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National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

<THE TOPIC OF THIS MONTH>
Japanese spotted fever 1999-2019

Japanese spotted fever is a tick-borne rickettsiosis that has been recently increasing; it was first reported in 1984 in Tokushima prefecture, Japan, based on the difference in the Weil-Felix reaction for scrub typhus (tsutsugamushi disease), which is endemic in Japan. It is caused by *Rickettsia japonica*, an obligate intracellular bacterium classified as a member of the spotted fever group rickettsia, causing fever and rash as major symptoms. Tick-bite sites and eschars are found in many patients. The rash extends from the extremities to the trunk, and is also noted on the palms and soles. The bite site is often smaller than that of scrub typhus, which is clinically similar. The primary risk of infection is outdoor activity and the incubation period from tick bite to disease onset is 2-8 days, which is shorter than that of scrub typhus (5-14 days). Japanese spotted fever is a Category IV Infectious Disease that requires reporting of all cases under the Act on the Prevention of Infectious Diseases and Medical Care for Patients of Infection (Infectious Diseases Control law; notification criteria are available at https://www.niid.go.jp/niid/images/iasr/38/448/de4482.pdf). Clinical differentiation from scrub typhus is difficult and laboratory diagnosis is required for notification.

National Surveillance: According to a survey by the Working Group for Tsutsugamushi Disease Surveillance, the Association of Public Health Laboratories for Microbiological Technology, which was the only national surveillance system before enactment of the Infectious Diseases Control Law, about 10 to 20 cases of Japanese spotted fever were confirmed annually from 1984 to 1998 in 10 prefectures west of the Kanto area (Tokushima, Kochi, Hyogo, Shimane, Kagoshima, Miyazaki, Wakayama, Mie, Kanagawa, and Chiba), with a cumulative total of 213 cases (see IASR 20: 211-212, 1999).

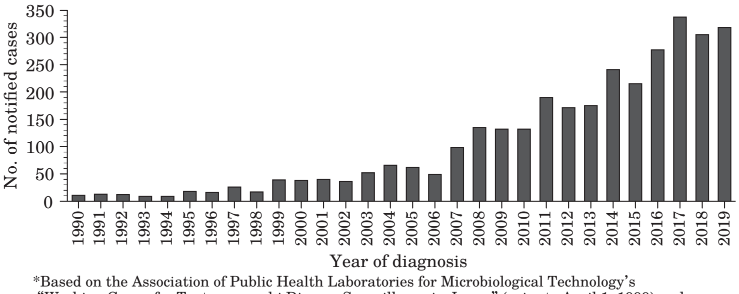
After Japanese spotted fever was designated as a Category IV Infectious Disease under the Infectious Diseases Control Law in 1999, the annual number of cases was 30-60 until 2006, but it increased to 337 in 2017, the highest number reported. Since then, more than 300 cases have been reported every year (Fig. 1, Table 1 and Table 2 on p.135) (see IASR 27: 27-29, 2006, 31: 120-122, 2010 & 38: 109-112, 2017), and as of July 2020, the number of reported cases has been at the same rate as in 2017, when the number of cases was the highest in the year. After the system for monitoring infectious disease occurrence was changed to the current central database system in 2006, 2,726 cases were reported between 2007 and 2019, and all cases were presumed to have been infected in Japan. Mie Prefecture had the highest number of reports (annual average 37.2 cases), followed by Hiroshima, Wakayama, Kagoshima, Shimane, and Kumamoto. In recent years, however, new cases suspected to have been infected in Fukushima, Niigata, Tochigi, Ibaraki, Ishikawa, Shiga, Nara, and other prefectures have been reported, and the suspected places of infection are thought to be expanding (Fig. 2 on p.134 and Table 2 on p.135).

Even within the same municipality, number of cases is increasing in some remote areas (see p. 136 of this issue). There are also reports of multiple cases occurring at around the same time in limited areas (see IASR 38: 171-172, 2017 & 41: 13-14, 2020). In addition to outdoor activities, neonatal cases caused by ticks, presumably brought indoors by family members, have been reported (IASR 33: 304-305, 2012).

Sex and age distribution: Among the cases notified during 2007-2019, 1,262 (46%) males and 1,464 (54%) females were reported, with the majority of patients being in their 60s or older (median 71 years, 69 years for males and 73 years for females).

