a past infection, but 11 of them (11.3%) were HEV-RNA and/or IgM positive. All HEV strains identified belonged to genotype 1 [76].

In Denmark different anti-HEV IgG seroprevalences were found among farmers, who worked with pig 144/286 (50.4%) and blood donors 94/456 (20.6%) [89]. A study carried out in a population of Danish prisoners and drugs users showed an anti-HEV IgG seroprevalence of 16.9% using an in-house assay. The assay used to test anti-HEV IgG was based on ORF2 of the Pakistani HEV strain SAR-55 expressed in baculovirus. The seroprevalence dropped to 4.1% with the Abbott commercial assay [90]. In 2011 in Belgium the HEV IgG seroprevalence was 14% from a total of 100 patients presenting at the gynecological or orthopedic clinics [91]. HEV specific antibodies were determined among Austrian adults, 407 professional soldiers and 590 civilians, (age range 18-59 years, 980 males and 17 females).The overall sero-positivity for HEV antibodies was 14.3% and increased with age. In fact among individuals aged up to 19 years, the seroprevalence was 8.1% and increased to a seroprevalence rate of 57.5% among individuals aged 50-60 years [92].

In Germany several HEV seroprevalences had been reported. A study analyzing prevalence in an adult population from 18-79 years old between 2008-2011 showed a IgG anti HEV positive of 16.8% and the prevalence increased with age, levelling off at >60 years of age [93]. In another study, anti-HEV IgG seroprevalence was 6.8% (69/1019), blood donors [94]. Between 2006 and 2007 again in Germany, 76/96 persons with HEV infection were reported with a routine surveillance system. The majority of peoples with travel-associated infection and autochthonous infection were males (62% and 76%, respectively). Individuals with travel-associated diseases were younger (median age, 37 years) than those with autochthonous (median age, 46 years). Sixty-six people had diseases that fulfilled the inclusion criteria: 45 (68%) had autochthonous infection and 21 (32%) had travel-associated diseases. Genotype 3 or 4 were present in 15 of 15 persons with autochthonous infection, and genotype 1 in 8/9 persons with travel associated infection [59].

In 2008 in Eastern Germany in a study on anti-HEV IgG, a seroprevalence of 18% among blood donors and a seroprevalence of 11% among forestry workers were found [95]; while in South-West Switzerland in 2011 among 550 blood donors HEV IgG prevalence was 4.9% (27/550) [96].

In Poland, sera from 45 Indian citizens studying in Poland were tested for HEV IgG and IgM. It a IgG positivity of 26.7% (12/45) was observed, and 3 sera were reactive for HEV IgM only [83].

In Romania, HEV IgG prevalence was 12.5% and 14% in students and health workers (doctors and nurses), respectively [97].

In Moldova, a study on the seroprevalence was conducted between 1997-1998 in 2 populations: swine farmers (n=264) and a group of people without occupational exposure to swine (n=255) were considered as the control group. A prevalence of anti-HEV was higher in the swine farmers group than in the control group (51.1% vs. 24.7%, $p<0.001$). In the occupational group, people >40 years had a significantly higher prevalence of HEV infection than person aged 18-30 years old (65.7% vs 40.0% p=0.006). A similar pattern of association of anti-HEV reactivity with age was noticed in the control

group (33% vs 17.9%) [98]; instead in Russia an anti-HEV IgG seroprevalence was observed in 62/341 children, 18.2% [99].

In South-East Hungary between 2001 and 2006 patients with an average age of 53 years old (range 16-85 years) showing acute hepatitis were positive for anti-HEV IgM 9.6% of case (116/1203) and 24.5% of them were HEV-RNA positive [100]. During the years between 1993-2005, 12,091 cases of communicable disease were imported to Czech Republic and 5% had viral hepatitis E [101]. In another study carried out in a group of patients excluding hepatitis-A,B,C, antibodies HEV IgG were detected in 27.8% with acute hepatitis [102].

In the Netherlands, anti-HEV was determined to be 11% for pig veterinarians and 6% for non-pig veterinarians and 2% in the general population, suggesting that direct exposure to swine may be an important risk factors for HEV infection [103]. In 4 Netherlands districts (North-East, South-East, North-West and South-West) between 2011 and 2012, 5,239 blood donors were tested for the presence of anti-HEV IgG and IgM and also for HEV-RNA in sample anti-HEV IgM positive. In total, the seroprevalence of HEV revealed that 26.7%, (1,401/5,239), blood donors were reactive for anti-HEV IgG; moreover 3.5% (49/1,401) resulted positive also for anti-HEV IgM and only 4/49 IgM positive were also HEV-RNA positive. Furthermore their observed that the seroprevalence in the Southeastern part was higher (30.5%) than in the rest of the country (p=0.0004) while in the Northwestern part it was lower (23.6%, p= 0.009). Anti-HEV IgG seroprevalence strongly increased with age, after the age of 30, that increased by 1,05% per year. The overall seroprevalence in males was higher than females (29.2 vs. 23.1%), but this difference can be attributed to the higher age of male donors (51.1 vs. 45.5 years) [104].

