

## Trends in Flavivirus Infections in Japan

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Although Japanese encephalitis has declined as an important cause of illness and death in Japan, infection with other flaviviruses has become a public health concern. Recently, reports of imported dengue cases, as well as isolations of tick-borne encephalitis virus, have increased.

The family *Flaviviridae* consists of approximately 70 viruses, nearly 40 of which cause human disease (1). Japanese encephalitis virus (JEV) was an important cause of illness and death in Japan for many years, with >1,000 Japanese encephalitis (JE) cases reported annually in the late 1960s. The number of JE cases has decreased dramatically, and fewer than 10 cases have been reported annually since 1992 (2). Infection by other flaviviruses, including an increase in imported dengue cases and isolations of tick-borne encephalitis (TBE) virus, is becoming a public health threat.

### Imported Dengue Cases

Dengue viruses are transmitted by infected mosquitoes, mainly *Aedes aegypti* and *A. albopictus* (3,4). The clinical manifestations of dengue virus infections range from asymptomatic infection to dengue fever and dengue hemorrhagic fever (5). Dengue epidemics caused by dengue virus type 1 occurred in Nagasaki, Osaka, Kobe, and Hiroshima from 1942 to 1945 (6,7). No outbreaks of dengue virus infection have been reported since then in Japan, and no domestic dengue virus infections have been identified. However, during this period there have been imported dengue cases (8,9) in persons who visited dengue epidemic areas, were infected with dengue viruses, and became ill after returning to Japan. In addition, some foreign visitors who were infected in their own countries became ill with dengue while in Japan.

Dengue virus infections were diagnosed in serum specimens of suspected dengue cases submitted from hospitals and clinics by IgM-

capture enzyme-linked immunosorbent assay, hemagglutination inhibition tests, and reverse transcriptase-polymerase chain reaction. Neutralization tests and virus isolation were also performed for some specimens. Dengue cases were confirmed by these laboratory tests at the National Institute of Infectious Diseases, Japan, from 1985 to 1999 (Table). The number of imported dengue cases has recently increased. Only two dengue hemorrhagic fever cases were identified, one each in 1990 and 1991; all the other cases were dengue fever. Most of these Japanese dengue patients became infected in Southeast Asia (Thailand, India, Philippines, and Indonesia), although some patients became infected in Central America and Africa in recent years. We believe that these dengue cases account for only a fraction of the total imported cases, although the exact number of imported cases is not known. Under a new infectious disease control law, which took effect on April 1, 1999, dengue fever/dengue hemorrhagic fever is a reportable disease. Thus, an accurate annual number of imported dengue cases will be known in the near future.

### Tick-Borne Encephalitis

Central European encephalitis and Russian spring-summer encephalitis (RSSE) viruses are TBE viruses prevalent in Eurasia (1). The presence of TBE virus in Japan was first confirmed when Negishi virus was isolated from an encephalitis patient in 1948. This virus was later determined by antigenic analysis to be TBE virus (10). No further cases of tick-borne encephalitis were identified in Japan until 1993, when Takashima et al. reported a tick-borne encephalitis case in Hokkaido, the northern island of Japan (11). The patient, a dairy farmer, had high fever, double vision, convulsions, and

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## International Update

Table. Cases of imported dengue and countries that persons visited before onset of symptoms, by year, Japan

Countries	'85	'86	'87	'88	'89	'90	'91	'92	'93	'94	'95	'96	'97	'98	'99	Total
No. of cases <sup>a</sup>	4	1	4	4	1	11 <sup>b</sup>	6 <sup>b</sup>	14	7	11	16	15	6	42	11	153
Asia																
Thailand	3	0	3	1	0	7	3	7	1	6	8	4	1	19	2	65
India	0	0	2	0	0	2	1	2	1	1	4	5	0	6	3	27
Philippines	2	1	1	1	0	1	3	1	3	1	1	1	1	8	1	26
Indonesia	0	0	0	1	0	0	0	3	1	2	2	3	1	5	0	18
Malaysia	0	0	1	0	0	2	0	0	0	0	1	2	0	1	1	8
Myanmar	0	0	0	0	0	0	0	0	0	0	1	0	0	3	4	8
Cambodia	1	0	0	0	0	0	0	0	1	0	1	0	0	3	1	7
Singapore	0	0	0	0	1	0	0	1	0	0	1	1	1	2	0	7
Nepal	0	0	1	0	0	0	0	1	0	1	0	0	1	1	0	5
Laos	0	0	0	0	0	0	1	0	0	1	0	0	1	2	0	5
Vietnam	0	0	0	0	0	0	0	0	0	1	0	0	1	2	0	4
Bangladesh	0	0	1	0	0	0	0	0	0	0	0	1	0	1	0	3
Maldives	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	3
Taiwan	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
China	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	2
Sri Lanka	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Oceania/South Pacific																
Australia	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
Fiji	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
New Caledonia	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
Tahiti	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Central America																
Dominica	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Guatemala	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Africa																
Nigeria	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Liberia	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Côte d'Ivoire	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1

<sup>a</sup>Some patients visited more than one country.

<sup>b</sup>In 1990 and 1991, one patient each year had dengue hemorrhagic fever.

motor paralysis. The 6- and 43-day serum samples showed highest neutralizing antibody titer to RSSE virus, but the level of neutralizing antibody to Japanese encephalitis virus was low. Serologic tests indicated that the encephalitis was caused by TBE virus. Takashima et al. demonstrated that sentinel dogs were seropositive for RSSE virus (11). They then isolated viruses from the dogs' sera and demonstrated that the isolated virus was related most closely to RSSE virus by nucleotide sequencing.

Takeda et al. isolated TBE virus from *Ixodes ovatus* ticks collected in the region and demonstrated that the isolated viruses were antigenically close to RSSE virus (12). They also showed that captured rodents had antibodies to TBE virus and that the viruses isolated from the rodents were also antigenically close to RSSE virus (13). These reports indicate that the TBE virus endemic in Hokkaido is closely related to

RSSE viruses. Further studies are necessary for understanding the ecologic features of TBE virus in other islands of Japan.

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