Signs and symptoms: According to the written notification forms during 2007-2019 (n=2,726), frequently reported signs/symptoms were fever (99%), rash (94%), liver dysfunction (73%), eschar (67%), headache (30%), and disseminated intravascular coagulation syndrome (DIC, 21%). The occurrence of eschar was lower than that in scrub typhus. Complications of acute infectious

Figure 1. Yearly number of notified Japanese spotted fever cases, 1990-2019*, Japan



*Based on the Association of Public Health Laboratories for Microbiological Technology's "Working Group for Tsutsugamushi Disease Surveillance in Japan" (prior to April 1, 1999) and "National Epidemiological Surveillance of Infectious Diseases" (from April 1, 1999); as of 10 June 2020

Table 1. Number of notified Japanese spotted fever cases and fatal cases, April 1999-December 2019, Japan

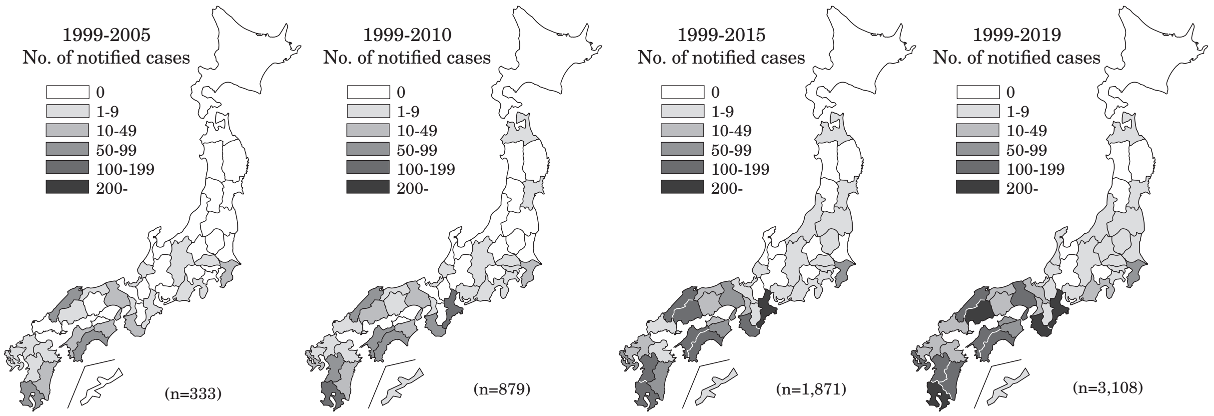
Year of diagnosis	No. of notified cases	Year of diagnosis	No. of notified cases
1999	39	2010	132 (3)
2000	38	2011	190 (2)
2001	40 (1)	2012	171
2002	36 (1)	2013	175 (1)
2003	52	2014	241
2004	66 (1)	2015	215 (5)
2005	62 (1)	2016	277 (3)
2006	49 (1)	2017	337 (6)
2007	98	2018	305 (4)
2008	135 (1)	2019	318 (13)
2009	132 (1)	Total	3,108 (44)

No. in parenthesis denote the no. of notified fatal cases
(National Epidemiological Surveillance of Infectious Diseases: as of 10 June 2020)

(Continued on page 134′)

(THE TOPIC OF THIS MONTH-Continued)

Figure 2. Number of notified Japanese spotted fever cases by prefecture, 1999-2019, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of 10 June 2020)

purpura fulminans (AIPF) were also reported (IASR 31: 135-136, 2010), and fatal cases were observed after DIC and multiple organ failure.

At the time of notification, 31 deaths (case fatality rate 1.1%, 31/2,790) were reported between April 1999 and the end of 2018, whereas 13 deaths (case fatality rate 4.1%, 13/318) were reported in 2019 alone (Table 1 on p.133).

Blood test findings in the acute phase include increases in liver enzymes and C-reactive protein (CRP), and decreased platelets (white blood cell count within a near-normal range), and information for clinical differentiation from severe febrile thrombocytopenia syndrome (SFTS), which has a similar epidemiological background, such as tick bites and geographic distribution, but with a different treatment regimen, is accumulating (p.137 of this issue).

Vectors: The number of reports of Japanese spotted fever cases by month increases from May to October, peaking from August to October, which coincides with the tick activity period. The causative *R. japonica* has been isolated or detected in eight tick species from three genera (unconfirmed in nine species from four genera, including *Amblyomma testudinarium*), but it is thought to be mainly caused by *Haemaphisalis* spp. ticks such as *H. hystricis* (p.138 of this issue). However, although some of these tick species are widespread throughout Japan, previously unidentified ticks from warmer regions have been found in the northeastern part of the country (p.139 of this issue), suggesting that the more widespread tick distribution is responsible for the expanded area of occurrence of Japanese spotted fever cases.

