Hepatitis E: an emerging infection in developed countries

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Hepatitis E is endemic in many developing countries where it causes substantial morbidity. In industrialised countries, it is considered rare, and largely confined to travellers returning from endemic areas. However, there is now a growing body of evidence that challenges this notion. Autochthonous hepatitis E in developed countries is far more common than previously recognised, and might be more common than hepatitis A. Hepatitis E has a predilection for older men in whom it causes substantial morbidity and mortality. The disease has a poor prognosis in the context of pre-existing chronic liver disease, and is frequently misdiagnosed as drug-induced liver injury. The source and route of infection remain uncertain, but it might be a porcine zoonosis. Patients with unexplained hepatitis should be tested for hepatitis E, whatever their age or travel history.

Introduction

Hepatitis E is an important public-health concern as a major cause of enterically transmitted hepatitis worldwide, and is responsible for over 50% of cases of acute viral hepatitis in endemic countries. The virus is transmitted primarily by the faecal-oral route and is associated with both sporadic infections and epidemics in areas with poor sanitation and weak public-health infrastructures. In developed countries, hepatitis E infections were traditionally thought to occur infrequently and only in individuals who had become infected while travelling in an area where the virus is endemic. However, cases of sporadic hepatitis E in people with no history of recent travel have been reported in developed regions such as North America, Europe, Japan, New Zealand, and Australia. The reporting of such infections together with the availability of more comprehensive molecular and serological data has led to the re-evaluation of hepatitis E virus (HEV) epidemiology, and the acceptance that autochthonous (locally acquired) hepatitis E is a clinical problem in developed countries.

The HEV virus

HEV is a single-stranded, positive-sense RNA virus and the sole member of the genus Hepevirus. Two major species of the virus are recognised: mammalian HEV, a virus that causes acute hepatitis in human beings and has a reservoir in pigs and possibly a range of other mammals; and avian HEV, causing big liver and spleen disease in chickens. This Review focuses on mammalian HEV, since avian HEV differs genetically from mammalian HEV, has never been recovered from mammals, and has not been associated with human cases.

Figure 1: Rooted phylogenetic tree of hepatitis E genotypes, showing the relation of partial nucleotide sequences from open reading frame (ORF2)

The four groupings show the geographical distribution of the genotypes. Sequences derived from swine are shown in bold, illustrating the close homology between swine and human sequences. ORF2 codes for a capsid protein.

Genotype 1

Genotype 2

Genotype 3

Genotype 4
HEV in developing countries

HEV was not recognised as a distinct aetiological agent until the 1980s; until then, epidemics of hepatitis in the developing world had been linked to hepatitis A virus (HAV) infections.25,26 The subsequent development of serological assays showed HEV to be endemic throughout tropical and subtropical countries, with periodic epidemics reported from the Indian subcontinent,27–30 southeast Asia,31,32 Africa,33–35 and Mexico.36 Although foodborne epidemics have been reported in China,37 most HEV-associated epidemics have been caused by contaminated water.38 Such epidemics usually follow heavy rainfall39 and can involve many thousands of cases.40 Sporadic cases of HEV have also been reported, occurring at much higher rates in endemic regions than in non-endemic regions.41,42

As expected, studies in endemic regions show high seroprevalence rates ranging from 15% to 60%.43–45 Notably, the age-specific seroprevalence profiles for HEV are found to differ from those reported for antibody to HAV even though, in endemic countries, the transmission routes for these two viruses are similar. Whereas the anti-HAV seroprevalence rate reaches more than 95% in children by the age of 10 years, anti-HEV is rarely detected in children, increasing to 40% in young adults without substantial increases later in life.46

The peak incidence in sporadic cases of hepatitis E in endemic regions occurs in 15–35-year-olds.25,26,43 This is unlikely to be because of differential exposure of this age-group to HEV, since 15–35-year-olds make up the bulk of cases in large waterborne epidemics when all age-groups are exposed.25 Additionally, HEV infections are predominantly reported in men with a male-to-female ratio ranging from 1/1 to 3/1.47 This sex bias is, however, not seen in children presenting with hepatitis E.48 The reason why men more commonly develop hepatitis E infection is not understood.

