Hepatitis E virus

Hepatitis E virus
Family of *Hepeviridae*
Genus Hepevirus

Virus

Characteristics and sources of the Hepatitis E virus

Main microbial characteristics

The hepatitis E virus (HEV), is a spherical, non-enveloped virus particle approximately 32–34 nm in diameter. The genome of HEV is a single-stranded, positive-sense RNA molecule approximately 7.2 kb in size. It encodes three Open Reading Frames named ORF1, ORF2 and ORF3.

HEV has considerable genetic diversity, with four major genotypes identified in mammals (genotypes 1 to 4) and one avian genotype. More recently, two new isolates, unrelated to known genotypes, have been identified in rabbits and rats.

Genotypes 1 and 2 are found only in humans, whereas genotypes 3 and 4 are found in both humans and several animal species (domestic swine [*Sus scrofa domesticus*], wild boar [*Sus scrofa*] and deer [*Cervus nippon*, *Cervus elaphus* and *Capreolus capreolus*]).

A single serotype has been described for the four major genotypes found in mammals.

Sources of the hazard

In industrialised countries, several animal species are capable of hosting the virus, but the principal animal reservoir of HEV is swine, and suidae generally. Infection in domestic or farmed swine is usually asymptomatic, but they replicate and shed the virus extensively. Other suidae, such as wild boar, are also targets.

All studies suggest that the virus is distributed widely on pig farms throughout the world, with close to 100% of farms having been in contact with the virus (meaning at least one animal found to be serologically positive).

At the scale of individual pigs, at the age of slaughter (about 6 months), mean seroprevalence is usually lower, with high variability between studies (between about 20% and 80%). In mainland France, a national survey currently under way suggests very high seroprevalence, with more than 90% of farms found to be positive and rates of serological prevalence in animals from given farms varying from 2.5% to 80%. Seroprevalence in individual animals tested in slaughterhouses is 50%.

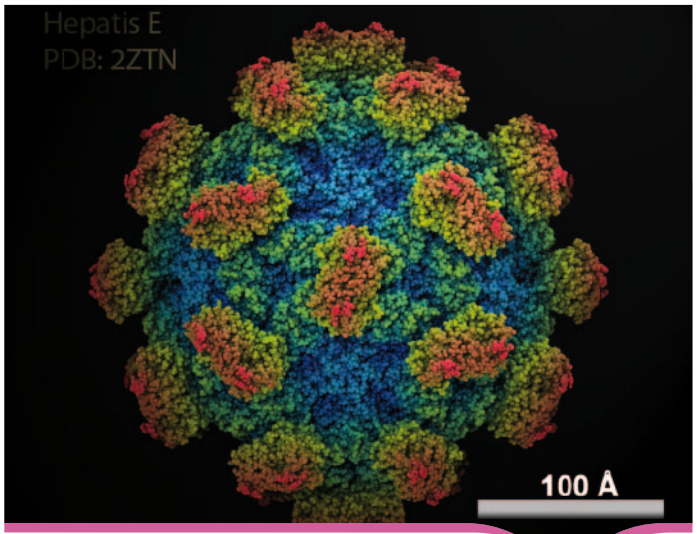
Regarding viremia, HEV RNA can be detected in serum from about the age of 2 months. The prevalence of viremic animals then increases to a maximum between 2 and 4 months before decreasing again to almost zero at the age at which pigs are slaughtered.

Regarding viral shedding, the HEV genome can be detected in faeces from the age of 2 months and the prevalence of shedding animals then rises to a maximum between 2 and 4.5 months. Unlike the pattern with serum, however, the prevalence of animals whose faeces are found to be positive by PCR (presence of the viral genome) diminishes with age but does not seem to disappear. This means that viral shedding occurs in 8% to 40% of pigs old enough for slaughter, i.e. aged between 5 and 7 months. In France, in an ongoing study of 3715 pig livers, 4% of the livers analysed were found to contain the virus (presence of viral RNA).

Transmission routes

In endemic countries with poor hygiene, many cases are caused by a common source of infection (contamination of drinking water by infected human faecal matter, absence of sanitation systems for waste water). The animal reservoir seems to play a limited role in maintaining the level of endemicity. In these countries, pregnant women develop serious forms, which is considered a major public health concern. The risk of vertical transmission from mother to child has been calculated at between 40 and 78% of cases (NB: a low number of cases are reported).

In industrialised countries, HEV is not transmitted in the form of an inter-human epidemic and most cases are of unknown origin. Nevertheless, HEV can result from cases of foodborne zoonotic transmission. Indeed, there are two reports in the literature of investigations of cases of viral



© Jean-Yves Sgro

hepatitis E in which food was confirmed virologically as the source of contamination. These cases were observed in Japan: the first was related to the consumption of sliced raw venison from sika deer (*Cervus nippon*) and the second case was described after consumption of wild boar meat. Genetic analysis of the strain found in the meat and in the patients confirmed that there had been direct transmission. A case control study carried out in Germany showed that the consumption of offal was a risk factor for infection by HEV.