In France many studies in different geographical area were carried-out. In South-West France different populations were studied. Anti-HEV IgG seroprevalence carried out among 529 blood donors from Midi Pyrenée blood donors revealed 16.6% IgG positivity and none of subjects had traveled abroad in the prior six months [105]. In the Pyrenees region, in 2001-2002, among 431 patients with acute hepatitis of unknown etiology 10.7% (46/431) anti-HEV IgG positive samples it were found and none had travelled to endemic countries. Phylogenetic analysis revealed that all the strains were genotype 3 [106].

The evaluation of autochthonous cases has shown that populations at risk include swine veterinarians (anti-HEV 11%), non-swine veterinarians (anti-HEV 6%) and forest workers (anti-HEV 18%) [95,103].

In France from Alsace-Lorraine, Franche-Comite, Champagne-Ardenne and Bourgogne administrative regions, anti-HEV IgG were detected in 31.2% of the forestry workers in 2002 to 2003 [107]; while in the Toulouse region the seroprevalence in blood donors rose to 52% when a more assay sensitive assay was used [84]. Another study in the South West of France in Midi-Pyrenees region the seroprevalence anti-HEV IgG from blood donors sera was 3.2% [108].

In Spain, the HEV seroprevalence was determined in a cohort of 90 asymptomatic immigrants (sub-Saharan Africa) who had arrived in there (age range: 18-34 years; 53% female), and 863 voluntary Spanish blood donors, who represented the healthy Spanish population (age range: 15-65 years; 56% male). A total of 34/863 serum samples belonging to blood donors (3.9%) were reactive to anti-HEV IgG. Of these, 25 were confirmed by western blot. Anti-HEV IgM was not present in any of the anti-HEV IgG positive serum samples. Among the immigrants, anti-HEV IgG was detected in 5/90 serum samples (5.5%). All positive sera were confirmed by western blot. Anti-HEV IgM was not found in any of the anti-HEV IgG-positive serum samples [109].

Another Spanish study on anti-HEV IgG/IgM or both seroprevalence analyzed 2,305 serum samples from the general population. The samples had been collected in the year 2008 among people 2-60 years old in 2008 years and seroprevalence was 1.08% for HEV IgG [82].

Again in Spain (Madrid) 277 subjects with acute hepatitis of unknown etiology were analyzed for antibody anti-HEV. Evidence of acute infection by HEV was obtained for 30 patients in total (10%), and 16 cases were unrelated to recent international travel. On samples from 158 patients tested for both anti-HEV IgM and HEV-RNA at admission, the yield of IgM antibody testing (11.4%) was higher than the yield of HEV-RNA testing (9.5%) [110].

In Serbia during the spring of 2010, serum samples from 200 volunteer blood donors were collected with an average age of 39.3 ranging from 19 to 65. In total, 30/200 (15%) of the blood donors tested positive for anti-HEV IgG. No significant differences of anti-HEV IgG seropositivity were found between men and women (14.6% and 16.7% respectively). HEV seroprevalence increased with age as higher rates were recorded in individuals older than 51 years of age (21.5%) then in those between 31 and 50 years age, or than in those younger than 30 years of age [111].

The high rate of asymptomatic HEV infections worldwide has led to concern about infection via blood donation. Several authors evidenced that the virus could be transmitted by transfusion in industrialized countries in Europe [112] and genotype 3f was the most related to HEV transmission by blood donation [113].

Many studies have been performed in Turkey on HEV seroprevalence. In two studies seroprevalence was analyzed in pregnant women. The first included 245 pregnant women in the age range between 17-41 and 76 healthy women were used as control range between 19-42 of age. Antibody IgG were found in 12.6% pregnant women (31/245) while 11.8% (9/76) in the control group [114]. In a second study, serum samples from 386 pregnant women were screened for anti-HEV antibodies. IgG was detected in 7.0% (27/386) [115]. Other two Turkish studies were conducted on children. First, 515 students a primary school in Ankara, with median age of 7 years old, were examined at two times: in November 2003 and in January 2005. The seroprevalence of anti-HEV IgG was 1.7% and 2.1% at the first and second visits, respectively [116]. In the second study, 210 healthy children and young people were randomly selected in Konya (Anatolia region) with an age range of 1-18 years (one hundred lived in rural areas and one hundred and ten lived in urban areas) where socio-economic condition are low and the purification system is known to be unreliable, as its capacity is insufficient to supply all of the surrounding villages in the rural area. The HEV antibody IgG was 8.5% in rural areas and 5.2% in urban areas [117].

Another study suggests a special risk group for hepatitis E infection could be represented in agricultural workers that use water for irrigation [118]. In this study two groups of people were considered, 46 workers and 45 control subjects with a median age of 27.6 years for workers and 28.5 years for the control groups, most of them were male. None of the people had a recent history of jaundice or clinical illness. There was no detailed information about on how long the subjects had been exposed to waste water. Seroprevalence of anti-HEV IgG was 16/46 (34.8%) in the agricultural workers while 2/45 (4.4%) in the

control subjects and the risk of acquiring hepatitis E was 11.5 fold higher in farm workers than in controls [118].

In a population in North-Western Greece (Epirus region) the prevalence of anti-HEV IgG estimated was 4.85% among refugees from Southern Albania, 5.3% in patients with chronic viral hepatitis B and 1.34% in hemodialysis patients [119].

