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## <THE TOPIC OF THIS MONTH> Hepatitis E, 2014-2021, Japan

Hepatitis E (HE) is an acute hepatitis caused by hepatitis E virus (HEV) infection. The incubation period is long, ranging from 15 to 60 days. Hepatitis E exhibits clinical characteristics, such as fever, malaise, jaundice, nausea, vomiting, anorexia, and stomachache, but many are asymptomatic (see p.273 of this issue). Although HEV infection was not considered to be chronic in the past, chronic infection can occur among immunocompromised individuals such as organ transplant patients (see p.279 of this issue). In developing countries and refugee camps with poor sanitation, HEV, which is shed in feces, is transmitted via the fecal-oral route, and there are reports of large-scale outbreaks (see p.286 of this issue). HE has also been receiving attention as a zoonotic infection worldwide, including in Japan (see p.280 of this issue).

HEV, which infects humans, belongs to *Orthohepevirus A*, one of the four species in the family *Hepeviridae*. *Orthohepevirus A* is further classified into eight genotypes (G1-G8) and 36 subtypes (see p.282 of this issue). HEV genotypes G1 to G4 are the major genotypes that infect humans. HEV G1 is the main genotype that causes relatively large community epidemics in developing countries. In developed countries, HE mainly due to G3 is reported sporadically. Since G3 and G4 infect pigs and wild boars, eating undercooked meat or the organs of these animals is considered the primary source of infection in Japan (see p.285 of this issue). In recent years, human cases of HEV infection from animals other than pigs or wild boars have also been reported (see p.280 of this issue).

A few cases of HEV infection due to blood transfusion are reported every year. The HEV nucleic acid amplification test (NAT) for blood transfusion, initially introduced in Hokkaido Prefecture, was implemented nationwide in August 2020. Through this measure, the number of HE cases caused by blood transfusion is expected to decrease in regions other than Hokkaido Prefecture as well (see p.276 of this issue).

Hepatitis E is a Category IV infectious disease that requires immediate notification following diagnosis in Japan (The reporting criteria are found at <https://id-info.jihs.go.jp/niid/images/iasr/35/407/de4071.pdf>). The Ministry of Health, Labour and Welfare (MHLW) has issued "Securing specimens when hepatitis E occurs" (August 16, 2016, Health Service Bureau/Tuberculosis and Infectious Diseases Control Division Notification 0816 No. 3, Pharmaceutical Safety and Environmental Health Bureau/Food Monitoring and Safety Division Notification 0816 No. 2), and requested that local governments ensure the collection of patient specimens or submission of viral characterization results.

### National Epidemiological Surveillance of Infectious Diseases (NESID)

From January 2014 to September 2021, 2,770 cases were notified under the NESID system (as at October 26, 2021, Table 1). While 100 cases or fewer were reported annually in 2005-2011 (IASR 35: 1-2, 2014), more than 200 cases have been reported annually since 2015, with more than 400 cases being reported annually since 2018 (Table 1).

#### 1) Suspected place of infection:

The majority of patients (88%) were presumed to have been infected domestically (domestic cases), while 113 (4.1%) cases were presumed to have been infected outside of Japan (Fig. 1, Table 2 on p.272). Figure 2 shows the notification status of the 2,770 cases reported, by prefecture. There are many reports from Hokkaido Prefecture (see p.285 of this issue) and the Kanto Koshinetsu region, but few from the Shikoku region. Among the 113 cases presumed to have been infected abroad, Asia accounted for the majority, with China having the highest number (20%), followed by India (15%), Taiwan (7.1%), and Thailand (7.1%) (Table 2 on p.272).

