Epidemiology of domestically acquired hepatitis E virus infection in Japan: assessment of the nationally reported surveillance data, 2007–2013

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In recent years, there has been an increase in the number of reported hepatitis E virus (HEV) infections from developed countries. To describe recent trends in notification and potential risk groups and risk factors in Japan, HEV infection cases and demographic, food consumption, clinical and laboratory data reported during 2007–2013 were analysed. In total, 530 HEV infections were reported during 2007–2013. Amongst 462 domestic cases, the mean age was 56.5 years (SD 13.9) and 80.1 % were male. Forty-three cases (9.3 %) were asymptomatic, amongst which 11 were detected from blood donations. Whilst ~50 cases were reported annually during 2007–2011, the number of reported cases increased to 121 in 2012 and 126 in 2013. The increase was characterized by a rise in the number of domestic, symptomatic cases (P<0.05) and cases confirmed by anti-HEV IgA detection (P<0.01). HEV genotypes G3 and G4 were consistently dominant. The major suspected source of infection was food-borne, and the major suspected foods were pig, wild boar and deer meat. The observed increase during 2012–2013 was most likely due to the coverage of the anti-HEV IgA assay by the National Health Insurance system in Japan in October 2011 and its acceptance for surveillance purposes. However, the increase was not associated with detection of asymptomatic cases. Moreover, males aged 50–69 years remained as the high-risk group, and pork and other meats continued to be the most suspected items. Our findings indicated that HEV infection is an emerging and important public health concern in Japan.

INTRODUCTION

Hepatitis E is an acute hepatitis caused by infection with hepatitis E virus (HEV), a positive-sense ssRNA virus. Globally, HEV is the most common cause of acute viral hepatitis with an estimated ≥20 million cases believed to occur annually (Kamar et al., 2012; Rein et al., 2012). Hepatitis E shares many clinical characteristics with hepatitis A, including jaundice and general malaise, but its symptoms are often more severe and may include neurological complications. The case fatality rate (CFR) may be as high as 4.0% in some endemic areas (Kamar et al., 2012). There are at least four distinct genotypes of the virus: HEV genotypes G1–G4. In developing countries, outbreaks of HEV infection of variable sizes have been reported (Labrique et al., 2013; Naik et al., 1992; Teshale et al., 2010; Viswanathan, 1957; Zhuang et al., 1991), often associated with water-borne transmission. In these settings, HEV infections are mostly related to G1 or G2. In contrast, HEV G3 and G4 infections are associated with zoonoses (Kamar et al., 2012), and the pig appears to be one of the major reservoirs of HEV, in which the pig liver seems to be highly contaminated (Colson et al., 2010). Human infections of G3 and G4 have been linked to consumption of raw or undercooked pork and other meats (Colson et al., 2010; Kamar et al., 2012).

Decades ago, HEV infection was considered to occur mainly in developing countries, and cases occurring in developed countries were considered to be imported from developing

Received 9 January 2015
Accepted 9 May 2015

Abbreviations: CFR, case fatality rate; EHEC, enterohaemorrhagic Escherichia coli; HEV, hepatitis E virus; MHLW, Ministry of Health Labour and Welfare; NESID, National Epidemiological Surveillance of Infectious Diseases.
settings (Kamar et al., 2012). However, recent reports have shown domestic infections in Europe and New Zealand in relation to HEV G3 and G4 (Dalton et al., 2007, 2008; Garbuglia et al., 2013; Hewitt et al., 2014; Mansuy et al., 2004, 2009; Wichmann et al., 2008). Previous reports from Japan have also indicated that both HEV G3 and G4, but not G1 or G2, are present in the country (Mitsui et al., 2006; Miyamura, 2011; Mizuo et al., 2005). The prevalence of IgG in healthy Japanese was shown to be 1.9–14.1% (Li et al., 2000), which is similar to the proportion observed in India (Arankalle et al., 1995). In 2001, the first domestic case of transfusion-related HEV infection was reported in Hokkaido (Matsubayashi et al., 2004) and, in 2004, an outbreak of HEV infection in a family, including a fatal case, occurred in Hokkaido (Matsubayashi et al., 2008). In addition, consumption of deer meat resulted in a fatality, and pork consumption caused an outbreak, raising concerns about HEV infections (Miyashita et al., 2012; Tei et al., 2003).