In Albania a case-study was conducted to evaluate the seroprevalence of anti-HEV antibodies involving 109 patients with chronic liver disease and 190 in patients with no apparent liver disease considered as a control group. The anti-HEV IgG prevalence was 36.6% among people with chronic liver disease (40/109) and 12.1% among controls (23/190). None of the patients HEV IgG positive had traveled to areas considered to be endemic for HEV infection [120].

There are little data on the prevalence of HEV infection and the prevalence of circulating HEV antibodies in Italy. In Northern Italy, in Milan, between 1994 and 2009, 651 patients with acute non-A-C hepatitis were analyzed; 20.6% (134/651) of the patients tested had acute hepatitis E. All of them were anti-HEV IgM and IgG positive and 71.6% (96/134) were also positive for HEV-RNA. Moreover, 6% (39/651), were anti-HEV IgG positive but negative for anti-HEV IgM. A total of 81.3% patients (109/134) developed hepatitis E while travelling to endemic areas, 2.3% (3/134) acquired intra-familial infection from relatives who developed travel-related disease, while 16.4% (22/134) patients denied having travelled abroad [121].

In Southern Italy, HEV seroprevalence was determined in a cohort of 1,217 subjects, 412 of them were immigrants from Africa (mean age of 28.7) who had recently arrived in Italy (<2 months) and 805 were Italians divided in four groups, 151 volunteer blood donors with seropevalence anti-HEV IgG 1.3% (mean age 37.0), 450 subjects from the general population with seropevalence HEV IgG 2.7% (mean age 40.1), 100 HIV-positive with seropevalence HEV IgG 2.0% (mean age 39.1) and 104 haemodialysis patients with seropevalence HEV IgG 9.6% (mean age 65.1). Results show a prevalence of anti-HEV IgG 19.7% in immigrants and 3.9% Italians [122]. In Lecce a general population shows a seroprevalence of 2.9% while in drug users, hemodialized patients and immigrants the seroprevalence rates were 0.7%, 4.3% and 15.3% respectively [123].

In a study carried out in Italy between 1994 and 1997 the presence of HEV-RNA and antibody was determined in 218 patients (123 males and 95 females with a mean age of 37.5 years) diagnosed with acute viral non A-C hepatitis. The results showed that 10.1% (22/218) of the examined patients were diagnosed with acute hepatitis E; the main risk factor was traveling in endemic area. In fact, 77.3% (17/22) HEV positive patients developed acute hepatitis after their return from endemic areas (8 patients from India, 3 from Pakistan, 5 from Bangladesh and 1 from Somalia). One child (5 years old) developed acute hepatitis E two days after her return from Somalia. Four patients (18.2%) denied travel abroad, contacts with people coming from endemic areas or exposition to other risk factors such as drug addiction or shellfish consumption [38].

In another study performed in Southern Italy 6% of cryptogenic acute hepatitis were associated with HEV infection [124].

In 1998 in Portugal the authors carry out the first serological test to assess the presence of anti-HEV IgG in 50 blood donors and the results showed that the 4% (2/50) was anti-HEV IgG positive [125]. In Portugal, the first cases of acute autochthonous hepatitis E virus in humans were described in 2010 [126].

The main data concerning HEV seroprevalence are represented in Table 1.

Country	Population	Seroprevalence %	Assay	Reference
Albania	CLD	36.6	Abbott HEV EIA	[120]
Austria	C-S	14.3	ELISA, Fortress Diagnostics	[92]
Belgium	PT	14	Elisa Biorex, Antrim	[91]
Czech republic	AH	5 27.8	Not done Abbott HEV EIA	[101] [102]
Denmark	BD *Swine W*	20.6 50.4	In house assay	[89]
England	BD	16-25	Genelabs	[87]
Finland	PT	11.3	Genelabs	[76]
France	BD AH *FW*	52 16.6 3.2 10.7 31.2	Wantai Genelabs Genelabs Abbott HEV EIA MP Biomedicals	[84] [105] [108] [106] [107]
Germany	AD BD FW	16.8 6.8 11 18	Mikrogen Mikrogen Mikrogen Mikrogen	[93] [94] [95] [95]

