

ADVISORY COMMITTEE ON THE MICROBIOLOGICAL SAFETY OF FOOD**RISK ASSESSMENT OF THE ROLE OF FOODBORNE TRANSMISSION
OF HEPATITIS E IN THE UK****Discussion Paper****Introduction**

1. A form of enterically transmitted hepatitis distinct from hepatitis A has been recognised for many years, but the full range and scale of infection has only become apparent since the virus was identified and characterised as hepatitis E Virus (HEV) (Reyes et al, 1990).
2. Hepatitis E is the commonest cause of epidemic and sporadic acute hepatitis in a wide range of countries in Asia, Africa and South America. The burden of infection is reflected in high sero-prevalences in human populations (Nepal 15-30%, Vietnam 40%, Egypt >60%). Distinct patterns have been reported from different countries; in Egypt, a high prevalence of antibody is found in young children, which stabilises when reaching young adulthood. In contrast, childhood infection is uncommon in India. Large waterborne outbreaks have been described in many of these countries. In these hyper endemic regions, clinical rates are highest in young adults; secondary transmission to close contacts is low (<5%).
3. Imported infections acquired by travellers to hyper endemic countries have been reported but are infrequently recognised in U.K. In developed countries, there is a growing recognition that indigenously acquired hepatitis E infection occurs and that the high prevalence of anti HEV antibody (e.g. USA 18% blood donors sero-positive) cannot be accounted for by imported infection alone.
4. This paper will review current understanding of hepatitis E transmission and focus on the potential for foodborne transmission in U.K.

The Viruses

5. Hepatitis E is a single stranded RNA virus with a non-enveloped capsid. Four distinct genotype groupings of human and swine HEV are recognised. Type I is the prototype strain found in human cases of hepatitis E in hyper endemic areas. Type II is found almost exclusively in human cases in Central America, Chad and Nigeria. Types III and IV are found in humans and pigs in developed regions and in pigs in some hyper endemic regions.

Animals and HEV

6. Worldwide, antibodies to HEV have been detected in a wide range of mammals including pigs, boars, deers, monkeys, cattle, sheep and goats, dogs, cats, rats and mice. The precise relationship of the viruses infecting these animals to human and swine HEV and the scale of cross-species transmission are poorly understood. Although antibodies and virus have been detected in pigs worldwide, no specific disease has yet been observed in pigs, despite the very high sero-prevalences observed in many developed and developing countries. Most sero-conversions occur between 8 and 12 weeks of age and may be related to the decline of maternal immunity. Following experimental infection, sero-conversion occurs about 18-20 days post infection, virus is excreted in faeces for 3-4 weeks and the pigs are viraemic for 1-3 weeks. In addition to the liver, HEV may be detected in a range of other tissues where viral replication might also be occurring.
7. In the UK, the current HEV sero-prevalence of about 80% in the pig population has been maintained at that level since the mid 1980s. Endemicity in pigs is likely to be sustained by faecal-oral transmission.

Zoonotic Transmission

8. Zoonotic transmission of HEV has been demonstrated under experimental conditions; for example, human HEV has been transmitted to sheep and infectivity studies in pigs and rhesus macaques have confirmed cross-infectivity between swine and human HEV.
9. Because of the close homology among human and swine HEV strains, with up to 100% amino acid identity in the proteins compared, pigs are considered the principal natural reservoir of infection. One strain identified in rats was characterized to have a 95-96% homology with genotype 1 human strains circulating in Nepal from where it was identified. That HEV might be zoonotically transmitted to workers occupationally exposed to pigs is supported by the finding of an anti-HEV sero-prevalence rate of 20%-25% among American swine veterinarians. In a study conducted in Moldavia, where no human hepatitis E has been reported, the anti HEV sero-prevalence was 51% among swine farmers compared to 25% among those not occupationally exposed to swine. A study of homeless people attending a free clinic in downtown Los Angeles revealed 13% to be sero-positive for anti HEV, this high figure being attributed to exposure to rats.

