Hepatitis E virus infection: an emerging occupational risk?

A. De Schryver1,2, K. De Schrijver2, G. François2, R. Hambach2, M. van Sprundel2, R. Tabibi3 and C. Colosio3

1IDEWE Occupational Health Services, 3001 Leuven, Belgium, 2Epidemiology and Social Medicine, University of Antwerpen, Campus Drie Eiken DR 224, Universiteitsplein 1, 2610 Antwerpen, Belgium, 3Department of Health Sciences, University of Milan and International Centre for Rural Health, University Hospital San Paolo of Milan, 20142 Milan, Italy.

Correspondence to: A. De Schryver, Epidemiology and Social Medicine, University of Antwerpen, Campus Drie Eiken DR 224, Universiteitsplein 1, 2610 Antwerpen, Belgium. Tel: +32 3 265 25 24; fax: +32 3 265 28 75; e-mail: antoon.deschryver@uantwerpen.be

Background  Hepatitis E virus (HEV) infection is endemic in many developing countries, causing substantial morbidity. Transmission is primarily faeco-oral and is associated with both sporadic infections and epidemics in areas where poor sanitation and weak public health infrastructures exist. Recently, it has become clear that HEV is also an endemic disease in industrialized countries. Moreover, a porcine reservoir and growing evidence of zoonotic transmission have been reported in these countries, suggesting the possibility of occupational transmission to man.

Aims  To summarize the current knowledge on the epidemiology and prevention of transmission of HEV infection in occupational settings.

Methods  The following key words were used to explore PubMed: hepatitis E, disease, epidemiology, profession(al), occupation(al).

Results  After screening of the results, 107 publications were retained. In non-endemic regions, seroprevalence varied from a few per cent (2–7.8%) in Europe, Japan and South America to 18.2–20.6% in the USA, Russia, UK, southern France and Asia. A meta-analysis of 12 cross-sectional studies evaluating HEV immunoglobulin G (IgG) seroprevalence in individuals occupationally exposed to swine showed greater odds of seropositivity in the exposed group but also a high degree of heterogeneity. A funnel plot suggested publication bias.

Conclusions  There was a significant association between occupational exposure to swine and HEV IgG seroprevalence, but the level of prevalence detected depended also on the type of HEV IgG kits used. Further research, including on mechanisms and risk factors for infection, as well as the development of better serological tests for identification of infection, is required.

Key words  Disease; epidemiology; hepatitis E; occupation; profession(al).

Introduction  People infected with hepatitis E virus (HEV) can develop hepatitis. Unlike those infected with hepatitis B virus, these people do not have an increased risk of liver cancer. It is believed that many subclinical cases occur in the western world. Some studies have found a high prevalence of antibodies to HEV in the general population. The ratio of symptomatic to asymptomatic infection in outbreak settings is reported to range from 1:2 to 1:13. Most HEV-infected people recover completely. The overall case fatality rate is about 1%.

However, several population groups are at increased risk. Firstly, HEV is highly dangerous for pregnant women, who are at risk of serious illness and mortality. In the third trimester of pregnancy, mortality rates can be as high as 10–30%. Secondly, HEV potentially leads to decompensation and mortality in people with pre-existing chronic liver disease. Thirdly, in contrast to the situation in developing countries, an increasing number of cases progressing to chronic hepatitis and chronic liver disease are being reported in developed countries. Those at risk are people on immunosuppressive treatment following solid organ transplants [1].
HEV is endemic in many developing countries where it causes substantial morbidity. In these countries, the virus, particularly genotypes 1 and 2, is transmitted primarily by the faeco-oral route and is associated with both sporadic infections and epidemics in areas of poor sanitation and weak public health infrastructures [2]. In industrialized countries, HEV infections were traditionally thought to occur infrequently and only in individuals who had become infected while travelling in areas where the virus is endemic [3]. However, cases of sporadic HEV in people with no history of recent travel have been reported in industrialized regions [2]. The reporting of such infections together with the availability of more comprehensive molecular and serological data has led to the re-evaluation of HEV epidemiology and the acceptance that autochthonous (locally acquired) HEV might be a problem in industrialized countries. The source and route of autochthonous HEV infection in humans in industrialized countries is not certain. Virological evidence of mammalian HEV has been found in domestic pigs, wild boar, deer, mongoose and bivalves [4–6], possibly explaining the geographical clustering of genetically similar human and swine strains of HEV [7]. It is believed that swine could be a source of zoonotic HEV and therefore HEV could be considered an occupationally transmitted infection in people working with pigs. To further document HEV as an occupational disease, we performed a PubMed search.