Greece	R	4.85	Abbott GmbH Diagnostika	[119]
Hungary	AH	9.6	HEV Ab, Dia.Pro	[100]
Italy	AH	20.6	Genelabs	[121]
		6	HEV Ab Dia.Pro,	[124]
	I	3.9	HEV Ab Dia.Pro	[122]
	IM	19.7	HEV Ab Dia.Pro	[122]
	IM	15.3	Abbott HEV EIA	[123]
Moldova	*Swine W*	51.1	In house assay	[98]
Netherlands	PV	11	Abbott HEV EIA	[103]
	NPV	6	Abbott HEV EIA	[103]
	BD	26.7	Wantai	[104]
Poland	ST	26.7	HEV Ab Dia. Pro	[83]
Portugal	BD	4	Abbott HEV EIA	[125]
Romania	ST	12.5	Mikrogen	[97]
	HW	14		
Russia	CH	18.2	In house assay	[99]
Scotland	BD	4.7	Wantai	[88]
Serbia	BD	15	In house assay	[111]
Spain	BD	1.08	Diagnostic Bioprobes S.r.l.	[82]
		3.9	Abbott HEV EIA	[109]
	PT	11.4	Mikrogen	[110]
	I	5.5	Abbott HEV EIA	[109]
Sweden	BD	9.3	Abbott GmbH Diagnostika	[86]
	Swine W	13		
Switzerland	BD	4.9	Genelabs	[96]
Turkey	PW	12.6	Virotech	[114]
		7	Globe Diagnostics	[115]
	CH	2.1	HEV Ab Dia.Pro	[116]
		8.5	Not done	[117]
	AW	34.8	Biyoser S.r.l.	[118]
General populations: BD: Blood Donors; HW: Health Workers; AD: Adult Population; C-S: Civilians and Soldiers; IM: Immigrants; PW: Pregnant Women; CH: Children; ST: Student; R: Refugees; I: Italian People.				
Risk groups: *AH*: Acute Hepatitis; *PV*: Pig Veterinarians; *NPV*: Non-Pig Veterinarians; *CLD*: Chronic Liver Disease; *PT*: Patients; *Swine W*: Professional in animal care workers, *FW*: Forestry Workers; *AW*: Agricultural Workers. The risk groups are indicated in italics				

Table 1: Hepatitis E seroprevalence in different populations in Europe.

Seroprevalence and HEV Infections Features in Immunocompromised Patients

Hepatitis E is generally self-limiting, except in the immunosuppressed. Immunocompromised patients are at particular risk of fulminant hepatic failure upon HEV infection. In Europe chronic hepatitis E cases have frequently been described in HIV infected patients [127], solid-organ transplant recipients [62], patients with hematological disease and patients with haematological disorders who had undergone chemotherapy [128]. Chronic infection may lead to cirrhosis [62,129].

In an anti-HEV seroprevalent study in the UK, 138 HIV positive patients were compared with 464 patients, aged ≥ 18 years considered as control subjects. These patients had no history of liver disease [130]. Among the 138 HIV positive, 79% patients (109/138) were male with a median age of 43 years. Thirteen out of a hundred thirty-eight

individuals (13/138) were anti-HEV IgG positive, 9.4%, compared with 13.8% among the control patients (64/464). The seroprevalence of anti-HEV IgG in the control group increased with age from a rate of 4% at age 20 to 30% at age 80. There was no difference in anti-HEV IgG seroprevalence between the HIV infected patient population and the control group [130].

Recently, in Spain carry out on 238 selected HIV positive cases and 9% of patients (22/238) were anti-HEV IgG positive and none resulted IgM positive [131].

In another Spanish study, among the 45/448 HIV infected patients who were positive for anti-HEV IgG, 10.4%, only 1/45 was HEV-RNA positive [132].

In Switzerland, only 2.6% of the 735 HIV patients were reported to be positive for anti-HEV antibodies [133]. In France, a study analyzed, in sera, the prevalence of anti-HEV antibodies in two distinct immunocompromised patient populations. The authors analyzed 307 samples collected from 261 HIV infected patients (82% were males) with a median age of 41 years, and 46 kidney transplant patients (66% were males) with median age of 45 years. Anti-HEV IgG positive was found in 1.5% HIV infected patients (4/261) and 3 kidney transplant patients. None of the patients had anti-HEV IgM antibodies, thereby excluding any acute infection; the IgG avidity index confirmed previous HEV infection among the tested patients [134]. A retrospective study was carried out in 184 patients infected with HIV who were followed-up at the University hospital of Marseille, in Southeastern France [135]. Among the patients, 119 were men; their mean ± Standard deviation (SD) age was 42 ± 9.6 years (range, 15–69). The prevalence of anti-HEV IgG and IgM was 4.4% (8/184) and 1.6% (3/184), respectively [135]. HEV acute hepatitis related to genotype 4 was observed in French women, with immunosuppression due to leukemia. This genotype 4 was considered autochthonous since the women have not previously been to any endemic countries [136].

Infections with HEV in solid-organ transplant recipients can lead to chronic hepatitis in immune-compromised patients [137-139]. Recently chronic infections have been described in organ transplant recipients living in developed countries [137-141]. In France fulminant hepatitis E occurred in women a 73 years old woman old with leukemia. This patient, despite ribavirin treatment (600 mg twice daily) died with a deterioration of health condition. The HEV sequence obtained by serum samples belonged to genotype 3f, and the only risk factor of virus transmission was liver sausage (figatelli) consumption [142].

In organ transplant patients, chronic HEV infection shows a rapid progression towards liver fibrosis, and 10% of the patient's progress to cirrhosis as demonstrated by a study on sequential liver biopsies [68]. Treatment with the immunosuppressive drug tacrolimus drug and a low platelet count are the main factors predicting chronic HEV correlated hepatitis. The virus is cleared in more than 30% of patients when the dose of tacrolimus is reduced [68].