Laboratory diagnosis: A specific laboratory diagnosis of Japanese spotted fever is made by antibody detection using the indirect fluorescent antibody method or indirect immune-peroxidase method, and gene detection methods such as PCR. However, it is not covered by health insurance and the number of facilities where testing is possible is limited. If a patient is clinically suspected of Japanese spotted fever, testing is available at the National Institute of Infectious Diseases or Public Health Institutes through local health centers. As specific laboratory diagnoses are difficult except for municipalities where many patients have been reported, the Manual for Diagnosis of Rickettsial Infections was revised in 2019 (p.141 of this issue) to facilitate implementation at more institutions.

Treatment: Tetracyclines are most effective for rickettsioses, including Japanese spotted fever. Therefore, if rickettsiosis is suspected, immediate administration of antibiotics is recommended without waiting for the laboratory diagnosis. This is the international consensus for rickettsiosis, which can be fatal if untreated.

Diversity of spotted fever group Rickettsiosis in Japan and imported cases: Spotted fever group rickettsiosis suspected to be infected in Japan is not limited to Japanese spotted fever, and is also caused by *R. heilongjiangensis*, *R. tamurae*, and *R. helvetica*. A case reported as Japanese spotted fever in Miyagi Prefecture was later found to be Far-Eastern spotted fever caused by *R. heilongjiangensis*, which was found to be similar to *R. japonica* by subsequent detailed inspection (IASR 31: 136-137, 2010); and, one case in Aomori Prefecture was also likely to be Far-Eastern spotted fever (Table 2 on p.135). Many cases of spotted fever group rickettsiosis have also been reported as imported (IASR 20: 218-219, 1999, 27: 41-42, 2006, 31: 120-122, 2010, 31: 137-138, 2010 & 38: 123-124, 2017). Each species of spotted fever group rickettsia is genetically similar, and differences among strains of the same species, by year of isolation or by region, are very small (p.142 of this issue). The intensity of antigen cross-reactivity, influenced by genetic similarity, makes serological differentiation of spotted fever group rickettsiosis difficult, and the definition of the notification may need to be reconsidered, as in the United States.

Additional remarks: The number of cases of Japanese spotted fever is increasing and the geographical area is expanding. Although effective antibiotics are available, fatal cases are still being reported. In addition to Japanese spotted fever and other rickettsioses, various tick-borne infectious diseases have emerged, making it increasingly important to differentiate them based on clinical symptoms and geographical areas of occurrence. It is necessary to understand the disease information, patient information, and outbreak situation accurately, and, to enable more effective medical and public health responses, to strengthen and sustain surveillance systems, laboratory diagnostics systems, and information dissemination activities.

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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表2. 年別都道府県別日本紅斑熱患者届出数、1999～2019年
Table 2. Yearly number of notified Japanese spotted fever cases, by prefecture, 1999-2019