Foodborne Transmission

10. Human hepatitis E associated with foodborne transmission has been reported from Japan, Italy, China, Israel, Germany, Spain, U.K and Vietnam. Foodborne transmission has been associated with consumption of undercooked meat and un-pasteurised milk. Some cases of infection acquired in Europe have been attributed to the ingestion of uncooked or inadequately cooked shellfish, but the association between shellfish consumption and hepatitis E is not firmly established.
11. Evidence has recently emerged from Japan that hepatitis E may be transmitted via the consumption of raw or undercooked meat or viscera from pigs and other mammals. In one report, a cluster of cases of acute hepatitis E centred on a Japanese family that had consumed raw Sika deer meat some 3 weeks earlier. Sequence data from hepatitis E detected in unconsumed meat kept in the freezer showed 100% identity with the sequence obtained from stool samples of affected family members. Moreover, the sero-prevalence of anti HEV IgG was found to be significantly higher in Japanese who had consumed raw deer meat compared to those who had not. A more recent study reported that, of 10 patients presenting with acute or fulminant hepatitis E, 9 had consumed grilled or undercooked pig liver 2-8 weeks prior to the onset of disease symptoms. A survey of Japanese retail meat outlets revealed that 1.9% of raw pig livers carried detectable HEV. Evidence implicating the consumption of pork as a risk factor is also emerging from countries other than Japan. The islands of Lombok and Surabaya are, like most of Indonesia, predominantly Muslim. An exception is Bali, where the population is approximately 90% Hindu. Hindus eat pork whereas Muslims do not. The HEV sero-prevalence amongst apparently healthy subjects was 4.0% in Lombok and 0.5% in Surabaya but 20% in Bali; in contrast, the infection rates of hepatitis A did not differ significantly among the 3 islands.
12. The eating of raw or undercooked meat and viscera may therefore be a risk factor for non-travel associated hepatitis E in Japan. However, the relative importance of the foodborne route or direct contact with pigs or person-to-person spread in HEV infection in humans in different countries is not well understood.

Hepatitis E In U.K.

13. The diagnosis of hepatitis E is based on detection of hepatitis E IgM antibodies and is undertaken as a reference test by HPA Centre for Infections and at West Midlands HPA laboratory, Birmingham. Over the period 1996-2003, 186 cases from England and Wales were diagnosed. The majority of these cases (70%) had a recent travel history to a hyper endemic region, but a substantial minority (10%) had no travel history indicating that infection was acquired within U.K. The

following results obtained from analysis of 17 cases of non-travel indicated indigenous transmission within U.K:

- i. Cases tended to be in non-Asians, old (>50 years of age), and live in coastal and estuarine areas.
 - ii. The illness spontaneously resolved in most cases, but led to fulminant hepatitis in 2 patients.
 - iii. The illness was associated with infection by HEV belonging to genotype III.
 - iv. The genetic homology between U.K human HEV cases and U.K swine HEV strains was very close (>96-100%).
 - v. Patients with non-travel associated hepatitis E did not tend to live in high-density pig holding areas.
14. Enhanced surveillance was established following these findings and during the first six months of 2005, 24/181 confirmed hepatitis E cases had not travelled overseas. No common source was identified. There have been no population based serological studies for HEV antibodies in the general population or occupational groups (vets, pig farmers) in U.K. and no systematic investigation of hepatitis cases of unknown aetiology.

15. **Conclusions**

- HEV infects a wide range of animal species world wide and caused a substantial burden of disease in humans in hyper endemic countries in Asia, Africa and South America.
- Evidence is accumulating that human infection may be acquired through direct contact with infected animals and clinical disease through consumption of uncooked or poorly cooked meat from the infected animals.
- In the U.K., HEV infections have been very common in the pig population for >20 years. The burden of infection is poorly defined in the U.K. human population. Most recognised human cases have been linked to travel but a small number of human hepatitis E cases have been identified, who acquired infection within U.K. The source of infection is unknown but foodborne transmission cannot be ruled out. Infection is possible following consumption of undercooked meat or contaminated shellfish. There have been no systemic studies of indigenous HEV infection in hepatitis cases in U.K. or sero-prevalence studies in occupationally exposed groups or the general population.
- Very few of the non-travel associated cases in the most recent survey in the UK had any direct contact with pigs or were vegetarian.
- Evidence from other developed countries indicates that hepatitis E has a very high prevalence to incidence ratio, indicating a high proportion of subclinical infection.
- Current FSA recommendations, if properly implemented, should prevent foodborne transmission since proper cooking will destroy any virus present in meat.

- The risk of acquiring hepatitis E through the food chain in U.K. is likely to be low. However studies of the burden of infection, of transmission routes and of risk factors for acquisition are required to more accurately quantify the risk to occupationally exposed groups and consumers.

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