Hepatitis E infection in most individuals manifests as a self-limiting, acute, icteric hepatitis. Mortality rates associated with HEV are low and are thought to be about 1% in the general population.49 However, the mortality rate rises substantially to approximately 20% during pregnancy, when the disease is more severe.50,51 The reason for the poor outcome in pregnancy is unknown; there have been few descriptions of hepatitis E in pregnancy in developed countries. Reports of such cases are entirely restricted to travellers returning from endemic areas, and suggest that such patients develop severe hepatitis and liver failure.52

Autochthonous HEV in developed countries

Clinical and laboratory features

The clinical features of autochthonous hepatitis E infection range from asymptomatic infection to mild hepatitis to subacute liver failure.4–12,52 In a UK hospital-based study of patients with unexplained hepatitis, 40 patients with autochthonous HEV were identified, of whom 75% were icteric, with affected individuals presenting a range of other non-specific symptoms (table 1).52

The incubation period of autochthonous hepatitis E infection ranges from 2 to 9 weeks. The presentation of HEV in individuals infected in developed countries seems to be similar to that from endemic regions; however, the mortality rate is higher, ranging from 8% to 11% (table 2).

Peak viraemia occurs during the incubation period and the early acute phase of disease (see figure 2). Immediately before the onset of clinical symptoms HEV RNA can be detected in the blood and stool. The concentration of serum liver enzymes rises, with a predominant transaminitis, peaking at about 6 weeks’ post exposure before falling to normal levels by week 10. The abnormality in serum liver enzyme concentrations at presentation is variable (table 2), and except in the few patients who go on to develop liver failure, the rise in serum transaminases and bilirubin usually peaks at presentation. A few days to weeks after the onset of clinical symptoms, HEV RNA is
cleared from the blood; however, the virus continues to be shed in stool for another 2 weeks. The period of viraemia can be very brief in some patients. It is probable that most infections are asymptomatic or anicteric, or both. This would account for the discrepancy between the perceived rarity of clinically apparent infections and the relatively high anti-HEV IgG seroprevalence in some developed countries.

Compared with hepatitis E infections in the developing world, in developed countries most autochthonous hepatitis E infections are reported in middle-aged and elderly men (table 2). As in endemic regions, secondary and intrafamilial spread have rarely been reported. Most autochthonous HEV infections are self-limiting; however, comprehensive follow-up studies of 40 HEV-infected individuals showed that six (15%) patients developed complications. Moreover, 8–11% of HEV-infected patients develop fulminant hepatitis and liver failure (table 2). The outcome can be poor in those individuals with underlying chronic liver disease, with mortality approaching 70%. A study from India showed that patients with chronic liver disease who are “superinfected” with hepatitis E have a 1-year mortality rate of 70%.

Autochthonous hepatitis E in developed regions is frequently misdiagnosed as drug-induced liver injury, a common problem that occurs with increased frequency in elderly people. The diagnosis of drug-induced liver injury is based on the presence of all three of the following standard criteria (or two criteria plus worsening of liver biochemistry on rechallenge): a temporal association between the onset of drug therapy and biochemical evidence of liver injury; a temporal association between cessation of drug therapy and improvement in liver biochemistry; and the exclusion of alternative diagnoses. A retrospective analysis showed that 21% of 28 patients who met the standard criteria for drug-induced liver injury did not have the condition, but instead had autochthonous hepatitis E.

Until very recently, chronic infection with HEV was thought not to occur. However, chronic hepatitis E infection has been documented in patients receiving immunosuppressive therapy following organ transplantation. In a French study of hepatitis E infection in solid organ transplant recipients, of the 14 patients who developed hepatitis E infection post transplantation, eight patients went on to develop chronic liver disease with a persistently raised transaminase concentration, persistent viraemia, and progressive inflammation and fibrosis on liver biopsy; and the exclusion of alternative diagnoses. A retrospective analysis showed that 21% of 28 patients who met the standard criteria for drug-induced liver injury did not have the condition, but instead had autochthonous hepatitis E.