In Europe, various studies described anti-HEV testing in solid-organ transplant recipients. The first patient cohort was described by Kamar et al. [139]. Between 2004 and 2006, the prevalence of anti-HEV IgG in French patients who received a kidney transplant or a liver transplant was 14.4% for kidney recipients and 10.4% for liver [139]. Another study carried out from 2007 to 2011 on kidney transplant recipients in Southeastern France, revealed an average of 6% anti-HEV IgG positivity [140]. A case report describes the first human case of acute HEV infection with two genotype 3c and 3e viruses in a French kidney transplant recipient, probably acquired through consumption of uncooked pig liver (figatelli). The patient had not recently travelled abroad but reported haven eaten uncooked and cooked figatelli. In 2008, he was hospitalized for occlusive intestinal syndrome and he was icteric. The patient presented two viral sequences nearly identical to sequences recovered from figatelli [143]. Another study described the outcomes of HEV infections in a cohort of 1,350 kidney transplant recipients living in Southeastern France between 2007 and 2011. The median patient age was 51 years. Sixteen HEV infections were diagnosed with genotype 3c-3e-3f, and moderate transaminases or an increased glutamyl transferase (GT) level was observed in all of the cases. All patients were infected with autochthonous strains and one patient developed liver cirrhosis 14 months after infection [144].

In Germany, a study showed an anti-HEV IgG prevalence of 2.4% in pediatric renal transplant recipients, and 4.9% in pediatric liver transplant recipients [141].

A study carried out in the Netherlands showed that chronic HEV infection in heart transplant recipients may lead to rapid fibrosis of the liver. In 2.3% patients' chronic infection with genotype 3 was identified. All chronic HEV cases had elevated liver enzyme values, and IgM antibodies were positive in 33% patients (2/6). Liver histology in 67% patients (4/6) showed advanced fibrosis within 2 years after infection [145].

In Netherlands, an observation study over 5 years period from 2007-2012 the majority of the infected patients were immunocompromised; two third were males and ranged in age from 23 to 80 years old; 18 were solid organ transplant (SOT) patients and 9 were immune-compromised patients for other reasons; instead 7 patients diagnosed with HEV were immune-competent. Viral genotyping revealed genotype 3 isolates, mostly genotype 3c [146].

A study cohort was conducted in Austria on 468 adult lung transplant recipients; most of them had received tacrolimus as one of the immunosuppressive drugs. Two of the lung transplant recipients received a 4-month course of anti-viral treatment with oral ribavirin monotherapy. The samples were tested only for HEV-RNA, and 2.1% of them resulted positive for HEV genotype 3 (median age 40 years) [147].

In Europe, there is also considerable the anti-HEV seroprevalence among individuals receiving haemodialysis, but different findings have been reported on the prevalence of anti-HEV IgG antibodies prevalence in haemodialysis patients living in developed countries [148-151]. In England anti-HEV IgG seroprevalence of 36.8% was observed in haemodialysis patients and 2 patients were IgM positive, while renal transplants recipients showed an 18.2% was found IgG seroprevalence, which was very similar to that which was found in the control group (18.8%). On the contrary, in France there was no evidence of chronic HEV infection in the more than 500 haemodialysis patients tested prior to transplantation [152]. In another English study anti-HEV IgG/M and HEV-RNA positivity was investigated in 76 haemodialysed patients (45 males and 31 females) with median age of 70 years, and in 88 renal transplants (55 males and 33 females) with a median age of 55 years, compared with 670 in the control group, which included healthy people, >18 years old with no history of renal or liver disease. The control group was tested only for anti-HEV IgG. Anti-HEV IgG was positive in 36.8% (28/76) of the haemodialysis patients and in 18.2% (16/88) of the transplant patients. HEV-RNA was not found in any of the patients. In the control subjects, 18.8% (126/670) were anti-HEV IgG positive [153]. These patients, with a functioning

transplant, showed no difference in anti-HEV IgG seroprevalence compared to the controls. Patients receiving haemodialysis had a higher seroprevalence of anti-HEV IgG than the controls and the cohort of renal transplant patients. None of the haemodialysis patients had evidence of chronic infection [153].

In 2001 in a semi-rural geographic area of Greece (Thessaly region), the prevalence of anti-HEV antibodies among 351 haemodialysis patients (264 males with a mean age of 60 ± 14 years) was 4.8% (17/351), no association was found between positivity, age, and sex [150].

HEV Genotype Distribution among Reported Cases of HEV Infection

Autochthonous hepatitis E is an emerging disease in Europe and is generally caused by genotype 3, genotype 4 has rarely been described [59,90,136,154-156] whereas in travellers and immigrants infection is primarily associated with HEV genotypes 1 and 2 [4]. It has long been noted that, in addition to imported cases from endemic countries, especially in developed countries, the presence of autochthonous HEV has been strongly suggested since more than half of the patients presenting the infection were non-travellers [157]. A recent long-term prospective study showed that most cases of HEV are travel-related and caused by genotype 1, while autochthonous cases are caused by genotype 3 [121].

Several case reports on imported HEV hepatitis have been described: in UK from India and Saudi Arabia [158,159], in the Netherlands from Bangladesh, Somalia, and the Middle East [160] and in Sweden from Turkey [161]. These reports published in the 1990s are mainly brief case reports that describe clinical features that are similar to those in endemic countries.