In addition, people who come into contact with domestic pigs or wild animals (especially wild boar), such as veterinary surgeons, farmers, hunters or slaughterhouse workers, have significantly higher seroprevalence of HEV than the general population, suggesting that direct contact with infected animals, living or slaughtered, is also a risk factor for contracting HEV. At present, there seems to be only an exceptional risk of transmission by the transfusion of blood products.

Recommendations for primary production

- **Since there are insufficient data available on the dynamics of HEV in farms, it would be premature to issue recommendations on farming practices to be implemented to limit its spread. There is currently no vaccine available against HEV.**

Human foodborne disease

Nature of the disease

The characteristics of the disease are presented in Table 1.

Susceptible population groups[1]: people with an underlying liver condition with a risk of acute hepatitis; immunocompromised subjects with a risk of chronic infection and cirrhosis; pregnant women.

Dose-effect[2] and dose-response[3] relationships

There are no data from which to determine the precise probability of human infection as a function of the dose of HEV ingested. The information on the number of infectious particles per genome equivalent of HEV detected by gene amplification is still only partial, and very probably dependent on experimental conditions. Nevertheless, the available data allow an indirect estimate of the 50% infectious dose (ID_{50}) by oral route in humans, which would seem to be at least $10^{5.5}$ genome equivalents (quantification by PCR). This can be retained as a worst-case scenario, since it assumes that there is no species barrier between pigs and primates, which is probably a pessimistic hypothesis but which cannot be excluded in the current state of knowledge.

Epidemiology

Hepatitis E virus (HEV) remains the main cause of acute hepatitis circulating in endemo-epidemic mode in tropical and sub-tropical regions, where basic hygiene, particularly regarding access to clean drinking water, is lacking. In industrialised countries, autochthonous sporadic cases of infection have been diagnosed in patients with no record of travel to endemic regions. In France, the Hepatitis E National Reference Centre (NCR) has been monitoring hepatitis E since 2002. In 2010, the surveillance was reinforced (cases are now investigated systematically) in collaboration with the National Institute for Public Health Surveillance (InVS).

Since 2002, the number of cases of hepatitis E diagnosed by the NCR has increased regularly, reaching 250 cases in 2009, 72% of which were sporadic non-travel-associated cases, following a gradient of geographical prevalence increasing from north to south (M/F ratio: 2.6 to 4.6, mean age: 56-61 years (www.cnrvha-vhe.org)). An increase was also observed in the number of cases of hepatitis E diagnosed in immunocompromised subjects. Although fulminant forms are rare (1 or 2 deaths/year), they have been observed in subjects with underlying liver disease.

Role of food

Main foods involved

The presence of infectious HEV in commercially-sold pork livers (1 to 11%) has been shown in several studies (Japan, the Netherlands, India, South Korea and the United States). Consequently, the consumption of raw or lightly-cooked pork liver or liver-based preparations represents a high risk of contamination with HEV. In France, the consumption of raw *figatelli* (partly dried raw pork-liver sausage) has been associated with several clinical cases[4] (the French Ministry of Health issued a warning to consumers of these products in May 2009).

In the absence of reported clinical cases and/or serological data, an analysis of the other products based on raw pork-meat (raw and/or dried hams, sausage spreads, *longaniza* dry sausage, sobrasada sausage, traditional dry sausage, French *rosette* salami, chorizo) must be based on an evaluation of the exposure factors. There is no phase capable of inactivating HEV in the manufacturing process for these products. In consequence, the risk appears to be related to the frequency and the level of contamination of the raw materials (muscle or fat). Considering the viremia phase associated with dissemination in the body and the proven presence of HEV in muscle[5], it is probable that HEV can be found in these types of preparation. Furthermore, in the absence of complete data about the heat resistance of HEV, its fate in foods cooked at a low temperature (62°C) should also be studied.

(1) Susceptible population groups: people with a higher than average probability of developing symptoms or severe forms of the disease, after exposure to a foodborne hazard [definition used for ANSES datasheets].

(2) Relationship between the dose (the quantity of microbial cells ingested during a meal) and the effect on an individual.

(3) For a given effect, the relationship between the dose and the response, i.e. the probability that the effect may appear, in the population.

(4) Philippe Colson & Rene Gerolami. Hepatitis E - France: (Marseille) pig liver sausage. ProMED-mail PRO/AH/EDR 2009; 17 Sep: 20090917.3267. http://www.promedmail.org. Accessed 22 Feb 2010.