Globally, national surveillance of HEV infection is being conducted in several countries and areas, including Australia, Germany, Hong Kong, Japan, Taiwan and the UK (The Department of Health, Australia, 2013; Robert Koch Institute, Germany, 2007; The Department of Health, Hong Kong, 2014; The Department of Health, Taiwan, 2012; Public Health England, UK, 2010; MHLW, 2014). In Japan, national surveillance of HEV infection has been conducted under the Infectious Diseases Control Law.

Detection of anti-HEV IgM as well as HEV RNA is carried out in the national surveillance systems of Australia, Germany, Hong Kong, Japan and the UK (The Department of Health, Australia, 2013; Robert Koch Institute, Germany, 2007; The Department of Health, Hong Kong, 2014; The Department of Health, Taiwan, 2012; Public Health England, UK, 2010; MHLW, 2014). In Japan, national surveillance of HEV infection has been conducted under the Infectious Diseases Control Law.

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Data collection and analysis. Cases reported between 2007 and 2013 were extracted from the NESID database. Data included demographic characteristics, presence of symptoms, laboratory diagnostic methods, history of recent food consumption and history of blood donation. Data for the calendar year 2013 were provisional as of August 2014. Suspected geographical location of infection was assessed using the seven conventional regions of Japan: Hokkaido, Tohoku, Kantō, Chubu, Kinki, Chugoku/Shikoku and Kyushu/Okinawa. This study was conducted for public health purposes and did not require informed consent or ethical approval.

Calculation of notification rate. For each calendar year, each prefecture’s population as of 1 October was obtained from the MHLW and used as the mid-year population. The notification rate for each prefecture per year was calculated by dividing the number of cases reported by the prefecture by the respective prefecture’s population.

Statistical analysis. Two-tailed P values were calculated by the t-test for continuous variables and theχ²-test for categorical variables. P<0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 18 (SPSS).

RESULTS

Increase in the number of reported cases

Between 2007 and 2013, 530 cases of HEV infection were reported. During 2007–2011, ~50 cases were reported annually. The annual number of reported cases increased to 121 in 2012 and 126 in 2013 (Fig. 1). Of the 530 cases, 462 (87.1%) were domestic and 59 (11.1%) were imported cases.
Between 2007 and 2013, at the time of notification, two cases were fatal (CFR 0.4%) and two other cases developed hepatic encephalopathy. The proportion of symptomatic cases was higher in 2012–2013 relative to 2007–2011 (P=0.05) (Table 1). The highest rate of notification was detected by anti-HEV IgA along with or without other methods accounted for 90.5% of the reported cases. Of the 235 domestic cases reported between 2007 and 2011, 19/68 (27.9%) cases that consumed pork liver. Furthermore, 19/68 (27.9%) cases that consumed pork had consumed it raw, 10/20 (50.0%) cases that consumed deer had consumed it raw and 8/39 (20.5%) cases that consumed wild boar had consumed it raw.

### Laboratory tests of domestic HEV infection

Of the 235 domestic cases reported between 2007 and 2011, the majority were identified by PCR (62.1%), which was marked by a significant decrease during 2012–2013 (15.9%; Table 1). In contrast, the number of cases identified by anti-HEV IgA increased significantly between 2012 and 2013 (1.3 versus 67.0%, respectively). In 2013, detection by anti-HEV IgA along with or without other methods accounted for 90.5% of the reported cases. Virus genotypes were reported in 67 cases (14.5%), amongst which HEV G3 and G4 constituted the majority (Table 2). Twenty-nine of 31 G4 genotype cases were reported from Hokkaido, which included two fatal cases. A case with genotype G1 was identified for the first time in Japan 2007–2013.

