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Tuberculosis and Infectious Diseases
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<THE TOPIC OF THIS MONTH>
Dengue fever and dengue hemorrhagic fever, 2015-2019

Dengue fever (DF) is an infectious disease caused by the dengue virus (DENV). DENV belongs to the *genus Flavivirus* of the *family Flaviviridae* and consists of four serotypes, DENV-1, -2, -3, and -4. DENV is one of the mosquito-borne arboviruses, and the main vectors are *Aedes aegypti* and *Ae. albopictus*. DENV is mainly maintained in the human-to-mosquito-to-human transmission cycle. Currently, *Ae. aegypti* is not distributed in Japan, but *Ae. albopictus* inhabits a wide area excluding Hokkaido (see pp.91 & 92 of this issue). DENV infection in humans causes symptoms, such as fever, exanthema, and joint and muscle pain, after an incubation period of approximately 4 to 14 days (DF). In many cases, patients recover without sequelae. However, some DF patients develop severe symptoms, such as hemorrhage and/or neurological symptoms, including deterioration in consciousness, and may die due to multiple organ failure. Such a disease state is called severe dengue fever (SDF), and includes dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). There is no specific treatment for DF. A dengue vaccine is licensed and available in some countries (see p.99 of this issue). DF is mainly endemic in tropical and subtropical regions (see p.93 of this issue). Most DF patients in Japan were those, including returnees, infected with DENV in the endemic regions. Autochthonous outbreaks of DF were reported in 2019 for the first time in five years since 2014 (see p.94 of this issue).

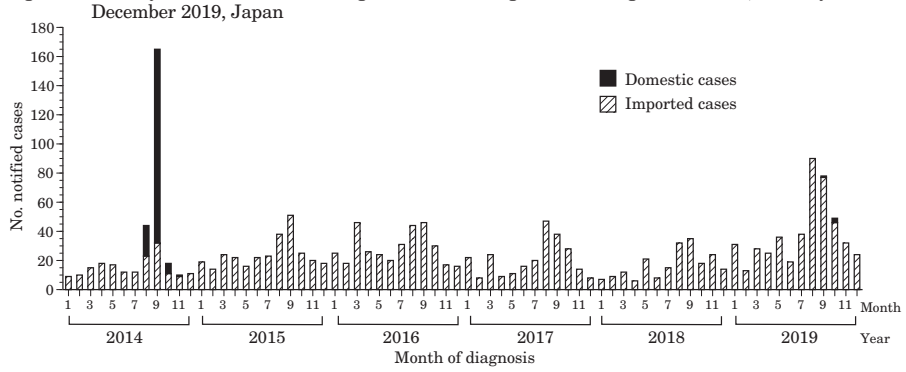
1. National Epidemiological Surveillance of Infectious Diseases (NESID)

DF is classified as a category IV infectious disease under the Infectious Diseases Control Law of Japan. Physicians who diagnose patients with DF must immediately notify the cases to their prefectural governors via local public health centers.

The reported number of DF cases has increased since the 9 cases in 1999 when data collection started. The number of reported cases of DF and DHF between 2015 and 2018 ranged from 201 to 343. In 2019, the number of cases was at a record high of 463 (Fig. 1 and Table 1). One hundred and sixty-two cases and four cases in 2014 and 2019, respectively, were reported to NESID as domestic cases of DF (see p.97 of this issue).

Cases of DENV infection by serotypes 1-4 are identified every year. Cases of DENV-1 infection were the most common in 2011-2015 and 2019, and cases of DENV-2 infection were the most common in 2016-2018. In more recent years, type DENV-3 has also been detected in greater numbers (IASR 36: 33-35, 2015) (Table 2).

Figure 1. Monthly number of notified dengue fever and dengue hemorrhagic fever cases, January 2014-December 2019, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of 8 April 2020)

Table 1. Number of notified dengue cases by year of diagnosis, 2014-2019, Japan

Year of diagnosis	No. notified cases	
	Dengue fever	(Dengue Hemorrhagic Fever*)
2014	341	(9)
2015	292	(5)
2016	343	(12)
2017	245	(6)
2018	201	(4)
2019	463	(7)
Total	1,885	(43)
2019 cases (imported vs. domestic)		
Imported	459	(6)
Domestic	4	(1)

*Dengue hemorrhagic fever reported number out of dengue fever

(National Epidemiological Surveillance of Infectious Diseases: as of 8 April 2020)

Table 2. Dengue virus serotypes detected among dengue fever and dengue hemorrhagic fever cases, 2014-2019, Japan

Year of diagnosis	Dengue virus serotype					No. notified cases
	Type 1	Type 2	Type 3	Type 4	Unknown	
2014	108	20	14	7	192	341
2015	63	56	24	20	129	292
2016	55	62	41	19	165	343*
2017	31	40	34	12	128	245
2018	20	34	26	3	118	201
2019	78	73	40	16	256	463
Total	355	285	179	77	988	1,885
2019 cases (imported vs. domestic)						
Imported	78	71	40	16	254	459
Domestic	-	2	-	-	2	4

* There was a single case coinfected with serotypes 1 and 3 in 2016

(National Epidemiological Surveillance of Infectious Diseases: as of 8 April 2020)

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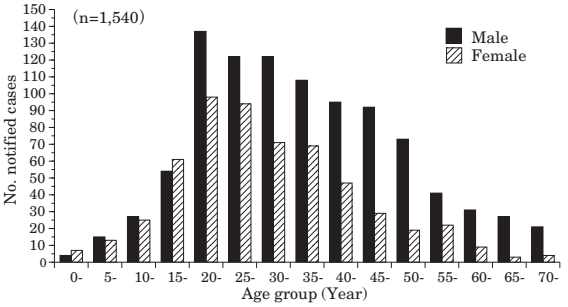
Seasonality: The highest number of DF cases is reported to NESID during August and September (IASR 36: 33-35, 2015) (Fig. 1 in p.89). This is due to the increase in the number of travelers and the prevalence of dengue fever at the destinations. Previous domestic DF cases were observed during the summer and autumn seasons (Fig. 1 in p.89).

