

Hepatitis E Virus

Annick Linden, Damien Thiry, Steven Van Gucht, Magali Wautier

Introduction

Hepatitis E is a disease caused by the hepatitis E virus (HEV), a member of the genus *Hepevirus*, Familia *Hepeviridae*.

HEV is one of the most important causes of acute hepatitis in adults in developing countries. Contrary to the old dogma, however, the virus is not restricted to developing countries, and sporadic cases are increasingly recognized in Europe.

Thus far, four HEV genotypes that infect humans are recognized. Genotype 1 is found in Asia and Africa, genotype 2 in Mexico, genotype 3 in Europe and the United States and Genotype 4 in Asia. Genotype 1 and 2 infections have been identified exclusively in humans, whereas genotype 3 and 4 viruses have been isolated from swine, deer, mongoose, cattle and rabbits, in addition to humans. Genotype 3 and 4 might be well distributed among swine and raw or undercooked pork may be a source of zoonotic infections.

From its discovery in 1983, documented HEV transmission was linked almost exclusively to contaminated water, with typically large outbreaks in developing countries (genotype 1). In Western countries, genotype 1 infections are typically imported after traveling to endemic regions. That association changed abruptly with the discovery of sporadic, non travel-related, sporadic hepatitis E cases in Europe (genotype 3). Often these sporadic genotype 3 cases were associated with consumption of uncooked deer or pork meat. HEV transmission by blood transfusion has also been described. The seroprevalence in blood donors in developed countries ranges from 1 to 3%. In the USA, a higher prevalence has been seen in persons working with swine. There are more and more indications that genotype 3 HEV is an emerging food-borne infection in Western countries.

In developing countries, genotype 1 causes an oro-faecally transmitted, water-borne, acute and self-limiting hepatitis that does not progress to a chronic disease. The infection can however be lethal in pregnant women.

In Europe, infections with genotype 3 usually cause mild hepatitis, but chronic cases are also documented, for instance in immune compromised solid-organ transplants recipients and HIV-infected individuals. The first chronic case was reported in Belgium in 2012. Genotype 3 infection might cause serious complications in patients with underlying chronic liver disease.

Hepatitis E Virus in animals

Domestic pig (*Sus scrofa*)

A study performed on 420 pigs, sampled throughout Belgium in 2010, showed an individual seroprevalence of 73% (± 4 ; 308/420). The individual seroprevalence was significantly different between the two regions ($\text{Chi}^2 = 4.83$; 1 degree of freedom; $P = 0.03$): 66% (± 8 ; 79/120) in the Walloon Region and 76% (± 5 ; 229/300) in the Flemish Region. Moreover, 93% of the tested herds were found to contain at least one seropositive pig. Serological assays cannot discriminate between different genotypes.

Four out of 420 pig sera were detected positive for HEV RNA by conventional nested RT-PCR. These 4 sera came from pigs aged between 3 and 4 months. All sequences from the 4 positive sera belonged to genotype 3, subtype f.

These results are in agreement with the major findings in other European countries, except for one genotype 4 virus found in Belgium. The relative low detection of HEV RNA (4 out of 420 pig sera) can be explained by the age of the sampled pigs, which were less than 6 months, but probably older than 2 to 4 months, when the peak of viraemia is usually observed.

Wild boar (*Sus scrofa scrofa*)

An apparent seroprevalence of 33% (± 4.6 ; 125/383) was obtained on a sample of 383 wild boar sera in 2010 in Wallonia. Five out of 61 livers and 4 out of 69 sera of young wild boars were detected viropositive and the sequences obtained belonged to genotype 3, subtype f. These data are in agreement with the situation observed in other European countries.

The link between HEV infection in pigs, wild boars and humans need to be further analyzed to support the hypothesis of a zoonotic transmission in Belgium (project SPF HEVEA).

Red deer (*Cervus elaphus*) and roe deer (*Capreolus capreolus*)

A sampling of the deer population was conducted in Wallonia during the 2012 hunting season: 189 sera from roe deer and 235 sera from red deer were used for serology; 84 sera from red deer and 68 sera from roe deer, aged of more than one year, were used for virology.

An apparent seroprevalence of 1% (± 1.4 , 2/189) and 3% (± 2.2 , 7/235) was obtained in red deer and roe deer respectively. Both positive red deer were between 1 and 2 years old and among HEV-positive roe deer, there were 3 less than 1 year and 4 over 1 year old. No serum was viropositive.