### DISCUSSION

The annual reported number of domestic cases of HEV infection in Japan increased by nearly twofold in 2012 compared with 2007–2011. This substantial increase was temporally coincident with the use of the anti-HEV IgA assay. Most likely, this rise was thus due to the anti-HEV IgA detection assay kit being covered by the National Health Insurance system in Japan in October 2011, followed by the inclusion of this assay as one of the acceptable laboratory detection methods for national surveillance purposes. According to one study, this kit represented slightly better specificity than the IgM assay (Takahashi et al., 2005); thus, it is noteworthy that adoption of this test resulted in an increase in reported cases and it is unlikely that the increase was due to an increase in the number of false-positive cases. Additionally, the IgA assay is easier to perform than PCR and an affordable method for local public health centres. Such advantages highlight the potential usefulness of this assay for diagnostic and surveillance purposes. To the best of our knowledge, Japan is the first nation to report a sustained HEV infection outbreak associated with consumption of wild boar and deer.

### Table 1. Characteristics of domestic cases of HEV infection, Japan 2007–2013

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=462)</th>
<th>2007–2011 (N=235)</th>
<th>2012–2013 (N=227)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age [years; mean (sd)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56.5 (13.9)</td>
<td>55.1 (13.7)</td>
<td>58.0 (13.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Female</td>
<td>370 (80.1)</td>
<td>186 (79.1)</td>
<td>184 (81.1)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Symptomatic [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>419 (90.7)</td>
<td>207 (88.1)</td>
<td>212 (93.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>No</td>
<td>43 (9.3)</td>
<td>28 (11.9)</td>
<td>15 (6.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>182 (39.4)</td>
<td>146 (62.1)</td>
<td>36 (15.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IgM</td>
<td>62 (13.4)</td>
<td>50 (21.3)</td>
<td>12 (5.3)</td>
<td></td>
</tr>
<tr>
<td>IgA</td>
<td>155 (33.5)</td>
<td>3 (1.3)</td>
<td>152 (67.0)</td>
<td></td>
</tr>
<tr>
<td>Multiple methods†</td>
<td>63 (13.6)</td>
<td>36 (15.3)</td>
<td>27 (11.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Food-borne [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>320 (69.3)</td>
<td>168 (71.5)</td>
<td>152 (67.0)</td>
<td></td>
</tr>
<tr>
<td>Pig</td>
<td>68 (21.3)</td>
<td>35 (20.8)</td>
<td>33 (21.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Wild boar</td>
<td>39 (12.2)</td>
<td>26 (15.5)</td>
<td>13 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Deer</td>
<td>20 (6.3)</td>
<td>14 (8.3)</td>
<td>6 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Multiple animals‡</td>
<td>13 (4.1)</td>
<td>9 (5.4)</td>
<td>4 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Not specified/missing</td>
<td>180 (56.3)</td>
<td>84 (50.0)</td>
<td>96 (63.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Characteristics were compared between 2007–2011 and 2012–2013 using the t-test for age and the χ² test for others.
†Multiple methods include any combination of PCR, IgM and IgA.
‡Multiple animals include any combination of animals.

**Demographic characteristics**

Domestic cases reported from 2007 to 2013 had a median age of 58 years (range 21–90 years), with males accounting for 80.1% and symptomatic cases representing 90.7% (Table 1). Except for 2008 and 2009, males aged 60–69 years showed the highest number of cases relative to other age groups. Amongst females, those aged 50–59 years showed the highest number of cases during 2007–2011, but were replaced by those aged 60–69 years in 2012–2013.

Between 2007 and 2013, at the time of notification, two cases were fatal (CFR 0.4%) and two other cases developed hepatic encephalopathy. The proportion of symptomatic cases was higher in 2012–2013 relative to 2007–2011 (P=0.05) (Table 1). The highest rate of notification was reported from the Hokkaido region (7.1 per million in 2012 and 4.6 per million in 2013) (Fig. 2), where 36 asymptomatic cases were detected. In addition, 13 of the 14 cases detected through blood donation to the Japanese Red Cross Society were from Hokkaido. Eleven cases out of the 14 cases were asymptomatic. The NESID data did not reveal epidemiological links between any of the 14 cases.

