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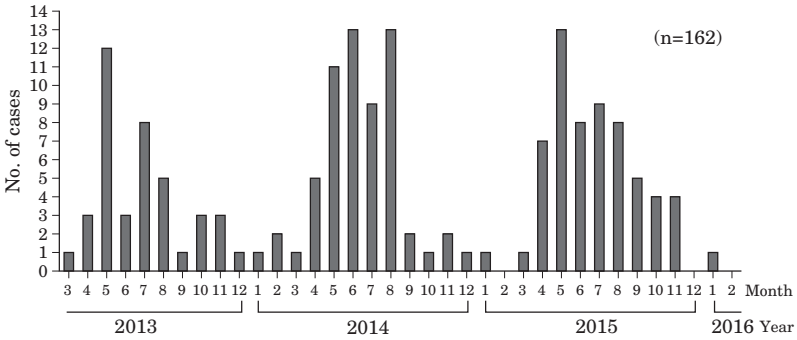
National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

<THE TOPIC OF THIS MONTH>
Severe fever with thrombocytopenia syndrome (SFTS) in Japan, as of February 2016

Figure 1. Reported number of severe fever with thrombocytopenia syndrome (SFTS) cases, by onset month, March 2013-February 2016, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of February 24, 2016)

Severe fever with thrombocytopenia syndrome (SFTS) is a tick-borne systemic infection caused by SFTS virus (SFTSV), which belongs to Genus *Phlebovirus*, Family *Bunyaviridae*. SFTS was first reported from China in 2011 as a novel bunyavirus infection. Since then, SFTS has also been reported from Japan and South Korea. Incubation period is 5-14 days. The signs/symptoms in the early phase of the disease are fever, gastrointestinal symptoms (anorexia, nausea, vomiting, etc.), headache and myalgia, followed by neurological symptoms (impaired consciousness) and bleeding (gingival oozing, bloody diarrhea, hematuria) in the later phase of the disease. Other somatic signs such as lymph nodes enlargement and epigastric tenderness are commonly observed. Laboratory findings include lymphopenia and thrombocytopenia in total blood cell counts (TBC), and increased level of AST, ALT and LDH in the serum chemistry. Among survivors, TBC begins to improve 1 week after onset, and becomes normal within approximately 2 weeks after onset. In severe cases, however, no recovery signs are observed in the later stage of the disease and signs/symptoms such as impaired consciousness and bleeding tendency appear. The pathophysiology of fatal SFTS patients are a combination of the disseminated intravascular coagulation and multiple organ failure. So far, the case fatality rate of notified SFTS patients in Japan has been approximately 30% at the time of notification.

Life cycle in nature and transmission route of SFTSV to humans: In nature, SFTSV is maintained in ticks and mammals through the tick-tick cycle (vertical transmission from adult ticks to their offspring through transovarial transmission) and tick-mammal cycle (transmission from infected ticks to mammals and then from mammals to ticks). SFTSV genome has been detected in several tick species in Japan, i.e., *Takasago testudinarium* (*Amblyomma testudinarium*), *Haemaphysalis longicornis*, *Haemaphysalis flava*, *Haemaphysalis megaspinosa*, and *Haemaphysalis kitaokai*. High prevalence of SFTSV seropositivity has also been demonstrated among deer, wild boars, dogs, and raccoon dogs (see pp. 50 & 51 of this issue), and indicates that the tick-mammal infection cycle is already established in Japan. While the main infection route of SFTSV to humans is via SFTSV-carrying tick-bite, transmission through direct contact with blood and/or body fluid of the SFTS patient to the patient's family members or medical providers has been reported in China and South Korea (see p. 48 of this issue).

Molecular epidemiology: SFTSV isolates in Japan, China, and South Korea are classified into two major clades, i.e., a Chinese clade consisting of 5 genotypes, C1 to C5, and a Japanese clade consisting of 3 genotypes, J1 to J3. In Japan, majority of the Japanese SFTSV isolates detected belonged to genotype J1. However, genotypes C3 to C5 have been detected from some Japanese SFTSV isolates on rare occasions, and conversely, genotype J3 has been detected from some Chinese and South Korean SFTSV isolates (see p. 44 of this issue).

SFTS patients in Japan: Since March 4, 2013, SFTS has been designated as a category IV infectious disease under the

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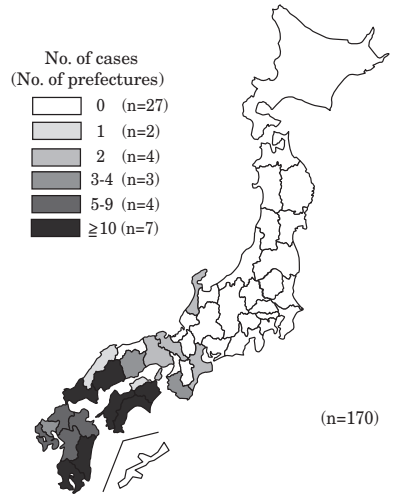
Table. Annual number of reported SFTS cases, Japan

