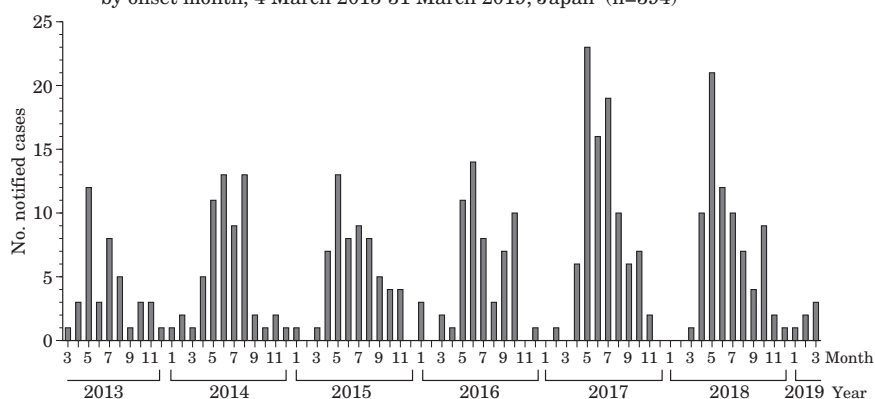


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<THE TOPIC OF THIS MONTH>

Severe fever with thrombocytopenia syndrome (SFTS) in Japan, as of June 2019

Figure 1. Notified number of severe fever with thrombocytopenia syndrome (SFTS) cases by onset month, 4 March 2013–31 March 2019, Japan (n=394)



(National Epidemiological Surveillance of Infectious Diseases: as of 22 April 2019)

Severe fever with thrombocytopenia syndrome (SFTS) was designated as a Category IV infectious disease under the Infectious Diseases Control Law on March 4, 2013 (see <http://www.niid.go.jp/niid/images/iasr/35/408/de4081.pdf> for notification criteria), and any physician who diagnoses SFTS is required to notify a local health center within 24 hours. In many cases, SFTS is a tick-borne infection. The causative virus was classified into the Genus Phlebovirus, Family Bunyaviridae, and was renamed “*Huayangshan banyangvirus*” of *Banyangvirus* Genus of *Phenuiviridae* Family by the International Committee on Taxonomy of Viruses (ICTV) in 2018. However, as it is widely referred to as the SFTS virus (SFTSV) in Japan and abroad, SFTS and SFTSV are used for the name of the disease and the virus, respectively, in this article. SFTS was first reported in 2011 by Chinese researchers and was subsequently confirmed to be endemic to Japan and South Korea. The incubation period is 5 to 14 days, and the major signs/symptoms in the early phase of the disease are fever, gastrointestinal symptoms, headache, and myalgia, which further associate with neurological symptoms (e.g., impaired consciousness) and bleeding symptoms (e.g., gingival bleeding and bloody diarrhea). Physical examination may reveal superficial lymph node enlargement and epigastric tenderness. Blood tests demonstrate leucopenia and thrombocytopenia, and increased AST, ALT, and LDH levels are observed by biochemical testing. In surviving patients, symptoms usually improve in approximately one week after onset and resolve after approximately two weeks. On the other hand, in fatal cases, multiple organ failure due to pathological conditions, such as respiratory and circulatory failure, and disseminated intravascular coagulation (DIC) is observed.

SFTS cases notified under the NESID system

A total of 402 SFTS cases were notified to the National Epidemiological Surveillance of Infectious Diseases (NESID) system between March 4, 2013 and March 31, 2019 (Table in p. 112), including 8 cases of onset before 2012 (2 cases in 2005, 1 case in 2010, and 5 cases in 2012). The occurrence increase between May and October each year (Fig. 1) and cases have been notified from 23 prefectures, mainly in western Japan (Fig. 2 in p. 112). One case was notified from Tokyo in May 2019, but the suspected area of infection was Nagasaki prefecture (see p. 114 of this issue). The patients comprised 196 (49%) males and 206 (51%) females (Fig. 3 in p. 112), with the majority being over 60 years old (range: age 5–96, the median: age 74). Symptoms in 394 patients with onset after 2013 included fever in 392 (99%), gastrointestinal symptoms (e.g., abdominal pain, diarrhea, vomiting, and anorexia) in 342 (87%), and blood tests confirmed thrombocytopenia and leukopenia in 380 (96%) and 351 (89%) patients, respectively.

Epidemiology of SFTS

The AMED (Japan Agency for Medical Research and Development) research group, “Research on the development of diagnosis, treatment, and prevention of severe fever with thrombocytopenia syndrome, and on the elucidation of infection risk to humans”, analyzed the epidemiology, clinical information, and prognostic risk factors of SFTS based on detailed patient information in 133 cases. Comorbidities were observed in 97 (73%), including hypertension (47 cases, 35%), diabetes mellitus (27 cases, 20%), dyslipidemia (15 cases, 11%), and malignant tumors (9 cases, 7%). There were many malignancies in patients who died. One hundred and nine patients (82%) performed outdoor activities within 2 weeks before onset, among whom 70 (53%) were farmers. The case fatality rate (CFR) during the study period was 27% (36 deaths), and there was no significant change in CFR from year to year (see p. 113 of this issue).