Methods

The following key words were used, alone or in different combinations, to explore PubMed, without any chronological and/or geographical restrictions: hepatitis E, disease, epidemiology, profession(al), occupation(al). The results were further screened for their relevance.

Results

After screening for relevance, 112 publications were eventually taken into consideration for use in this review.

The genome and structure of HEV are unique, so a new family was created after its first molecular characterization and sequencing in 1990. It is the sole member of the Hepeviridae family, genus Hepevirus [8]. HEV is a spherical, non-enveloped virus with icosahedral symmetry. Viral particles are approximately 32–34 nm in diameter and are composed of a capsid protein assembled into a highly structured multimer [9]. All HEV strains belong to a single serotype, but based on genetic diversity of HEV genome sequences four phylogenetically distinct HEV genotypes [2–5] have been defined [9]. Interestingly, the majority of HEV strains from human cases acquired in industrialized countries are genetically different from those isolated cases in, or imported from, hyper-endemic countries [3]. Genotypes 1 and 2 occur only in humans, while genotypes 3 and 4 have been detected in humans and animals like swine. Furthermore, HEV is being detected in an increasing number of animal species [10]. Genotypes 1 and 2 are mainly present in developing countries; in industrialized countries, genotypes 3 and 4 are often detected in swine, wild boar, deer and rabbits, and they can be associated with the reported autochthonous infections, suggesting the existence of zoonotic HEV infections [11]. Genotype 3 is mostly present in industrialized countries and genotype 4 in Asian countries [10].

The clinical symptoms of human HEV are not distinguishable from other types of acute viral hepatitis, so accurate diagnosis of HEV relies on laboratory tests [2,9]. The incubation period of HEV in human volunteers after oral exposure is normally 4–5 weeks. A more variable incubation period of 2–10 weeks has been reported during HEV outbreaks in which the time of water contamination was known. Research among non-human primates has shown a direct association between infective dose and disease severity but an inverse relationship to the incubation period [12].

In endemic areas, such as India and south-east Asia, studies on HEV seroprevalence have shown high rates, ranging from 27 to 80% in the general population. In these regions, HEV epidemics affect thousands of people, mostly young adults [2]. In non-endemic regions, seroprevalence varies from a few per cent (2–7.8%) in Europe (Italy, Spain, northern France, Germany, Greece, the Netherlands, Portugal), Japan and South America (Brazil, Argentina, Chile) to 18.2–20.6% in the USA, Russia, UK, southern France, Hong Kong, Korea and China [2,13]. In a study on 100 outpatients in Belgium, the prevalence was 14% [14].

Studies from the UK using enhanced surveillance have confirmed that the overall changes in case numbers between 2003 and 2012 were accounted for by the rise and fall in numbers of indigenously acquired HEV infections. The case numbers associated with travel remained relatively stable over the study period [15]. In a recent study of around 3500 subjects with suspected acute viral hepatitis from Lothian region (Scotland), the frequency of detection of HEV infection was over 31 times higher than that of HAV and seven times higher than that of HBV, confirming that HEV is an increasingly important cause of acute hepatitis [16].