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Figure 2: Schematic representation of HEV infection, showing virus detection at different sites and serological response

Table 2: A comparison of demographics, laboratory values, and outcome for patients with hepatitis E in developed (UK, Japan, France) and developing (India) countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of cases</th>
<th>Age Number of men (%)</th>
<th>Mean bilirubin concentration at presentation</th>
<th>Mean alanine aminotransferase concentration at presentation</th>
<th>Number of patients with hepatic complications</th>
<th>Number of patients with non-hepatic complications</th>
<th>Number of deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalton et al (2008), UK</td>
<td>40</td>
<td>Mean 65 years (range 35–86)</td>
<td>31 (78%)</td>
<td>105 μmol/L (range 3–417)</td>
<td>1380 IU/L (range 50–3346)</td>
<td>3/40 (8%)</td>
<td>3/40 (8%)</td>
</tr>
<tr>
<td>Okamoto et al, (2003), Japan</td>
<td>46</td>
<td>Mean 60 years (range 38–86)</td>
<td>40 (87%)</td>
<td>-</td>
<td>-</td>
<td>5/46 (11%)</td>
<td>-</td>
</tr>
<tr>
<td>Peron et al (2006), France</td>
<td>23</td>
<td>Mean 54 years (SD 17)</td>
<td>17 (74%)</td>
<td>9.4 times upper limit of normal (SD 10.3)</td>
<td>55.4 times upper limit of normal (SD 48.6)</td>
<td>2/23 (9%)</td>
<td>0/23</td>
</tr>
<tr>
<td>Khuroo (1980), India</td>
<td>275</td>
<td>21–30 years</td>
<td>153 (56%)</td>
<td>102 μmol/L, (SD 63.9)</td>
<td>-</td>
<td>10/275 (4%)</td>
<td>-</td>
</tr>
</tbody>
</table>

*not reported. †Two of three deaths due to subacute liver failure. ‡One of two deaths due to liver failure. §All deaths were due to liver failure, six of whom were pregnant women.

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Hepatic histopathology
Most patients with autochthonous hepatitis E do not require a liver biopsy since they have a self-limiting illness. A few patients will have more severe hepatitis with worsening liver blood tests and therefore a liver biopsy is sometimes helpful. There are few data on the hepatic histopathology of acute autochthonous hepatitis E, and such reports are limited to patients with severe disease.

Liver histology of acute autochthonous hepatitis E in the non-cirrhotic liver is similar to that seen in acute viral hepatitis, with lobular disarray with reticulin framework distortion. Portal tracts are expanded by a severe mixed polymorph and lymphocytic inflammatory infiltrate. Moderate to severe interface hepatitis and cholangiolitis are also present (figure 3). In one study of three patients with autochthonous hepatitis E, polymorphs were shown to be concentrated at the periphery and interface of the liver, with lymphocytes—including aggregates—concentrated centrally. These findings might be helpful in distinguishing autochthonous hepatitis E from other causes of hepatitis—for example, autoimmune hepatitis—but are based on a small number of cases and require confirmation.

In patients with hepatitis E who have underlying cirrhosis, the liver histology is non-specific and could easily be mistaken for alcoholic hepatitis in the context of established ethanolic cirrhosis (figure 4).

In the small number of immunosuppressed transplant patients who have developed chronic infection with HEV, the liver histology shows progressive fibrosis and portal hepatitis with lymphocytic infiltration and piecemeal necrosis, with progression to cirrhosis.

Laboratory diagnosis
Although HEV particles have been visualised by electron microscopy in the stools of infected human beings and there has been recent progress with cell culture, the routine laboratory diagnosis of hepatitis E depends on serology and nucleic acid amplification techniques. The antibody response to HEV infection follows a conventional course with specific IgM usually detectable at the onset of symptoms or deranged liver function. IgG reaches a peak shortly after and can persist for years (figure 2).

Most primary serological testing uses an EIA format, although rapid immunochromatographic assays have been developed, which make near-patient and field testing feasible. A small number of commercial EIA assays are in general use and several “in-house” EIA assays have been developed. These assays use recombinant antigens derived from different strains of HEV. This diversity of strains should not affect the accuracy of the assays because it seems that HEV viruses of different genotypes constitute a single serotype. IgM serology is often used to identify acute cases, but it is not always detectable and false-positive results occur.