**Suspected sources of infection**

During the study period, ~70% of the reported domestic cases had consumed food sources suspected of being contaminated with HEV (Table 1). Amongst these cases, 68 cases had consumed pig, 39 wild boar and 20 deer, and 13 multiple animal species. Cases associated with pork consumption were mostly distributed in the northern and eastern regions [54/68 (79.4%): Hokkaido, n=29; Kanto, n=19; Tohoku, n=6], whereas those associated with wild boar consumption were distributed in the western regions [33/39 (84.6%): Chubu, n=17; Kyushu/Okinawa, n=6; Chugoku/Shikoku, n=6; Kinki, n=4]. Of the 68 cases suspected of having acquired infection through pork consumption, 34 (50.0%) had consumed pork liver. Furthermore, 19/68 (27.9%) cases that consumed pork had consumed it raw, 10/20 (50.0%) cases that consumed deer had consumed it raw and 8/39 (20.5%) cases that consumed wild boar had consumed it raw.
country to introduce the anti-HEV IgA assay as a laboratory detection method for HEV infection for surveillance and reporting purposes.

Despite such possible surveillance bias, ~70% of the domestic cases of HEV infection were consistently associated with consumption of suspected food items, with the most suspected item being pork (Table 1). The current study revealed that, amongst cases, 27.9% of pork consumers, 50.0% of deer consumers and 20.5% of wild boar consumers had consumed them raw. Although well-cooked pork is consumed by a large part of the population, consuming these meats raw is not common. In addition, amongst the 68 cases suspected of having acquired infection through pork consumption, 34 (50.0%) had consumed pork liver. These dietary behaviours amongst cases may explain possible routes of HEV infection, which is in line with previous studies that point towards pork and deer meat as possible risk factors (Colson et al., 2010; Kamar et al., 2012; Miyashita et al., 2012; Tei et al., 2003). In marked contrast, infections with enterohaemorrhagic Escherichia coli (EHEC) originate from cows, and EHEC cases have been associated with consumption of raw beef. Following an EHEC O111/O157 outbreak with fatalities that occurred in 2011 after consumption of raw bovine liver (Watahiki et al., 2014), the serving of raw bovine liver in restaurants was banned in 2012 (MHLW, 2012a). After the ban, however, it was found that restaurants serving raw meat had reportedly tended to switch to serving raw porcine liver (MHLW, 2012b); such emerging concerns are being actively discussed by the MHLW and partners. The MHLW thus directed all local governments to inspect restaurants in December 2012 and found that 80 restaurants had served raw porcine meat,

Table 2. Genotypes of domestic cases of HEV infection, Japan 2007–2013. Cases tested by IgA are shown in parentheses.

<table>
<thead>
<tr>
<th>Year</th>
<th>Total cases</th>
<th>Genotyped</th>
<th>Proportion genotyped (%)</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G1</td>
</tr>
<tr>
<td>2007</td>
<td>40</td>
<td>6</td>
<td>15.0</td>
<td>0</td>
</tr>
<tr>
<td>2008</td>
<td>32</td>
<td>9</td>
<td>28.1</td>
<td>0</td>
</tr>
<tr>
<td>2009</td>
<td>51</td>
<td>17</td>
<td>33.3</td>
<td>0</td>
</tr>
<tr>
<td>2010</td>
<td>57 (1)</td>
<td>14</td>
<td>24.6</td>
<td>0</td>
</tr>
<tr>
<td>2011</td>
<td>55 (5)</td>
<td>9 (1)</td>
<td>16.4</td>
<td>0</td>
</tr>
<tr>
<td>2012</td>
<td>111 (64)</td>
<td>8 (2)</td>
<td>7.2</td>
<td>0</td>
</tr>
<tr>
<td>2013</td>
<td>116 (105)</td>
<td>4 (2)</td>
<td>3.4</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>462 (175)</td>
<td>67 (5)</td>
<td>14.5</td>
<td>1</td>
</tr>
</tbody>
</table>
including liver (MHLW, 2013). Consumption of other meats was also suspected to cause HEV infection. For instance, wild boar was recorded as the suspected source of infection in 39 cases (12.2%) out of 320 food-borne suspected cases. A recent study supported by the MHLW in fiscal year 2013 revealed that ~42% of wild boar in the Chugoku region had a history of HEV infection and 4% of wild boar in the region had detectable HEV RNA in blood.

