One Health Outlook

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Severe fever with thrombocytopenia syndrome (SFTS) in Thailand: using a one health approach to respond to novel zoonosis and its implications in clinical practice

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Abstract

Severe fever with thrombocytopenia syndrome (SFTS), a tick-borne disease caused by *Dabie bandavirus* (SFTSV) is an emerging infectious disease of substantial concern in East Asia. In 2019, Ongkittikul S et al. reported the first case of SFTS in Thailand. Our report describes a One Health investigation of SFTS zoonosis examining the index case and suspected animal reservoirs using real-time RT-PCR and immunoassays. We add to the report on the first confirmed case of SFTSV infection in a human in Thailand by conducting a limited but informative One Health surveillance study. Dogs and cats tested positive for SFTSV antibody using IgG ELISA. We conclude that domestic dogs and cats might serve as potential reservoirs for SFTSV spread due to their closer proximity to the index case than other non-domestic animals. Notably, we did not detect SFTSV in synanthropic cats or dogs—nor did we detect SFTSV in *Rhipicephalus sanguineus* ticks—using RT-PCR. We propose that One Health investigations coupling genomic and serologic assays in response to new SFTS cases could play a pivotal role in preventing and managing SFTS among humans and animals in East Asia. As such, we are establishing a collaborative response to SFTS in Thailand through human outbreak investigations that align with principles of One Health, through environmental surveys and animal RT-PCR and immunoassays. Our investigation highlights the importance of coupling RT-PCR with seroprevalence assays as principal elements of One Health surveillance for SFTS in order to shed light on potential animal reservoirs and track emerging zoonosis.

Keywords Thailand, SFTSV, SFTS, Emerging zoonosis, One health, Seroprevalence, ELISA

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Epidemiological background

Dabie bandavirus, also known as severe fever with thrombocytopenia syndrome virus (SFTSV), SFTS bunyavirus [1, 2], SFTS phlebovirus [3] and *Huaiyangshan banyangvirus* [4, 5], is a viral threat escalating in East Asia. SFTSV is an enveloped, single-stranded RNA virus with a negative sense genome. First identified in China [1], severe fever with thrombocytopenia syndrome (SFTS) caused by SFTSV has a mortality rate ranging from 3 to 47% [6]. Since 2009, SFTSV has reportedly spread to Korea [7–9], Japan [10], Vietnam [11], Taiwan [12], Pakistan [13], Myanmar [14], and recently Thailand [15–17] (Fig. 1). Most epidemiological data about SFTS have been generated in China, Korea and Japan, where outbreaks are most prominent. For instance, between 2010 and 2019 in China, there were 13,824 reported cases of SFTS with 8,899 lab-confirmed cases and 4,925 probable cases [18]. Epidemiological data on SFTS in other countries are limited, particularly regarding the prevalence and geographic distribution of SFTSV. Gaps also remain in deciphering SFTSV host range and transmission dynamics. In this paper, we report on the index case of SFTS in Thailand and provide early detection strategies through a One Health approach. In addition, we make the case for One Health surveillance as a useful epidemiological strategy [19–21] not only in responding to a potential SFTS outbreak but also in elucidating the true epidemiology of SFTSV, meaning its interactions with both humans and the environment [22, 23].

SFTS is a vector-borne disease, and vector-borne viruses such as SFTSV have a particular mobility and zoonotic advantage. Vectors provide viruses with an array of potential targets, allowing them more opportunities to multiply, mutate, and eventually spill over into new hosts [24]. Ectoparasitic ticks drive SFTSV, most prominently the Asian longhorned tick *Haemaphysalis longicornis* which live in East Asia, Australia, and eastern Russia, and are notably regarded as an invasive species emerging in North America [25]. There are several other tick species which have been found to harbor SFTSV; namely, *Ha. flava*, *Amblyomma testudinarium*, *Ixodes nipponensis*, *Rhipicephalus (Boophilus) microplus* [8], *Dermacentor nuttalli*, *and Hyalomma asiaticum* [26]. The most common tick species in Thailand are *Ha. longicornis*, *Amblyomma spp.*, *Dermacentor spp.*, *R. (Boophilus) microplus* (common on cattle) [26], and *R. sanguineus* (common on dogs and sometimes found on cats) [27, 28], all of which are known as hard ticks of the family Ixodidae. Along with *R. sanguineus*, *Ha. longicornis* is also a common tick found on dogs and cats in Southeast Asia [29], though its prevalence in dogs and cats in Thailand is not well documented. In addition, *Ornithodorus hermsi* is a common soft tick species found in Thailand [30]; however, SFTSV has yet to be discovered in soft ticks of the family Argasidae.