The duration of IgM positivity varies between patients and also depends on the assays used, but strongly positive results are rare after 3 months.
Specific IgG is usually produced early in infection and concentrations rise rapidly afterwards. Estimates of the duration of the IgG response and immunity to subsequent infection vary, but antibody has been detected for at least 12 years after acute infection. This variation might result in part from differences in the assays used and from the extent of continued exposure to HEV. The negative seroconversion rate has been estimated at 1-4% per year in China and secondary infections have been documented, implying that protection is not lifelong. IgG assays have been adapted to quantify the antibody response and although there is a WHO standard for measuring anti-HEV IgG, the protective levels of antibody have not yet been established. The ability to determine protective levels of vaccine-induced antibody will be useful if immunisation against HEV is to be developed. Determination of antibody avidity in the early post-hepatitis period can be used to distinguish between IgG produced following a recent or distant infection, but this technique requires further validation.

Conventional and real-time RT-PCR assays have been used to detect HEV RNA in clinical specimens (mainly blood) and seem to be more sensitive than serology for hepatitis E diagnosis. Assuming that contamination of blood) and seem to be more sensitive than serology for hepatitis E diagnosis. Assuming that contamination is non-specific and reflects cross-reacting antibodies. Subclinical infections certainly occur. Similarly, acute hepatitis E is not recognised in many cases either because serology is not done or because cases are assigned to other causes such as drug-induced hepatitis. Finally, there is the question of the specificity of the antibodies detected by HEV IgG assays in population studies. This is difficult to assess in the absence of a history of proven infection. However, sera tested in IgG assays based on a variety of HEV antigens give broadly concordant results, which suggests that the antibodies are truly directed at HEV. Immunoblot assays have confirmed the reactivity of sera in seroprevalence studies and an interesting new development is the use of interferon-based assays of cell-mediated immunity to confirm previous exposure to HEV. Thus, it often seems that positive HEV IgG serology does reflect previous exposure to HEV, but that seroprevalence data are dependent on the population tested and the assays used. High IgG rates in developing countries are a reflection of high rates of clinical infection; in developed countries much of the primary infection is unrecognised.

HEV incidence

As previously noted, the seroprevalence data from industrialised countries suggests that subclinical or unrecognised infection is common. However, the incidence of autochthonous hepatitis E is not known. The number of documented cases in the UK has risen substantially over the past few years. This rise is almost certainly a result of increased and improved testing and case ascertainment rather than any true increase in incidence. Moreover, recent data from the UK has shown that hepatitis E is more common than hepatitis A.

Data from France and Japan show similar trends. Although autochthonous hepatitis E has been reported from a wide range of developed countries, the literature contains very few reports from the USA, despite anti-HEV IgG seroprevalence of up to 21% in US blood donors. The reason for this disparity is uncertain. It could be that in the USA for some reason HEV causes fewer cases of clinical disease, or that transmission routes are qualitatively or quantitatively different. Another explanation is that most cases are simply “missed” because hepatitis E infection is not considered a diagnostic possibility in patients with unexplained hepatitis.

Epidemiology and source of infection

The source and route of infection of autochthonous hepatitis E in human beings in developed countries is not certain. In addition to human beings, virological evidence of mammalian HEV has been found in domestic pigs, wild boar, deer, mongoose, and bivalves. In all these animals—with the exception of a report from Cambodia of a pig with a genotype 1 virus—the HEV identified was either genotype 3 or 4. Antibodies to HEV (but not...
HEV RNA) have been detected in a wide range of domestic and feral mammals including cats, dogs, cattle, sheep, goats, horses, macaques, donkeys, rats, and mice.\textsuperscript{22,36–31}\n
Evidence for differences in genotype virulence is not abundant. Based on experimental cross-infection data,\textsuperscript{23} the genotype 3 strains are considered by some to be attenuated for human beings. There is little published evidence to date, however, of comparative assessments of the relative morbidity and mortality of travel-associated (genotype 1 or 2) and autochthonously acquired (genotype 3 or 4) hepatitis E. In reciprocal cross-infection trials using non-human primates and pigs, genotype 1 strains produced more severe pathology than genotype 3 strains.\textsuperscript{23} A recent study of the immunodominant neutralisation domain of the capsid gene (ORF2) identified aminoacid 497 as a determinant of zoonotic potential and host selection.\textsuperscript{32} There is also evidence from India that subtype differences might be responsible for the apparent inability of the genotype 4 HEV strains to infect human beings.\textsuperscript{32} Investigators showed 26 aminoacid substitutions of Indian HEV genotype 4 strains, compared with genotype 4 strains found in pigs and people in China, Japan, and Taiwan.