Transmission of HEV in industrialized countries has been reviewed recently [3]. In that review, the authors found no evidence of one main transmission route or risk factor for HEV infection or disease in Europe, but multiple routes of transmission were thought to exist [3]. Potential risk factors and transmission routes were discussed. Autochthonous HEV genotype 3 (gt3)-associated cases were on average older than the general population and predominantly male, which could be due to higher
likelihood of pre-existing comorbidity or difference in behaviours (e.g. dietary preferences) [3]. A recent study confirmed the increased risk for older males but could not identify any specific associated risk factors [15].

Increasingly, cases of acute HEV were being reported with chronic liver diseases, liver cirrhosis, history of high alcohol consumption, diabetes mellitus, compromised immune status, hypertension, obesity, arthritis, ischaemic heart disease or previous HAV infection [3]. Even though some of these comorbidities were associated with the comparatively older age of the patients, pre-existing diseases or behaviour affecting the liver did seem to have an impact, not on infection but on whether HEV infection resulted in clinical disease. This hypothesis is further strengthened by the fact that in 14 out of 18 seroepidemiological studies the authors found no association between anti-HEV immunoglobulin G (IgG) positivity and comorbidities [3].

The detection of widespread HEV gt3 RNA suggests that swine HEV is ubiquitous in pigs in Europe [3]. During HEV infection, the virus is shed mostly via the faeces. Consequently, HEV RNA has been found in the pig farm environment [17]. Rabbits may also be a significant source of infection for humans [18]. HEV gt3 nucleotide sequences from pigs, rabbits and wild boar and those from human cases have been found to be closely related. Such sequence comparison data suggest that HEV carried by pigs, rabbits and humans is genetically closely related and that cross-species transmission is occurring [3,19]. Despite the ubiquity of HEV in a considerable proportion of pig herds in Europe, there have been no studies proving that contact with pigs is a risk factor for developing HEV infection [3]. Direct zoonotic transmission of symptomatic HEV from infected meat to human beings has been documented only twice [20,21]. However, there is ample indirect evidence of zoonotic transmission of HEV and transmission between pigs, wild boar or deer and humans is of particular concern [10].

The high rate of asymptomatic HEV infection worldwide has raised concern about infection via blood donation. Post-transfusion hepatitis E has been reported in many countries [9]. A study of blood donors in London, UK, showed 11% of donor sera to be HEV IgG reactive and 0.7% IgM reactive [22]. 0.7% of plasma minipools from English donors contained HEV RNA [23].

### Table 1. Descriptive summary of 12 studies comparing HEV immunoglobulin G (IgG) seroprevalence in groups with and without occupational contact with swine