Discovering the pool of potential reservoirs and/or intermediate hosts of SFTSV is an ongoing effort. Across East Asia, evidence of SFTSV has been reported in a wide variety of mammals, from even-toed ungulates of the order Artiodactyla (goats, sheep, cattle, deer, pigs, boar), to Carnivora (dogs, cats) and Rodentia (rodents), to the order Eulipotyphla (shrews, hedgehogs). SFTSV has even been reported in birds of the order Galliformes (chickens) and Anseriformes (geese) [24, 26], and it has been proposed and debated that a mechanism of SFTSV spread is via the migratory patterns of birds [8, 31, 32]. Tick-borne SFTSV is currently understood to have sustained in nature through two means of transmission: transovarial or transstadial, which is viral transmission from tick to tick—either via adult to larva or nymph or through two ticks sharing a blood meal on the same animal; or tick-to-mammal during a blood meal [26]. However, reports in recent years reveal that transmission dynamics of SFTSV are much more complicated than tick-borne transmission alone.

Understanding the transmission dynamics of SFTSV between various vectors and hosts is relevant in particular to One Health. SFTSV can be transmitted from livestock, wildlife and companion animals to humans through the transstadial route from tick bites, but there are cases of direct zoonosis from animals to humans, such as through an animal bite or direct contact with animal secretions [33, 34]. Additionally, human-to-human transmission of SFTSV has been reported, such as cases where SFTSV is spread to family members or healthcare workers through droplets or direct contact with infected blood [35, 36], though these events are rarer and more sporadic than zoonosis. Human-to-animal transmission of SFTSV is currently unknown; thus, humans are considered accidental, plausibly dead-end hosts [37].

Clinical background

SFTS is diagnosed in humans by high fever and thrombocytopenia, as indicated by its name, but also manifests clinical symptoms such as gastrointestinal disorders, anorexia, leukocytopenia, neurologic problems and signs of hemorrhaging [26]. Dogs and cats have been shown to manifest SFTS upon infection with SFTSV, sharing a similar pathology to humans. Dogs infected with SFTSV have experienced fever, anorexia, vomiting, thrombocytopenia, leukocytopenia, and death at a considerable mortality rate [38–40]. Dogs also develop anti-SFTSV neutralizing antibodies within 9 to 12 days post-infection [41]. Cats who contracted SFTSV infection from ticks experienced anorexia, thrombocytopenia, leukopenia, hyperbilirubinemia, jaundice and even lethal hemorrhagic fever [42–44]. Research on SFTS convalescence