Year of diagnosis	No. of cases			No. of reporting prefectures
	Male	Female	Total	
2013	22	26	48	13
2014	26	35	61	13
2015	28	32	60	16
2016*	1	–	1	1
Total	77	93	170	20**

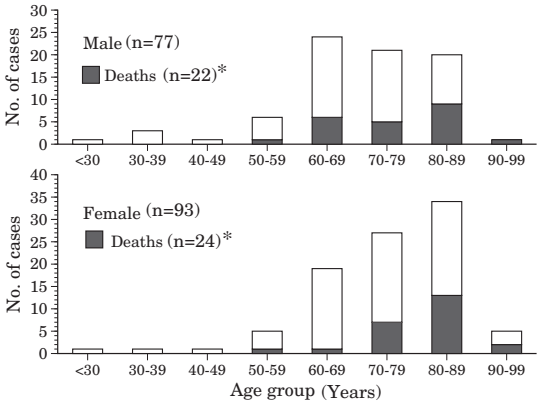
* Provisional as of week 7, 2016
**No. prefectures that reported SFTS during 2013-2016
(National Epidemiological Surveillance of Infectious Diseases: as of February 24, 2016)

Figure 2. Reported number of severe fever with thrombocytopenia syndrome (SFTS) cases, by prefecture, March 2013-February 2016, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of February 24, 2016)

Figure 3. Age distribution of severe fever with thrombocytopenia syndrome (SFTS) cases, by gender, March 2013-February 2016, Japan (n=170)



* At time of notification
(National Epidemiological Surveillance of Infectious Diseases: as of February 24, 2016)

Infectious Diseases Control Law in Japan (see http://www.nih.go.jp/niid/images/iasr/35/408/de4081.pdf for notification criteria). Therefore, a physician, who diagnoses a patient as having SFTS, must notify the case within 24 hours to a local health center. SFTSV must be handled as a class III pathogen under the Infectious Diseases Control Law.

A total of 170 SFTS patients have been notified in Japan as of February 24, 2016 (Table). Among them, 162 had onset in 2013 or afterwards (Fig. 1), while 8 had onset before 2013 (2, 1, and 5 cases in 2005, 2010, and 2012, respectively). Majority of patients were reported during May to August (Fig. 1) and were from 20 prefectures located mostly in western Japan (Fig. 2). Among 162 patients reported since 2013, 77 (45%) were male and 93 (55%) were female. The majority were older than 60 years of age (range 5-95 years; median 74 years) (Fig. 3). A pediatric case was reported in 2015 for the first time in Japan (see p. 42 of this issue). Forty-six patients (27%) were fatal at the time of notification (Fig. 3). Majority of patients had fever (168 cases, 99%) and gastrointestinal symptoms including abdominal pain, diarrhea, vomiting, and anorexia (150 cases, 88%). Thrombocytopenia and leukopenia were found in 162 (95%) and 150 (88%) patients, respectively (see p. 41 of this issue).

SFTS in other countries (China and South Korea) (see p. 47 of this issue): In China, approximately 3,500 SFTS patients have been reported through 2014, with the case fatality rate ranging from 7.8-12.2%. In South Korea, since a fatal SFTS patient was confirmed in August 2012, 36 cases (17 fatal) and 55 cases (15 fatal) have been reported in 2013 and 2014, respectively. The estimated case fatality rate in South Korea ranged from 27-47%.

Laboratory diagnosis in Japan: Virological tests for SFTS include detection/isolation of SFTSV from patients' blood or other body fluids (throat swab, urine, etc.), and/or demonstration of a significant rise in IgG antibody titer against SFTSV in paired sera. Prefectural and municipal public health institutes (PHIs) conduct the conventional one-step RT-PCR (see p. 43 of this issue), while the National Institute of Infectious Diseases (NIID) conducts the quantitative one-step RT-PCR upon request (see p. 45 of this issue). Physicians who are concerned regarding laboratory tests should consult their local health center.

Challenges for the future: The first SFTS patient in Japan was reported in January 2013, and SFTS infections are expected to continue to occur. Studies such as those conducted by NIID and PHIs and the Ministry of Health, Labour and Welfare-funded program, "Comprehensive studies for the control of SFTS", have increased our knowledge and understanding of the SFTS patients' geographical distribution, clinical picture, and pathology, and also regarding the lifecycle of SFTSV in nature, transmission route(s), and risk factors of SFTSV infection.

The most important preventive measure against SFTS is avoidance of tick-bite. During spring to autumn when ticks are most active, exposed areas of the skin should be minimized when entering areas inhabited by ticks. Repellents containing DEET are effective to some extent. Other information regarding tick-bite prevention is available at http://www.nih.go.jp/niid/ja/sfts/2287-ent/3964-madanitaisaku.html.

No vaccines or specific therapeutics against SFTS are currently available. While there has been progress in developing therapeutics against SFTSV (see p. 49 of this issue), as the prognosis of SFTSV infection is quite poor, further research is imperative.

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 Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.

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