The first evidence of a zoonotic source of autochthonous hepatitits E resulted from the observation in the USA that the partial nucleotide sequences of two pig and two human HEV strains were very closely related genotype 3 strains.\textsuperscript{24,27} In many developed countries, compared with travel-related cases, the human autochthonously acquired cases showed the closest genetic homology to pig strains from the same region\textsuperscript{7,23–25} (figure 1). Additionally, high to very high seroprevalences of HEV (100% in some USA populations) were reported in the pig herds of many countries, both developed and developing.\textsuperscript{27,28,130} Occupational exposure to pigs was also identified as a risk factor for hepatitis E in human beings. This evidence was based not on clinical cases, since there are only a few documented,\textsuperscript{13,10} but on reports of veterinarians and other pig industry workers who presented with high HEV IgG seroprevalence.\textsuperscript{152–155} The available data show that at any one time, more than 20% of pigs in pig production units are excreting HEV in faeces,\textsuperscript{114,115} and large quantities of HEV most probably enter watercourses as a consequence of run-off from outdoor pig farms. HEV has been detected in slurry lagoons on pig farms,\textsuperscript{114–118} from urban sewage works, and from pig slaughterhouses.\textsuperscript{116,118} We do not know the risks of spreading untreated slurry on farmland. However, HEV recovered from sewage and slurry has been shown to infect rhesus monkeys.\textsuperscript{156,118}

The strongest evidence of zoonotic transmission of hepatitis E is from Japan, where consumption of uncooked or poorly cooked wild boar and deer meat resulted in hepatitis E infection, with identical viruses recovered from the meat and from the patients.\textsuperscript{140–142} Contamination of retail pig liver with HEV has been reported in Japan, the USA, and the Netherlands, but could not be detected in a sample of UK pig livers.\textsuperscript{143–146} In the USA, HEV was found to be infective after heating to 56°C for 1 h, but was inactivated at an internal liver temperature of 71°C for 5 min,\textsuperscript{145,147} which means that light cooking might not eliminate the risk of infection from contaminated meat.

In 1985 Nanji and French\textsuperscript{148} reported a strong correlation between pork consumption and mortality from chronic liver disease, based on data from the mid 1960s and mid 1970s from 16 different developed countries and ten Canadian provinces. These findings have never been adequately explained. A provisional report using data from 1990–2000 confirms that there is indeed a relation between pork consumption and mortality from chronic liver disease in 18 developed countries.\textsuperscript{149} Multivariate regression analysis showed that alcohol consumption, pork consumption, and hepatitis B virus (HBV) seroprevalence were all independent risk factors for death from chronic liver disease, but beef consumption was not. The reason for these observations is uncertain. It could be a result of factors in pig meat (eg, pork fat) that cause cirrhosis.\textsuperscript{150} Another possible explanation is that an infectious agent found in pig meat causes increased mortality in patients with pre-existing chronic liver disease.\textsuperscript{149} A candidate for the latter hypothesis is HEV, since viable HEV has been found in pig meat in the human food chain,\textsuperscript{141} and HEV superinfection in patients with chronic liver disease carries a high mortality.\textsuperscript{59–61} Moreover, hepatitis E infection is rarely considered a diagnostic possibility as a cause of decompensation in patients with chronic liver disease in developed countries, and even when it is the diagnosis can be difficult (figure 4).\textsuperscript{67} Should the above hypothesis prove to be correct, this might mean that HEV could have a—a currently unrecognised—important role in the natural history of chronic liver disease in developed countries, as has been clearly demonstrated in India.\textsuperscript{151} A systematic study is currently underway looking for the presence of HEV in patients with decompensated chronic liver disease in the UK. The results are awaited with interest.