Age and gender distribution amongst reported cases also remained similar throughout the study period. Men aged 50–69 years appeared to be at higher risk of domestic infection than others, which is consistent with previous studies from Europe (Dalton et al., 2008; Garbuglia et al., 2013; Mansuy et al., 2004, 2009). Previously, a seroprevalence study in the UK suggested that the risk of HEV infection appeared to be associated with both age and birth cohort, and also male gender (Ijaz et al., 2009). However, the specific reasons for the observed age and gender distribution were unknown (Ijaz et al., 2009). Likewise, in Japan, the relationship between food consumption behaviour and age groups and gender remains unknown. As the NESID is not designed to capture specific behaviours, further investigation is necessary.

Genotyping is important for determining the source and route of HEV infection. Studies showed that cases caused by HEV G3 were not successfully detected by the anti-HEV IgA detection test due to <70% sensitivity (Aggarwal, 2013; Herremans et al., 2007). However, even after the introduction of the anti-HEV IgA detection assay, G3 remained the predominant genotype detected and the adoption of the assay apparently led to a greater number of symptomatic cases being detected. As reporting for surveillance does not require HEV genotyping, the introduction of the anti-HEV IgA detection test could reduce the number of genotyped cases. In the case of outbreak investigations that require the identification of the source and route of infection, it is thus prudent to consider genotyping.

The analyses of the geographical distribution of HEV infection showed that Hokkaido was the region with the highest notification rate. Indeed, in 2001, the first domestic case of transfusion-related HEV infection was reported in Hokkaido (Matsubayashi et al., 2004) and, in 2004, an outbreak of HEV infection in a family, including a fatal case, occurred in Hokkaido (Matsubayashi et al., 2008). To prevent further infection, the Japanese Red Cross Society initiated HEV screening of donated blood in Hokkaido using the HEV RNA detection test in 2005; thus, such a policy change likely led to the increase in the reported number of asymptomatic cases in Hokkaido. As a result, prevalence of HEV RNA-positive individuals amongst blood donors in the region during 2005–2013 was calculated as 0.011% (1/8737) (Matsubayashi, 2014). Moreover, with 91% of the asymptomatic cases reported from Hokkaido during the study period, it is likely that the high notification rate from this region partly reflected their enhanced testing policy and that more blood donors were potentially HEV carriers but remained undetected in other regions. Globally, the need for HEV screening of donated blood is being actively debated. One opinion is that the test should be considered in endemic countries such as Sweden (1/7986 positive for HEV RNA), Germany (1/4525 positive for HEV RNA) and France (Féray et al., 2014). Five out of 367 transplantations resulted in chronic hepatitis E in France (Coïly et al., 2013). In south-east England, where blood donations are not screened, 1/2848 blood donors were HEV RNA positive and 42% of recipients from viraemic donors had evidence of infection (Hewitt et al., 2014). In Japan, further in-depth discussion is needed to determine whether to implement the policy nationally or not.

This study, based on NESID data, has several limitations. (i) Whilst animal meat consumption such as pork appeared to be a risk factor, a comparison group was lacking, and approximately half of suspected food items were not specified or missing. (ii) Whilst Hokkaido had the highest notification rate, considering the higher proportion of asymptomatic cases in the Hokkaido region compared with those in other regions, cases in other regions were likely to be under-reported. (iii) As only a small proportion of cases were genotyped and the reason for genotyping was unknown, the distribution of genotypes may not be representative; however, the predominant genotypes were consistently G3 and G4, similar to other developed countries.

In summary, whilst the reason for the recent increase may be due to changes in detection methods, a truer picture of the HEV burden in Japan has emerged. With an ageing population, possible blood transfusion-related transmissions, and challenges pertaining to food culture and evolving dietary practices, HEV infection is an emerging public health concern.

ACKNOWLEDGEMENTS

We thank Dr James Fielding (Victorian Infectious Diseases Reference Laboratory, Melbourne, Victoria, Australia) for reviewing the manuscript. We are also thankful to all the staff members of local public health centres and prefectural and municipal public health institutes and clinicians for providing surveillance data on HEV infection via NESID. This study was supported by Health Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan (H24-Shinkou-Ippan-014 and H23-Shokuhin-Ippan-009).

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