In contradiction to the prevalence detected in wild boars (33%) (± 4.6 , 125/383) and pigs (66%) (± 8.4 , 79/120) in the same region (Wallonia), deer do not seem to represent an epidemiologically significant reservoir host.

Hepatitis E Virus in humans

Since 2008, the National Reference Centre for Hepatitis Viruses of the WIV-ISP, receives samples for HEV diagnosis. The number of suspected and confirmed cases increases year by year.

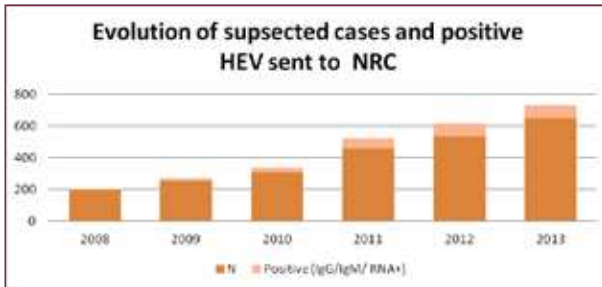


Figure 52. Evolution of suspected cases and laboratory-confirmed HEV cases analyzed at the National Reference Centre of Hepatitis Viruses of the WIV-ISP.

In 2012, the WIV-ISP received 614 suspected cases. Thirteen percent were IgG-positive. The seroprevalence was higher in men than in women, and in people older than 65 years. 32 cases with recent infection (presence of IgM and/or RNA in the serum) were detected. Twelve virus-positive samples were genotyped: 2 belonged to genotype 1 (imported cases) and 10 belonged to genotype 3 and probably represented locally acquired cases.

In 2013, 731 samples were tested for hepatitis E. 11.2% tested positive for IgG. Men were again more seropositive than women, and the average age of cases was between 50 and 54 years old. 35 recent infection cases (IgM and/or RNA-positive) were observed. The virus of 16 cases could be genotyped: all belonged to genotype 3.

The phylogenetic analysis showed that most of the virus-positive samples of 2012-2013 belonged to genotype 3, with a predominance of subtype 3f and 3c, which are typical for European swine strains.

In Belgium, most clinical hepatitis E cases in humans are caused by genotype 3 strains, which are closely related to European swine strains. Our data are therefore indicative of zoonotic transmission from swine.

Figure 55. Consensus phylogenetic tree of ORF2 sequences of selected viruses (red color) typed in Belgium during 2008-2013. Most Belgian strains from human patients belong to genotype 3 and are closely related to European swine strains.

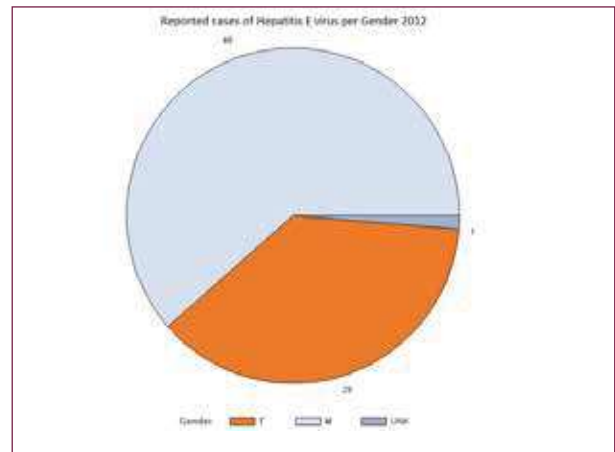


Figure 53. reported cases (IgG and/or IgM and/or RNA positive) of Hepatitis E virus per gender for 2012

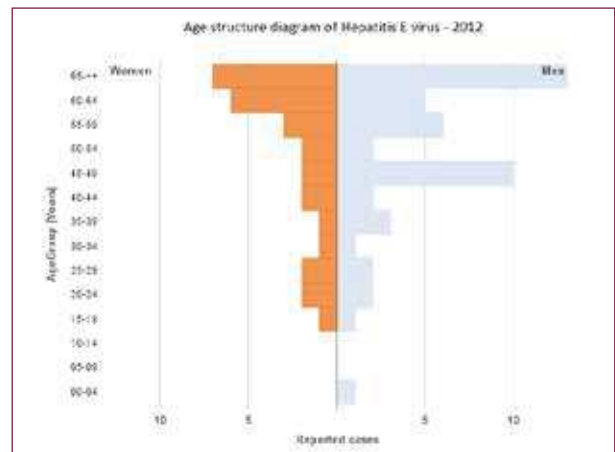


Figure 54. reported cases (IgG and/or IgM and/or RNA positive) of Hepatitis E virus per gender and age for 2012