#### 2) Age and gender distribution:

There were 2,134 male cases (suspected place of infection: 1,865 domestic; 90 abroad (i.e., imported); 179 unknown) and 636

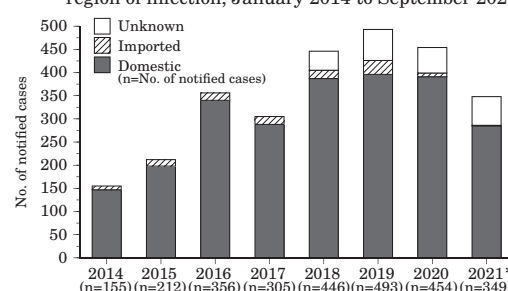
Table 1. Diagnostic test used for notified hepatitis E cases, January 2014 to September 2021, Japan

Year of diagnosis	Gene detection PCR (%)	Antibody detection (%)			No. of notified cases
		IgM (%)	IgA (%)	IgG (%)	
2014	18 (12)	13 (8)	137 (88)		155
2015	32 (15)	7 (3)	195 (92)		212
2016	62 (17)	13 (4)	311 (87)		356
2017	70 (23)	14 (5)	266 (87)		305
2018	110 (25)	10 (2)	412 (92)		446
2019	124 (25)	17 (3)	460 (93)		493
2020	100 (22)	15 (3)	399 (88)		454
2021	70 (20)	9 (3)	271 (78)		349
Total	586 (21)	98 (4)	2,451 (88)		2,770

Includes cases in which multiple diagnostic test methods were recorded  
14 cases diagnosed by RNA-NAT tests (12 cases tested only by NAT are not included in the PCR test category)

\*Proportion of notifications accounted for by diagnostic test method  
(National Epidemiological Surveillance of Infectious Diseases: as at 26 October 2021)

Figure 1. Yearly number of notified hepatitis E cases by suspected region of infection, January 2014 to September 2021, Japan



\*January to September  
(National Epidemiological Surveillance of Infectious Diseases: as at 26 October 2021)

(THE TOPIC OF THIS MONTH-Continued)

Figure 2. Number of notified hepatitis E cases by prefecture, January 2014 to September, Japan

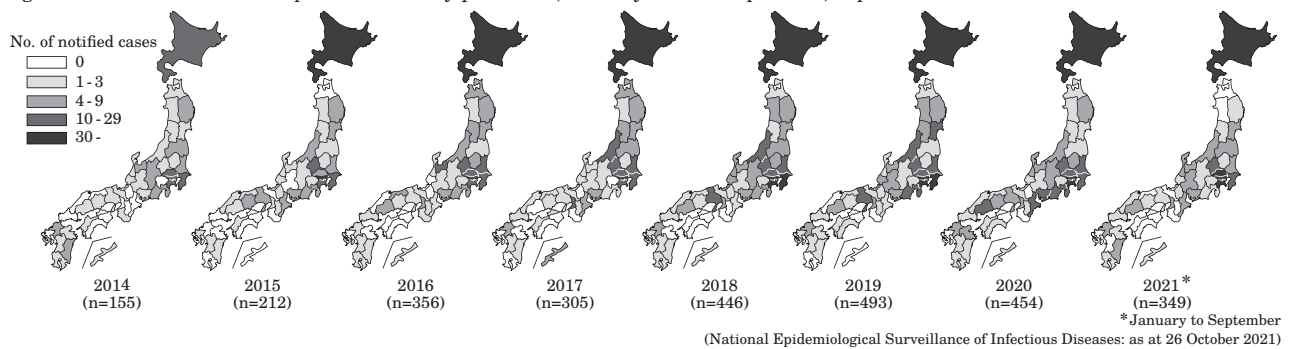


Table 2. Suspected place of infection for the notified hepatitis E cases, January 2014 to September 2021, Japan