都道府県	Prefecture	診断年 Year of diagnosis																					合計	人口100万対†
		1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019*	Total	Per 1,000,000†
北海道	Hokkaido	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
青森県	Aomori	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	1	0.08
岩手県	Iwate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
宮城県	Miyagi	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	1	0.04
秋田県	Akita	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
山形県	Yamagata	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
福島県	Fukushima	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	1	2	0.10
茨城県	Ibaraki	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2(1)	2 (1)	0.07
栃木県	Tochigi	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	1	2	0.10
群馬県	Gunma	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1	0.05
埼玉県	Saitama	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	2	0.01
千葉県	Chiba	2	9	-	-	-	4	-	-	1	7	6	5	3	4	4	6	5	10	9	11	5	91	1.22
東京都	Tokyo	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	1	-	1	-	-	4	0.03
神奈川県	Kanagawa	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	1	-	-	1	-	-	3	0.03
新潟県	Niigata	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	1	0.04
富山県	Toyama	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
石川県	Ishikawa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1	2	0.17
福井県	Fukui	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	1	-	1	-	-	-	3	0.25
山梨県	Yamanashi	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
長野県	Nagano	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	3	0.10
岐阜県	Gifu	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
静岡県	Shizuoka	-	1	-	-	-	-	-	-	-	-	-	-	-	-	1	-	2	2(1)	6(1)	3	10	25 (2)	0.65
愛知県	Aichi	-	-	-	-	-	-	-	-	-	-	1	-	3	-	-	-	-	1	-	1	-	6	0.08
三重県	Mie	-	-	-	-	-	-	2	6(1)	20	34	36(1)	26(2)	37(1)	38	51	34	25	48(1)	42(1)	51	42(1)	492 (8)	26.65
滋賀県	Shiga	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2(1)	2 (1)	0.14
京都府	Kyoto	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	2	-	3	3	4	14	0.54
大阪府	Osaka	-	-	-	1	-	-	-	1	-	1	-	1	-	-	1	5	1	5	6(1)	8(1)	8	38 (2)	0.41
兵庫県	Hyogo	9	6	4(1)	3	3	1	1(1)	1	4	4	5	1	1	1	5	11	9	13	7	9	19(2)	117 (4)	1.61
奈良県	Nara	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	1	2	0.15
和歌山県	Wakayama	-	4	2	2	-	3	2	7	16	16	11	20	21	24	18	34	17	17	51(1)	32	30	327 (1)	31.85
鳥取県	Tottori	-	-	-	-	-	-	1	-	1	2	-	-	3	1	2	2	10	10	6	2	-	40	6.81
島根県	Shimane	-	10	8	11	13	12	12	3	10	13	3	3	11	8	4	6	10	15	10	16(1)	16(1)	194 (2)	18.01
岡山県	Okayama	-	-	-	-	-	-	-	-	-	-	2	-	3	-	2	4	3	5	7	5	3	34	1.77
広島県	Hiroshima	2	-	-	-	-	-	2	1	5	4	17	16(1)	20(1)	25	27	30	45(1)	36	69	41	67(3)	407 (6)	14.14
山口県	Yamaguchi	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	2	2	4	2	3	4	19	1.35
徳島県	Tokushima	1	-	-	2	4	10	5	1	2	2	3	5	10	1	2	13	6(1)	6	10	4	12	99 (1)	10.05
香川県	Kagawa	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1	7	9(2)	7	8(1)	11	6	50 (3)	5.12
愛媛県	Ehime	-	-	-	-	2	6	4	8	4	5	10	17	13	7	5	12	14	13	14	9	10(2)	153 (2)	9.60
高知県	Kochi	15	3	14	7	14	13(1)	10	3	1	6	6	7	15	4	1	7	4	13	6	13(1)	10	172 (2)	12.77
福岡県	Fukuoka	-	-	-	-	-	-	1	-	-	-	-	-	2	2	3	2	-	6	11	4	6(1)	37 (1)	0.71
佐賀県	Saga	1	-	-	-	-	-	-	-	-	-	-	-	1	1	1	5	3	8	3	10(1)	8	41 (1)	4.80
長崎県	Nagasaki	1	-	-	-	-	-	-	2	2	2	2	3	9	6	2	14	13	8	20	19	15	118	8.35
熊本県	Kumamoto	-	-	-	1	-	-	-	2	11	18	16	8	20	22	20(1)	18	11(1)	19	14(1)	7	6(1)	193 (4)	10.64
大分県	Oita	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	2	3	2	2	-	2	12	0.94
宮崎県	Miyazaki	7	-	4	3	2	3	5	1	4	8(1)	5	6	4	9	10	7	9	6(1)	8	19	8	128 (2)	9.33
鹿児島県	Kagoshima	-	5	8	6(1)	14	11	17	13	16	11	9	11	9	17	14	14	11	22	18	22	18	266 (1)	11.65
沖縄県	Okinawa	-	-	-	-	-	-	-	-	-	-	-	1	1	1	-	-	-	-	1	-	-	4	0.28
総　数	Total	39	38	40(1)	36(1)	52	66(1)	62(1)	49(1)	98	135(1)	132(1)	132(3)	190(2)	171	175(1)	241	215(5)	277(3)	337(6)	305(4)	318(13)	3,108(44)	2.14

1999年以降の（ ）内は死亡例（死亡例は発生動向調査の届出時での情報であることから, 自治体情報とは異なる場合があります）, *2019年は暫定値, †人口は2015年国勢調査を基にした年平均報告数

Nos. in parenthesis denote the no. of reported fatal cases since 1999. (The number of fatal cases are as of the time of NESID notification and therefore may differ from information reported by subnational levels.)

*Provisional data from 2019 †Per 1,000,000 person-year (2015 population Census of Japan)

（感染症発生動向調査：2020年6月10日現在届出数）

(National Epidemiological Surveillance of Infectious Diseases: as of 10 June 2020)