Despite the serological, clinical, and molecular genetic evidence suggesting that autochthonous hepatitis E might be a porcine zoonosis, a direct connection between the disease and either consumption of pig meat or exposure to pigs is sparse. In addition to the cases in Japan, a pet pig in France was shown to be the most likely source of infection for its owner\textsuperscript{152} and a slaughterhouse worker in Spain was infected with an HEV strain with close homology to those recovered from the slaughterhouse effluent.\textsuperscript{153} Moreover, a detailed epidemiological investigation of 33 confirmed and 67 suspected autochthonous hepatitis E cases in the UK in 2005 failed to indicate a risk factor related to contact with pigs or ingestion of pig products, or indeed any other obvious risk factors, leaving the source and route of most of the transmissions unknown.\textsuperscript{67} We know that ingestion of infected animal tissue is one zoonotic transmission route, but the evidence indicates that several routes could be contributing to the burden of human HEV infections.
in developed regions. Confirmed, suspected, and potential transmission routes in developed regions are shown in figure 5. Central to understanding the transmission routes is the ability to estimate the environmental survival of HEV, a topic that is currently receiving much attention.

More recent findings have led to speculation of an additional route of transmission for hepatitis E virus. Higher HEV seroprevalence levels in specific groups such as paid blood donors positive for other bloodborne viruses and in repeatedly transfused haemodialysis patients have led to suggestions that HEV could be acquired parenterally.151,152 Subsequent reports of transmission of HEV through blood transfusions from Saudi Arabia, Japan, and more recently the UK have added weight to this argument.153–155 When characterised, the strains involved in the cases from Japan and the UK were shown to be indigenous viruses.153,155 Of additional concern is that studies from Japan have shown that a small proportion of their blood donors were viraemic and
potentially able to cause transfusion-associated HEV in the absence of raised alanine aminotransferase concentrations and signs or symptoms of hepatitis. Such data indicate that there is a risk of post-transfusion hepatitis E, and this should be considered in areas that are thought to be non-endemic.

Treatment and prevention

The treatment of autochthonous hepatitis E is supportive. Patients with pre-existing chronic liver disease who develop hepatic failure as a result of hepatitis E infection should be considered for liver transplant, since such patients have a poor outcome.

Hepatitis E is a major cause of morbidity in the developing world and the most important future development in this regard will be the introduction of an effective vaccine. Several hepatitis E vaccines are under development, including a vaccine that has now completed a phase II randomised placebo-controlled trial in Nepal. The vaccine was shown to have an efficacy of 95-5% (95% CI 85.6–98.6%) in 898 Nepalese male army recruits over a 2–3-year period, with 66 (7%) of 896 participants in the placebo group becoming infected with HEV during the study. At 2 years’ follow-up, only 56% of individuals who had been vaccinated had detectable anti-HEV antibody (more than 20 Walter Reed antibody units per mL). It is uncertain if individuals with antibody levels below this cut-off point are susceptible to infection.

These results are encouraging but some questions remain to be answered. The most important is the vaccine’s safety and efficacy in women, since mortality is high in pregnant women infected with HEV. The second issue that requires clarification is the durability of vaccine-induced immunity. Finally, it is uncertain how a vaccine programme would be financed, because some of the countries in greatest need are among the poorest in the world.

Recommendations regarding prevention of autochthonous hepatitis E in developed countries are difficult to make, since the incidence, source, and route of infection are currently uncertain, and no vaccine is yet available. Thus, the key imperative in terms of prevention is to identify whether pigs are the true source of infection. Until then, it would seem sensible to advise that pork should be cooked thoroughly (above 56°C) and infected, vaccination should be targeted at these individuals. Patients with chronic liver disease are currently advised to be vaccinated against HAV and HBV. Including HEV vaccine in this programme would seem logical, since superinfection with any of these viruses in the context of pre-existing chronic liver disease carries a high risk of mortality. The problem with this approach is that unidentified compensated chronic liver disease is common in the community, and so all “at-risk” individuals would not be vaccinated. A more vigorous approach would be to vaccinate whole populations, possibly at the age of 40 years. This would be a huge undertaking and would need careful cost-benefit analysis before introduction.

Conclusions

Hepatitis E in developed regions is far more common than previously recognised and could have a zoonotic source. The disease has a predilection for older men in whom it carries a substantial morbidity and mortality, particularly in patients with chronic liver disease. Hepatitis E should be included in the differential diagnosis in patients with unexplained hepatitis, whatever their age or travel history. The incidence of autochthonous hepatitis E in developed countries is unknown, as is the mode of infection. Until these data are established it is difficult to know what preventive strategies are most appropriate.

Conflicts of interest

HRD has had travel and accommodation costs paid by GlaxoSmithKline. All other authors declare that they have no conflicts of interest.

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