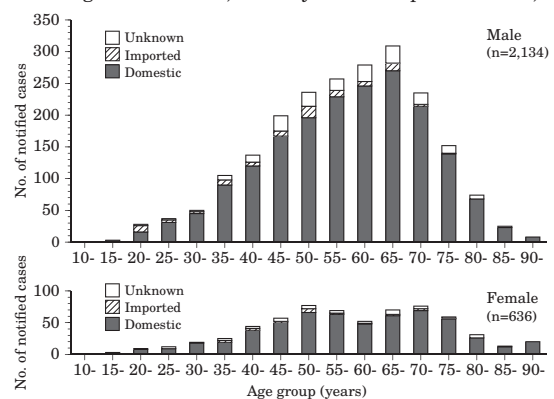
Domestic cases	2,432
Imported cases	113
China	23
India	17
Taiwan	8
Thailand	8
United States	7
South Korea	6
Pakistan	5
Philippines	4
Malaysia	2
Vietnam	2
Bangladesh	2
Germany	2
Singapore	2
Australia	2
Others*	9
Two or more countries	7
Country unknown	7
Unknown**	225
Total	2,770

\*Country with 1 case

\*\*Case in which the place of infection (domestic or imported) could not be determined

(National Epidemiological Surveillance of Infectious Diseases: as at 26 October 2021)

Figure 3. Age distribution of notified hepatitis E cases by suspected region of infection, January 2014 to September 2021, Japan



(National Epidemiological Surveillance of Infectious Diseases: as at 26 October 2021)

female cases (567 domestic; 23 abroad; 46 unknown), with males in their 40s to 70s accounting for 57% of all domestic cases reported. Among imported cases, there was no substantial difference between males (4.2%) and females (3.6%), with both reported from a wide age range (Fig. 3).

### 3) Diagnostic method:

In the past, gene detection by RT-PCR and IgM antibody detection by ELISA were the major methods used for definitive diagnosis (IASR 35: 1-2, 2014); however, in October 2011, the IgA antibody detection kit became covered by medical insurance, and since then, diagnosis by IgA antibody detection has become the major method (Table 1 on p.271) (see p.275 of this issue). In 2013, the detection of IgA antibodies was added to the list of testing methods under the NESID notification criteria.

### 4) Suspected routes of infection:

Of the 2,770 notified cases, 1,035 domestically infected cases had a suspected route of infection recorded, of which 428 (41%) was pork consumption (including meat or liver). Others included 99 (10%) cases from wild boar meat, 88 (9%) cases from deer meat, 218 (21%) cases from meat (including raw or grilled) from unidentified animals, and 79 (8%) cases from unidentified animal liver (includes more than one route). Among the 113 cases infected abroad, 5 (4%) were recorded as water and 30 (27%) as the consumption of pork or meat from unidentified animals. It should be noted that the described infection routes are presumptive and may not necessarily be valid, and the source of infection is rarely identified.

**HEV infections among animals:** HEV infection in pigs has been reported in many parts of the world, and in a survey in Japan, the HEV genome was detected at high frequencies in the feces of pigs 2-3 months of age; in addition, it has been reported that 90% or more of the pigs at the time of shipment (6 months old) had anti-HEV antibodies, indicating a history of infection. On the other hand, although the HEV genome is detected in serum from pigs at the time of shipment and in pig livers in the market, the frequency is considered to be low. Although the seroprevalence in wild boars in Japan is lower (34%) than that in pigs, it has become clear that HEV is widespread among them. Recently, cases of human infection with HEV from dromedary camels, rabbits, and rats have also been reported (see p.280 of this issue).

**Prevention of HEV infection:** In 2004, the MHLW issued a notice on HEV infection, reminding hunters, meat handlers, and consumers to avoid eating raw meat or the livers of pigs or other wild animals, and to consume these foods only after thorough cooking (Pharmaceutical Safety and Environmental Health Bureau/Food Monitoring and Safety Division Notification No. 1129001, November 29, 2004: <http://www.mhlw.go.jp/topics/syokuchu/kanren/kanshi/041129-1.html>). Since the number of reported HE cases has been increasing in recent years, and as most of them are considered to be domestic infections, it is important to further communicate the risk of HEV infection to the Japanese public. When traveling to endemic areas, it is also necessary to be careful with drinking water and to avoid undercooked foods. Although there is a recombinant vaccine for HE approved in China, there are no other vaccines approved for human use.

*The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Environmental Health and Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.*

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