<table>
<thead>
<tr>
<th>Country</th>
<th>Populations studied</th>
<th>Prevalence in % (no. sampled)</th>
<th>Crude OR (95% CI)</th>
<th>Significance level (statistical test)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>SW, GP</td>
<td>75.9 (340)</td>
<td>1.74 (1.24–2.44)</td>
<td>P &lt; 0.05 (multivariable logistic regression)</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td>(i) Upstream from swine production</td>
<td>50.1 (425)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(ii) Downstream</td>
<td>61.2 (1295)</td>
<td>1.29 (1.02–1.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>SW, GP</td>
<td>67 (52)</td>
<td>8.09 (4.49–14.5)</td>
<td>P &gt; 0.01 (χ²)</td>
<td>[32]</td>
</tr>
<tr>
<td>China</td>
<td>SW, GP</td>
<td>31.6 (985)</td>
<td>1.73 (1.48–2.01)</td>
<td>P &lt; 0.01 (χ²)</td>
<td>[33]</td>
</tr>
<tr>
<td>Denmark</td>
<td>F, GP</td>
<td>50 (283)</td>
<td>2.11 (1.42–3.14)</td>
<td>P &lt; 0.05 (χ²)</td>
<td>[34]</td>
</tr>
<tr>
<td>Italy</td>
<td>SW, GP</td>
<td>3.3 (92)</td>
<td>1.14 (0.35–3.66)</td>
<td>NS</td>
<td>[35]</td>
</tr>
<tr>
<td>Moldova</td>
<td>SW, GP</td>
<td>51 (264)</td>
<td>3.45 (2.37–5.04)</td>
<td>P &gt; 0.001 (χ²)</td>
<td>[25]</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>SV, GP</td>
<td>11 (49)</td>
<td>5.55 (1.89–16.3)</td>
<td>P &lt; 0.05</td>
<td>[28]</td>
</tr>
<tr>
<td>Spain</td>
<td>SW, SV, GP</td>
<td>19 (97)</td>
<td>5.39 (1.76–16.48)</td>
<td>P &lt; 0.05 (bivariate logistic regression)</td>
<td>[27]</td>
</tr>
<tr>
<td>Sweden</td>
<td>SW, GP</td>
<td>13 (115)</td>
<td>1.47 (0.63–3.43)</td>
<td>P &lt; 0.05</td>
<td>[36]</td>
</tr>
<tr>
<td>Taiwan</td>
<td>SW, GP</td>
<td>27 (30)</td>
<td>4.18 (1.14–14.4)</td>
<td>P &lt; 0.05 (χ²)</td>
<td>[37]</td>
</tr>
<tr>
<td>USA</td>
<td>SW, GP</td>
<td>10.9 (165)</td>
<td>5.06 (1.46–17.6)</td>
<td>P &lt; 0.01 (χ²)</td>
<td>[38]</td>
</tr>
<tr>
<td></td>
<td>SV, GP</td>
<td>23 (295)</td>
<td>1.61 (1.12–2.31)</td>
<td>P &lt; 0.05 (univariable logistic regression)</td>
<td>[26]</td>
</tr>
</tbody>
</table>

CI, confidence interval; F, farmers; GP, general population; NS, not significant; OR, odds ratio; SV, swine veterinarians; SW, swine workers. Samples were appropriately matched for geographical location, sex and age.
findings have been reported in China and a global investigation into plasma fractionation pools reported that 10% of the pools tested were HEV RNA positive [9]. The implication is that transmission of HEV associated with transfusion must be occurring but is currently underdiagnosed because donated blood is not tested for HEV and most resulting infections are asymptomatic.

Studies on different population groups have shown that people in animal handling occupations, such as pig breeders, veterinarians or slaughterhouse personnel, are statistically more frequently positive for anti-HEV antibodies, suggesting an occupational risk. Studies in the Netherlands have shown a seroprevalence of 6% in non-swine veterinarians and 11% in swine veterinarians [4–7,13,24–28]. Recent data show that in the Benelux countries 7–15% of pigs in pig production units were excreting HEV in faeces [29] and large quantities of HEV most probably enter watercourses as a consequence of run-off from outdoor pig farms. HEV has also been detected from urban sewage works [17], but the results of studies on occupational risk in sewage workers have been inconsistent [30].

Table 1 shows a descriptive summary of 12 studies comparing HEV IgG seroprevalence in groups exposed or unexposed to occupational contact with swine [7,25,27,28,31–38]. Their design was essentially cross-sectional and 10 of 12 studies reported greater odds of seropositivity in the exposed group.

Data regarding seroprevalence might however be affected by the different laboratory kits used in the analysis, which show significant variability in levels of sensitivity [8,39]. Most of the currently available anti-HEV IgG assays have been validated against sera obtained from patients with recent infection and their ability to detect distant infection is unknown. The variability must be taken into account when interpreting HEV seroprevalence data in the current literature. The use of more sensitive IgG assays has led to increases in seroprevalence estimates, by a factor of 3–4 [40,41]. For example, in a study using an insensitive ‘first generation’ IgG assay, the seroprevalence was 3.6%, rising to 16% when a more sensitive, partially validated assay was employed [40]. By using the same sensitive IgG assay, direct comparison of seroprevalence between populations in distinct geographical areas can now be made.