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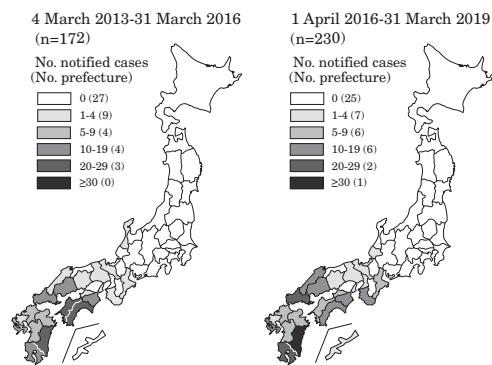
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Table. Yearly number of notified SFTS cases, 2013-2019, Japan

Year of diagnosis	No. of notified cases			No. of notifying prefectures
	Male	Female	Total	
2013	22	26	48	13
2014	26	35	61	13
2015	28	32	60	16
2016	35	25	60	18
2017	41	49	90	20
2018	40	37	77	19
2019	4	2	6	5
Total	196	206	402	23

(National Epidemiological Surveillance of Infectious Diseases: as of 22 April 2019)

Figure 2. Notified number of severe fever with thrombocytopenia syndrome (SFTS) cases by prefecture, March 2013-March 2019, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of 22 April 2019)

from adult ticks to juvenile ticks via transovarial and transstadial transmission (tick-tick cycle), and by ticks infecting animals with SFTSV when they feed on them and then acquiring SFTSV by subsequently feeding on infected animals (tick-mammal cycle). At present, only humans, dogs, and cats (including cheetahs) are known to be affected, but wild animals, such as wild boars, deer, and raccoons, and domestic animals, such as cows, pigs, sheep, goats, and horses, in China and South Korea were also reported to be infected (see p. 116 of this issue).

Transmission of SFTSV from companion animals to humans

When cats or dogs are infected with SFTSV, they exhibit symptoms specific to SFTS. Human cases of SFTSV infection due to direct contact or bites with these symptomatic cats or dogs have been confirmed (see p. 117 of this issue). In recent years, infection from symptomatic animals to their owners and veterinary workers is becoming a major concern. In July 2017, two cheetahs died from SFTSV infection in a zoo. Thus far, SFTSV infection has been confirmed in 120 cats, 7 dogs, and 2 cheetahs. It is unclear whether asymptomatic animals can be a source of infection, but all cases of animal-to-human SFTSV infection reported to date have been from symptomatic animals. In order to prevent infection, it is important to avoid direct contact with cats and dogs with symptoms from an unknown cause. Moreover, veterinary workers who have a higher risk of SFTSV infection should always take standard precautions (see p. 118 of this issue).

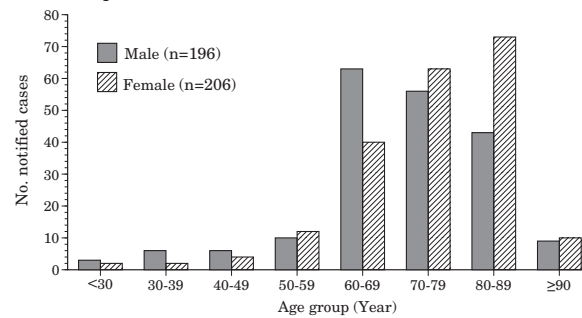
SFTSV antibody positivity among residents living in SFTS-endemic regions in Japan

The antibody-positive rate survey is carried out for residents of regions with many SFTS reports in Japan. In Ehime prefecture, SFTSV antibody tests were conducted on 694 subjects (319 males and 375 females) who were considered to be high-risk groups for SFTS; aged 50 years old or older, and engaged in agriculture and forestry in SFTS-endemic areas. Only one subject (0.14%) was SFTSV-antibody positive. A similar survey was also conducted in the endemic areas in Kagoshima prefecture, and among 646 subjects, two (0.3%) were SFTSV antibody-positive. Although the antibody-positivity among the inhabitants in these endemic areas was not high, further investigations are necessary (see p. 119 of this issue).

Challenges for the future

People living in areas where SFTSV exists in nature are at risk of infection. Although it is a tick-borne disease, it has been confirmed that humans infected with SFTSV from companion animals, such as cats and dogs, can not only develop the disease but may also die. In Japan, a case of suspected human-to-human SFTSV transmission among family members was reported, and in China and Korea, cases of infection from patients to medical workers were also reported. Preventing work-related infections is an important and urgent challenge. Currently, as there is no effective vaccine or therapy, symptomatic treatment is administered for SFTS, and the development of specific therapeutic agents is anticipated (see p. 120 of this issue). At present, clinical research on favipiravir (see p. 121 of this issue), which is expected to be an effective anti-SFTSV drug, and studies on other anti-SFTSV drugs are being conducted. Six years have passed since the identification of the first SFTS patient in Japan, and the need for studies on treatment and prevention is increasing.

Figure 3. Age distribution of severe fever with thrombocytopenia syndrome (SFTS) cases by gender, 4 March 2013-31 March 2019, Japan (n=402)



(National Epidemiological Surveillance of Infectious Diseases: as of 22 April 2019)

SFTS in other countries (China, South Korea, and Vietnam)

The number of reports in China has been increasing, exceeding 1300 in 2016. In South Korea, the number of reports has also been increasing, reaching 259 in 2018. Although SFTS patients were reported only from China, South Korea, and Japan, a retrospective survey reported SFTS patients in Vietnam in 2019 (see p. 115 of this issue).

Laboratory diagnosis in Japan

Prefectural and municipal public health institutes (PHIs) throughout Japan conduct the SFTSV gene detection test by conventional one-step RT-PCR. The National Institute of Infectious Diseases (NIID) conducts gene amplification tests by quantitative one-step RT-PCR and antibody detection tests against SFTSV using paired sera, upon request.

SFTSV infection in animals

SFTSV is maintained in nature by SFTSV being transmitted

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.