In the Czech Republic genotypes 3e, 3f, and 3g were identified from 10 human clinical samples. Their genetic relatedness with Czech animal strains suggests an autochthonous source, likely linked to the consumption of contaminated pork [162]. Recently, a study carried out on 51 adult patients with hepatitis between the years 2009 and 2012 were evaluated in Czech Republic. Anti-HEV immunoglobulin was identified in 98% of patients (50/51). Two of these patients reported traveling to endemic regions (India and Thailand). One patient died 10 days after admission due to bleeding in the gastrointestinal tract. HEV-RNA was detected in a least 1 sample of serum or stool originating from 43 patients [163].

Between 2006 and 2012, several sporadic cases of autochthonous of HEV-infection were reported in different areas in Germany [164-167].

Between April and August 2010, a total of 200 raw porcine liver samples were purchased in 81 butcher shops and grocery stores in Regensburg (Southeastern Germany). Specimens from 4% (8/200) had detectable amount of HEV-RNA. Sequence determination and phylogenetic analysis allowed identifying 2 novel isolates HEV genotype 3, subtype a (swR437) and c (swR269), respectively. Both novel swine HEV isolates showed high sequence homology to isolates from patients with acute HEV infection from the same geographic region. These results support the role of undercooked pig products as a source of zoonotic HEV infection in human [34]. Recently, an autochthonous HEV 3c subtype infection was reported in a 27 years old German pregnant woman; this was closely related to other European isolates [168]. In a German study carried out on 16,125 blood donors, 0.08% were found to be HEV-RNA positive (13/16,125) and all donor sequences resulted genotype 3a, 3c or 3e [169].

The first human cases of 3c hepatitis E infection were reported in France. A 46 year old men presented a 2 day history of diffuse polymyalgia and arthralgia. A neurological examination was normal. Biological tests revealed increased levels of liver enzymes. Diagnosis of HEV infection was established by the detection of of anti-HEV IgM and IgG in serum. HEV-RNA detection, confirmed by HEV sequencing within the ORF-2 region, found HEV-RNA positive genotype 3c. The patient did not report any recent travel in HEV hyper endemic areas [170].

In Marseille, France, a total of 11 cases of HEV infection were confirmed by anti-HEV IgM testing, and detection of HEV-RNA in serum samples. The mean age of the patients was 57 years. Of the 11 case-patients, 10 were males and 3 were kidney transplant recipients. HEV infection was clinically asymptomatic in all transplant recipients; the infection was diagnosed after routine transplant laboratory tests. Phylogenetic analysis showed that 4 patients each had HEV genotype 3c or 3f [154]; instead HEV genotype 4 RNA was found in 2 patients who had eaten uncooked pork liver sausage [154]. Again in Marseille, a 77-year-old woman presented the first case of fatal fulminant liver failure associated with HEV infection, autoimmune hepatitis and excessive paracetamol intake. The patient did not report any travel abroad. The HEV-RNA was resulted genotype 3 [171].

A swine owner in France was reported to have been contaminated by his pet swine; the pig urinated and defecated outside, and the patient regularly changed the litter. The animal often entered the house and was frequently handled by his owner. Diagnosis revealed that he resulted antibody IgM and HEV-RNA positive for genotype 3. This genotype was similar to those of other European isolates but specific to this case, which suggested autochthonous local transmission [172]. In France genotype 3c strain was isolated in a clinically asymptomatic immunocompetent patient of European origin [32], while another study HEV sequences identified in patients with autochthonous hepatitis E infection in 106 patients were compared with sequences amplified from 43 swine. Phylogenetic analysis showed the same proportions of subtypes 3f, 3c and 3e in human and swine populations [173].

Between 1997 and 2005 in France, seven patients with encephalopathy were diagnosed with acute HEV. All patients were positive for IgG antibodies but real time PCR products from only five patients are sequenced and all resulted genotype 3. Five patients were active drinkers and six had chronic liver disease [174].

In a study in France investigated 38 cases of HEV, using the serological test, quantified virus and genotyping the virus in plasma samples, and found that 58% (22/38) patients developed chronic infection. All samples were genotype 3 [175].

Many studies were conducted in UK. In England and Wales, between 1996 and 2003, 478 patients were tested for anti-HEV IgM/IgG. A total of 186 hepatitis E patients were serologically diagnosed; and 9% (17/186) of them were not associated with recent travel abroad. A total of 69% (129/186) cases were associated with travel to countries where HEV is hyper endemic. The non-travel associated cases were infected by HEV genotype 3 strains [176].

Another study included 333 patients with unexplained hepatitis who were tested for HEV infection markers over a 7-year period; their median age was 67 years (range 35-83). The authors found that 6.3%

(21/333) presented anti-HEV antibodies (IgG or IgM), autochthonous hepatitis E genotype 3, which bore close sequence homology to the HEV circulating in UK pigs [75].