Suspected place of infection: Patients diagnosed with DF between 2015 and 2019 (excluding cases of domestic infection) traveled to at least 45 countries/regions (Table 3 in p.91). Of the 1,540 patients infected outside Japan, 1,350 (88%) visited Asian countries. The majority visited Southeast Asia, likely reflecting the prevalence of DF in these regions and the increase in the number of people entering Japan. Other patients presumed to have been infected in Oceania, Latin America and the Caribbean, the Middle East and Africa, and Europe and the United States have also been reported. In 2019, there were large outbreaks of DF in Southeast Asia and other parts of the world, and the number of imported cases from these regions increased (see pp.93 & 100 of this issue). In 2019, autochthonous outbreaks of DF were found, and three out of four domestic DF patients were infected with DENV-1 in Japan (see p.96 of this issue).

Figure 2. Age and sex distribution of notified dengue fever and dengue hemorrhagic fever cases, 2015- 2019, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of 8 April 2020)

Gender and age: Among 1,540 patients infected overseas who were reported to NESID in 2015-2019, 969 (63%) were men and 571 (37%) were women. The number of patients in their 20s, 30s, and 40s was 259 (17%), 230 (15%), and 187 (12%), respectively. Males were slightly more frequently infected and those in their 20s comprised the highest number of cases (Fig. 2).

Dengue hemorrhagic fever: There were 5 (1.7%), 12 (3.5%), 6 (2.4%), 4 (2.0%), and 7 (1.5%) cases of DHF reported to NESID in 2015, 2016, 2017, 2018, and 2019, respectively (Table 1 in p.89). The ages of patients in these 34 cases ranged from 13 to 79 years (median 31.5 years). There was no difference between males and females, with 20 and 14 cases, respectively, accounting for 2% of the total number of cases. One death due to SDF was reported in 2016.

2. Laboratory diagnosis

DENV isolation, RT-PCR-based DENV genome detection, and DENV nonstructural protein 1 (NS1) antigen detection methods are the main virological tests for suspected DF in the early phase of the disease. Identification of the DENV serotype is possible by virus isolation and viral genome detection. Using the NS1 antigen detection kit, results can be obtained quickly and easily. For serological diagnosis, detection of specific IgM antibodies, and significant increases in specific IgG and neutralizing antibodies using paired sera from the acute and convalescent phases are useful (Table 4). However, as other flaviviruses that serologically cross with DENV are also prevalent in dengue fever-endemic areas, antibody titers against these viruses should be examined as necessary. Prefectural and municipal public health institutes (PHIs) and the National Institute of Infectious Diseases (NIID, Department of Virology 1) conduct these laboratory tests for DF.

3. Countermeasures in Japan

Japan is a non-endemic country for dengue fever. In 2014 and 2019, cases of dengue fever caused by DENV infection were reported in Japan, but both epidemics ended sporadically from late autumn to winter when the activity of the vector mosquito *Ae. albopictus* decreased. As hundreds of imported DF cases have been reported annually in recent years, there is a risk of DF outbreaks in Japan during the seasons when mosquitoes become active.

To prevent the spread of mosquito-borne infectious diseases, such as DF, chikungunya fever, and Zika virus disease, the Ministry of Health, Labour and Welfare released guidelines to control mosquito-borne infectious diseases in 2015. The guidelines include encouraging preventive measures against mosquito vectors on a routine basis, rapid identification of mosquito-borne diseases, measures against mosquito vectors in the event of an outbreak of mosquito-borne infections, and providing patients with appropriate medical care. In addition, "Clinical Examination Guidelines on the Mosquito-Borne Infections 5th Edition" was released by the NIID. These guidelines provide a series of practical procedures for epidemiology, pathology, diagnosis, notification, treatment, and prevention of mosquito-borne infectious diseases. National and local administrative agencies, medical institutions, and research institutes must cooperate to take measures against mosquito-borne infectious diseases such as dengue fever. The early detection of domestic DF epidemics through surveillance is essential. As the number of imported DF cases has increased in recent years, it is important to prevent DENV infection by correctly using repellents when traveling to DF epidemic areas abroad.

Table 4. Method of laboratory diagnosis among dengue fever and dengue hemorrhagic fever cases*, 2014 -2019, Japan

Year of diagnosis	Virus detection			Serology			No. notified cases
	Isolation**	PCR	NS1§	IgM	HI	NT	
2014	12	188	211	128	-	1	341
2015	11	177	214	19	-	-	292
2016	15	199	241	16	1	1	343
2017	7	132	194	10	-	-	245
2018	5	92	144	12	-	-	201
2019	13	230	343	21	-	1	463
Total	63	1,018	1,347	206	1	3	1,885
2019 cases (imported vs. domestic)							
Imported	13	228	340	21	-	1	459
Domestic	-	2	3	-	-	-	4

* Includes testing by more than one method ** Isolation of infectious viral particles
§ DENV nonstructural protein 1 (NS1) antigen detection methods

(National Epidemiological Surveillance of Infectious Diseases: as of 8 April 2020)

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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