A meta-analysis of 12 cross-sectional studies compared HEV IgG seroprevalence in individuals occupationally exposed to swine and the general population [7]. The pooled estimate effect and corresponding 95% confidence intervals although statistically significant (P < 0.05) were not reported, due to a significant (P < 0.05) Q statistic of 47.7 and an F statistic of 77.0 suggesting a high degree of heterogeneity [42]. A funnel plot suggests publication bias was present in this set of studies [43].

Discussion

The results of our review indicate that swine populations are probably a source of zoonotic HEV. The quantitative summary of evidence, based on meta-analysis of 12 cross-sectional studies, identified a statistically significant association (P < 0.05) between occupational exposure to swine and human HEV IgG seroprevalence. However, the statistically significant (P < 0.05) Cochran’s Q statistic and the high (>75%) I² indicate a high heterogeneity across studies precluding reporting of pooled estimated odds ratio. Possible sources of heterogeneity include variations in susceptibility of different populations, of infectiousness of HEV strains or of intensity of exposure to swine/pork and variation in test performance.

As already mentioned, the performance of different ELISA tests to identify human exposure to HEV has been debated for the past two decades [8,39,44]. The cross-sectional studies mentioned, studying the association between exposure to swine or pork and human HEV seropositivity, employed a variety of ELISA tests, both commercial and in-house, reporting different cut-off values for identifying seropositivity. The overall impact of the heterogeneity across tests on the association between exposure to swine and human HEV seropositivity is unknown, but it suggests that the reported and pooled estimates of association between exposure and outcome are uncertain. Consequently, at present, the answer to the question ‘Does exposure to swine or pork cause increased odds of HEV IgG seropositivity?’ is that at present there is insufficient evidence to confirm a cause-and-effect relationship.

From the viewpoint of occupational epidemiology further suggested research is summarized in Box 1 [6,7]. The resulting information would allow quantification of the risk to public health posed by zoonotic HEV acquired by human exposure to swine, as well as evaluating potential control options. More concretely, a better knowledge of HEV transmission to humans could lead to practical preventive measures for those in direct contact with swine and would further stimulate HEV vaccine research.

In 2011, the first vaccine to prevent HEV was registered in China. Although it is not available globally it could potentially become available in a number of other countries [45]. In the absence of the vaccine, prevention can only be based on the application of hygienic measures for food of animal origin and in animal breeding and meat processing facilities.

In conclusion, a diverse body of evidence suggests swine and possibly other animals act as a reservoir of zoonotic HEV infection, and there is a significant association between occupational exposure to swine and HEV IgG seroprevalence. Evidence of an association between exposure to swine/pork and locally acquired HEV infections has been established. Anti-HEV IgG seroprevalence studies have reported that those working with pigs are at increased risk of infection in some countries in
Hepatitis E virus infection is endemic in many developing countries. It has recently become clear that this is also the case in industrialized countries. A meta-analysis of 12 cross-sectional studies showed a significant association between occupational exposure to swine and hepatitis E virus immunoglobulin G seroprevalence but also a high degree of heterogeneity. Further studies, including large long-term cohort studies, are required. Improved serological assays should be applied. Case–control studies should help to further define risk factors such as age, gender and occupation, including working conditions.

European but not in others. A statistical association exists between positive HEV serology and contact with swine or their environment. A similar situation is observed with slaughterhouse personnel.

The presence of high rates of HEV seropositivity in populations where acute infection is rarely diagnosed suggests that subclinical or unrecognized infection is common and because our knowledge of the epidemiology of HEV (and particularly about any occupational infection risk) remains incomplete, additional studies are needed in these fields. Further research should include investigation of mechanisms and risk factors for infection, as well as the development of sensitive and specific serological tests for identification of infection.

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