(5) Virus found in the muscles of infected animals by contact (Bouwknegt, M., Rutjes, S.A., Reusken, C.B., Stockhofe-Zurwieden, N., Frankena, K., de Jong, M.C., de Roda Husman, A.M., Poel, W.H. The course of hepatitis E virus infection in pigs after contact-infection and intravenous inoculation. BMC veterinary research Volume 5, 2009, Page 7).

Table 1. **Characteristics of the disease**

Mean incubation time	Target population	Main symptoms	Duration of symptoms	Duration of contagious period (shedding)	Complications	Asymptomatic forms
40 days (15-60 days)	Industrialised countries: M/F ratio: 2.5 to 5 Mean age (50-55 years)	Jaundice: 75% Anorexia: 45% Flu-like syndrome: 40%	1-4 weeks	1 to 3 weeks (immuno-competent subjects)	Persistent forms (> 6 months): 60% in cases of immuno-compromised subjects Lethality: 1% to 4% (immunocompetent subjects) 12 to 35% of these cases concern pregnant women (endemic countries)	Yes (proportion non-quantified in endemic countries)

Inactivation treatments in industrial environments

The only quantitative study available shows that HEV undergoes a reduction in infectious titre of about 2 to 3 log after 72 hours at 60°C in a liquid environment in the presence of proteins. Under the same conditions, no infectivity (reduction of titre > 4.5 log) was detected after 24 hours at 80°C. The degree of reduction of titre in the food matrices was not tested.

Furthermore, viruses present through natural contamination are inactivated by achieving a core temperature of 71°C in diced pork liver (0.5 to 1 cm^2) either by frying for 5 minutes at 191°C, or by cooking for 5 minutes in boiling water. Inversely, incubation for 1 hour at 56°C is insufficient for total inactivation. However, it is difficult to interpret these results as the level of initial contamination was unknown. Information is consequently partial, as the methodology makes it impossible to verify how far it can be extended to livers with different levels of contamination.

Monitoring in foods

There are no regulations concerning the monitoring of HEV in pig farms, nor in pork-derived foods.

Although HEV cannot be routinely cultivated, it can be detected by gene amplification (PCR). There is no standardised method for detecting the HEV genome in food matrices. However, several methods have been validated for use in diagnosis in the field of public health. These methods are used routinely on serum or faeces samples from patients with suspected hepatitis E. The same techniques are used to detect HEV in pigs (serums, faeces and liver) during surveys.

Recommendations for operators

- **Take HEV into consideration during the hazard analysis to be undertaken by the operators, and take appropriate measures as a result.**
- **Start to collect data concerning the monitoring of HEV on pig farms.**

Domestic hygiene

We recommend that foods that are to be consumed cooked (figatelli, bacon lardons) should be fully cooked through, particularly for population groups susceptible to this hazard (see above).

Pig farmers, veterinary surgeons and slaughterhouse workers, as well as people coming into contact with meat from pigs, wild boar and deer (hunters, butchers and especially pork-butchers) should wash their hands and also utensils and surfaces coming into contact with living animals, carcasses or pork products.

There is no literature on the efficacy of common surface disinfectants on the survival of HEV. However, when the characteristics of HEV, a non-enveloped RNA virus, are taken into account, the efficacy of antiseptics is probably comparable to that observed on most enteric viruses (French AFNOR NF T 72-180 standard concerning virucidal agents).

Recommendations for consumers

- **Wash your hands and clean utensils and working surfaces after handling raw pork liver.**
- **Cook food sufficiently: ensure that risk foods, to be eaten cooked, are fully cooked through.**
- **These recommendations should be followed meticulously by population groups with a particular susceptibility to this virus: pregnant women and patients on immunosuppressive therapy or with underlying liver conditions.**

References and links

General references

- Review of the subject: Pavio N, Meng XJ, Renou C. Zoonotic hepatitis E: animal reservoirs and emerging risks. (2010) Vet Res. 2010 11-12;41(6):46. Epub 2010 Apr 2.
- Opinion by AFSSA, of 23 September 2009 on methods for detecting hepatitis E viruses and the behaviour of the virus in pig slurry and during cooking, drying, salting and smoking of pork-liver based products. http://www.anses.fr/Documents/MIC2009sa0146EN.pdf

Useful links

- For hepatitis A & hepatitis E: *Centre National de Référence des virus des hépatites à transmission entérique*. For hepatitis E specifically: *Laboratoire de Biologie Clinique*, HIA Val-de-Grâce, 74 bd de Port-Royal, 75230 Paris Cedex 05. Contact: Dr Elisabeth Nicand. http://www.cnrvha-vhe.org/
- UMR 1161 Virology Unit, ANSES-LSA, ENVA, INRA. 23 av. du général de Gaulle, 94706 Maisons-Alfort cedex. Contact: Nicole Pavio.