During 2011, an HEV outbreak involved 5 case-patients in an area of Lazio, Italy, who did not travel to disease-endemic areas, so these cases were considered autochthonous. The sequence data from ORF1 and ORF2 regions identified a genotype 4d strain. ORF1 nucleotide sequences from the outbreak showed high similarity among patients and identity with HEV4d swine hb-3 and human T1 isolates in China [57]. Another study, carried out on 43 patients with acute hepatitis symptoms, revealed 39.5% HEV positive cases (17/43), 12 patients harbored genotype 1, which was correlated to travel in endemic areas, and 5 cases harbored genotype 3 and were autochthonous [48]. Another study characterized the HEV genotypes circulating among the migrant population of Southern Italy [177]. Forty samples from patients not exhibiting symptoms of acute hepatitis (24 men and 16 women), aged between 18 and 47 (mean, 27.5years), were tested for HEV-RNA. Only 2/40 (5%) were found to be positive for HEV-RNA with genotypes 1 and 3 [177].

In Northern Italy, in Milan, between 1994 and 2009, sequencing and phylogenetic analysis of ORF2 PCR products of 39 viral isolates, derived from patients with acute HEV who travelled abroad, showed that they all were infected with a virus of genotype 1a or 1c. On the contrary, ORF2 sequences from 5 patients with no history travel abroad, belonged to genotype 3 [121].

Recently, in Italy, a case of acute fulminant hepatitis E virus was described. This patient, 79 year old men, resulted positive to HEV genotype 3e, and was very similar to a German strain with an identity of 99.2% [39].

In Spain 3/11 cases were confirmed as acute HEV, IgM positive, but all 11 cases were shown to be IgG positive. Three different HEV strains were identified in the serum of the patients; two were autochthonous genotype 3 and one genotype 1 was imported from Africa [22].

In different regions of Spain, viral genome fragments were amplified from 13 RNA serum samples. The analysis of the sequences lead to identify six genotype 1a (belonging to travelers from India and Bangladesh), six genotype 3f (who did not travel abroad recently) and one genotype 4 viral strain (from a traveller who had returned from Vietnam). Furthermore, genotype 3f subtype is responsible for locally acquired HEV infection in different regions of Spain [77].

In Europe, the first case report of HEV in pregnant women was identified in South-East France who was infected with genotype 3 [178].

Severe cases of fulminant autochthonous hepatitis E caused by genotype 3 have been reported in Europe, often in older males with underlying chronic liver disease or in immune-compremised patients as observed above (Table 2) [174,179].

In addition, a case report in Spain described a case of fulminant HEV hepatitis in a woman taking contraceptive medication and who was admitted to a hospital for a liver transplant evaluation. This woman was a 37 year old office worker with no history of alcohol consumption and no close contact with animals. She presented asthenia epigastralgia, nausea and a 5-day evolution of fever. The diagnosis was based on the presence of anti-HEV IgM and IgG in serum and confirmed by isolation of a genotype 3f strain [180]. In another study, 5 cases of fulminant HEV were described in patients with median age 49.6 years [181].

In France fulminant hepatitis E occurred in women a 73 years old woman old with leukemia. The HEV sequence obtained by serum samples belonged to genotype 3f [142] (Table 2). Several HEV sequences isolated from humans in different European countries are listed in Table 3.

Country	Number patients	Sex	Age	Significant co-morbidity	HEV genotype	Reference
Czech Republic	1	Man	70	Alcohol abuse	3	[163]
Italy	1	Man	79	none	3e	[39]
France	1	Woman	77	Autoimmune hepatitis without hepatocellular failure	3	[171]
France	7	2 Women 5 Men	range: 50 ± 78	3 patients with cirrhosis and 2 bridging fibrosis	3	[174]
France	1	Woman	73	B cell lymphone	3f	[142]
Spain	1	Woman	37	None	3f	[181]

Table 2: HEV fulminant hepatitis in Europe.

Treatment of HEV Infection

Acute hepatitis E usually follows a self-limiting course which only requires symptomatic treatment; however, it is not uncommon for it to take on a severe acute form with the rapid development of acute fulminant hepatitis [182]. In addition to the supportive care, severe acute hepatitis E and fulminant hepatitis may require treatment with an antiviral agent [183-185].

Ribavirin has been found to be efficacious for the treatment of chronic hepatitis E in the cases of solid organ transplant recipients, including renal, lung, heart and pancreas transplanted patients. Ribavirin monotherapy has also been found to be beneficial in the treatment of severe acute hepatitis E in both immune competent and immune compromised patients with prompt viral clearance and rapidly improved liver function [183-185].

Country	HEV genotype	Region (ORF)	GenBank accession number	Reference
Czech Republic	3 1	1	GU299812 GU299813 GU299815 KC924921to KC924927 KC924929 to KC924938 KC924928	[163]
	3		GU299812 GU299813 GU299815 GU299817	[162]
England and Wales	3 1	2	AJ879566 to AJ879574 AY362357 AY582797	[176]
Finland	1	1	FJ890338 to FJ890342	[76]
France	3	2	FJ951641 GQ427003	. [69]
			AF110390	[105]
			EU116340	[62]
			EU116336	[170]
			EF028801 EF028802	[113]
	1	1 2	EF514587 EF050798	[172]
	4	2	KC437301to KC437308 GU982294	[155]
	4 3	1	JN794589 JN794587	[154]
	4	2	GU982294	[136]
	3	2	JF730329 to JF730340	[173]
			GQ427015 to GQ427018 GQ427002 GQ427003 GQ426987 GQ426988 GQ426992 EU116338 EU116340 JQ697492 JQ697493 JF900626 JF900628 JF900630	[144]

			FJ951640	
			HQ688787 HQ682232	[32]
		1 2	KF921518 KF921517	[171]
			KM887852 to KM887862	[142]
			FJ665422 FJ665426 FJ665429	[190]
Germany	3	1 2	AJ889194 AJ889196	[164]
		1	JQ863406 to JQ863418	[169]
		1 2	HE605115 HE605117	[167]
		1	EU879112 GQ266391	[165]
	4	3	JN257704 JN257711	[156]
Hungary	3	2	EF530659 EF530676 EU057982 AY940427	[100]
Italy	1	2	HM446588 to HM446631	[121]
	4		JX401928	[57]
	3	1	JX898218 JX898219	[177]
			FJ998019	[39]
Netherlands	3	2	JK645320 to JK645333 KC223601 JX645320 JX645333 JX645334 JX645340 JX678984 KC223601	[104]
			AB385842 to AB385852 DQ200273 to DQ200295	[73]
Spain	3 3 4	1 2 1	AY570904 AY540113 to AY540115 AY570905	[22]
	3 4	1	FJ464731 FJ464732 FJ464733	[77]

	1		FJ464734	
	3		FJ464735	
	1		FJ464736	
	3		FJ464737	
			FJ464738	
	1		FJ464739 to FJ464743	
	3	2	FJ464744 to FJ464746	
	1		FJ464747	
	3		FJ464748	
			FJ464749	
	1		FJ464750	
	1		FJ464751	
	3		FJ464752	

Table 3: Some representative Human HEV sequences described in European countries.

Ribavirin therapy is contraindicated in pregnancy owing to teratogenicity, however the risks HEV transmission from untreated to mother to fetus are high, and therefore treatment may be offered. Furthermore, available evidence regarding ribavirin administration during pregnancy shows no adverse maternal and fetal outcomes [186,187].

A daily dose of 600 mg of ribavirin has been found to be satisfactory in most of the cases of hepatitis E. It has been observed that a dose reduction in dose, due to treatment related side effects, such as anaemia, are associated with viral rebound and resistance [184,188]. However, when used in conjunction with reduced tacrolimus immunosuppressive therapy, valganciclovir, another drug for HEV infection, also showed HEV clearance in a liver-transplanted patient co-infected with herpes virus-6 [189]. Other studies confirmed that after a lower dose of tacrolimus immunosuppressive therapy, liver transplant recipients with chronic hepatitis E have benefited most when treated with pegylated interferon for about three to twelve months [190,191].

Recently, co-infection with hepatitis E in HIV patients has been observed and the co-infected subjects had undergone ribavirin monotherapy treatment [192,193] pegylated interferon alone [194] as well as a combination therapy with ribavirin and pegylated interferon [195].

Vaccines

A hepatitis E vaccine showed efficacy to one HEV genotype and may be able to provide protection against other genotypes of HEV [196,197].

Two main anti-HEV vaccines candidate have been developed.

The first-one, HEV 239, is a recombinant vaccine based on the genotype-1 capsid protein expressed in *Escherichia Coli*. In a phase-3 trial conducted in China, more than 100,000 healthy people were randomized to receive either three doses of HEV 239 at 0, one and six months, or hepatitis B vaccine as a placebo. The vaccine was well tolerated and protected against hepatitis E, with an efficacy of 100% [198]. The HEV 239 vaccine has recently (2012) been approved for marketing in China.

The second vaccine, named rHEV, was produced in insect cells (*Spodoptera frugiperda*) and its safety and efficacy was evaluated in a study conducted in Nepal on a total of 1,794 volunteers from the Nepalese army (898 in the vaccine group and 896 in the placebo group). The rHEV vaccine was well tolerated, and the efficacy of a three dose vaccination was 95.5% [199]. Both vaccines seem very useful for individuals travelling to areas considered endemic for hepatitis E. These vaccines may also be useful for people who are at higher risk of severe disease following HEV infection, such as transplant recipients, persons with pre-existing chronic liver disease and immunosuppressed persons at risk of chronic HEV infection [200].

Conclusion

The data described in this review suggests that the hepatitis E, which over previous decades was considered to be an endemic infection prevalently in low-income countries, is a widespread infection, even in industrialized countries. In Europe, the serum prevalence varies greatly, depending on the geographic areas considered and the populations studied. This variability of serum prevalence may be due to the diagnostic assay used for the detection of antibodies [201]. However, contact with pigs or consumption of uncooked pork meat are objective risk factors of transmission of infection, given the high seroprevalence observed in veterinarian, pig farmers [94,97,102,106,118], and in the population who usually consumes uncooked pork food [57,71]. These findings are in agreement with a recent report where the European Food Safety Authority's Biohazard expert declared that, more studies on HEV circulation are necessary to clarify farm-to-table risk assessments [202].

This review also highlight the increasing number of cases of fulminant hepatitis related to genotype 3 and to the status of patient immunosuppression, which is different to what has been observed in regions of South-East Asia and Africa, where most of HEV hepatitis fulminant cases occurred among pregnant women.

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