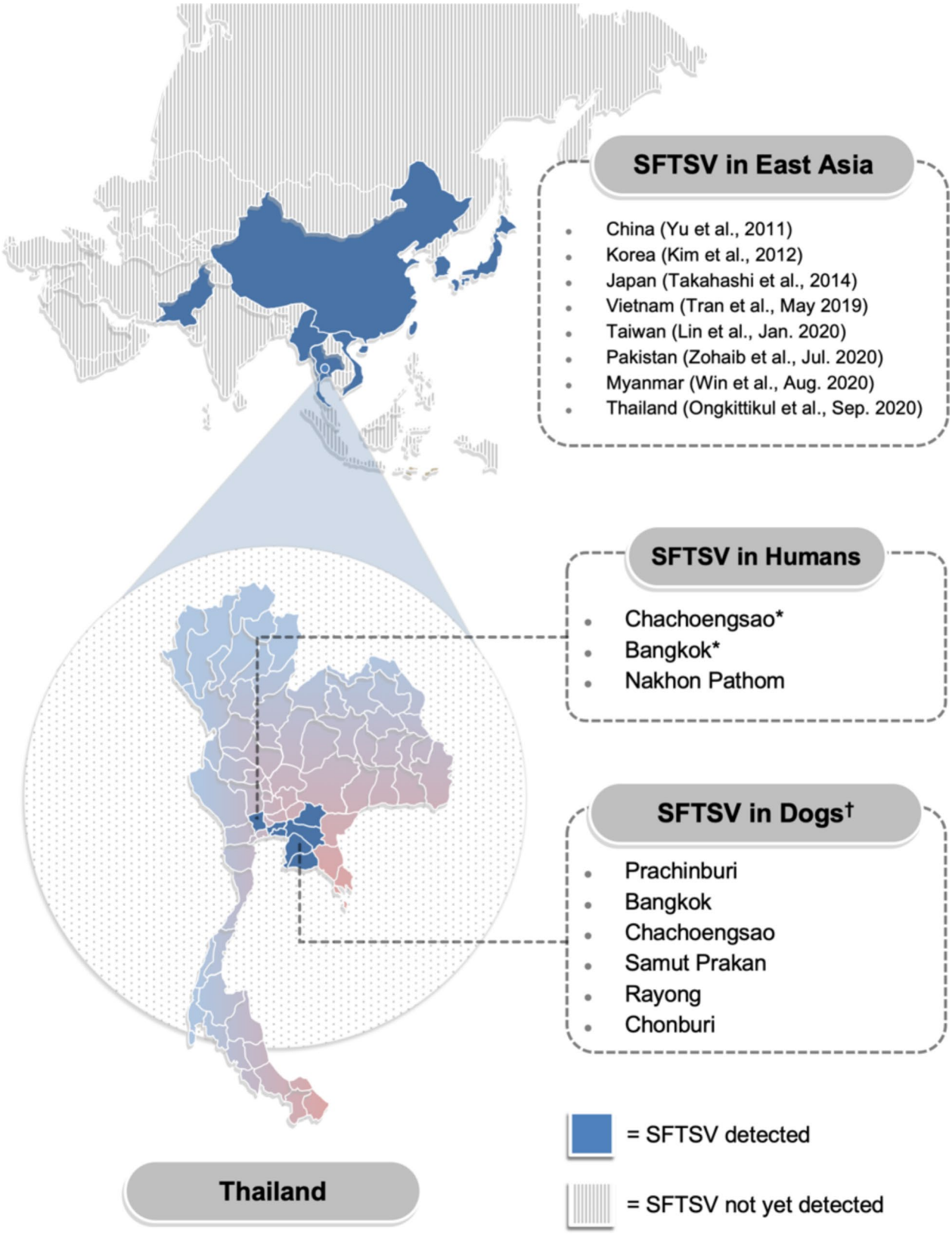

Fig. 1 Known SFTSV prevalence in East Asia, particularly in Thailand.* = RT-PCR data from Rattanakomol et al., 2022 – Chachoengsao (16 years old male, May 10, 2020), Bangkok (60 years old male, November 14, 2019; 52 years old female, October 19, 2020) [16]. † = Data from Ishijima et al. (2023) [17]

in dogs and cats is limited [45, 46] and remains to be explored.

Responses to SFTS are primarily focused on human morbidity and do not mount a One Health approach. To date, there are no specific medicines to prevent or treat SFTS, but medical countermeasures have included symptomatic treatment and administering antiviral compounds such as ribavirin and favipiravir [47, 48], and steroid therapy [49]. SFTSV has an incubation period of about 3 to 15 days [50]. SFTS by tick bite is described clinically as having four stages: SFTSV incubation stage, fever stage, multiple-organ dysfunction (MOD) stage, and convalescent stage [47]. The incubation stage lasts 5–14 days after the tick bite depending on viral titer, while the fever stage lasts 5–11 days, and the range of MOD stage and convalescent stage vary widely per person, though elderly patients are associated with more severe illness and higher likelihood of death [51].

Detecting acute SFTS in humans is usually performed using IgM and IgG immunoassays [52]. In a long-term follow-up study on convalescence in humans, it was found that IgM antibodies seroconverted about 3 days after infection and would maintain in serum for about 6 months, while IgG antibodies seroconverted after about 17 days and would maintain at peak levels for up to 2 years [53]. Underlying conditions are associated with higher SFTS mortality rates, such as comorbidities of viral hepatitis, diabetes, chronic obstructive pulmonary disease and hyperglycemia [54]. Notably, in the case of both humans and animals, the "severe" part of severe fever with thrombocytopenia syndrome can be misleading in SFTSV infections that do manifest severe illness, as it can lead to overlooking asymptomatic spread. Reinfection of SFTSV in humans is likely to occur in cases where the first infection led to subclinical outcomes [55], while fatal SFTS is in part caused by a failure of the host to mount an effective IgG response [26].

Index case in Thailand

On October 12, 2019, the Division of Epidemiology, Department of Disease Control (DDC), Ministry of Public Health, Thailand was notified by King Chulalongkorn Memorial Hospital (KCMH) that there was a severe fever with thrombocytopenia syndrome (SFTS) case at Nakhon Pathom province. The index case was a 70-year-old Thai female admitted to a private hospital in Bangkok. Using a One Health approach, the Joint Investigation Team conducted an investigation aimed to confirm the diagnosis, describe an epidemiological characteristic of the index case, and identify potential reservoirs of SFTSV. The timeline of events is shown in Fig. 2.

Investigation processes: The investigation comprised four parts: (i) descriptive study, (ii) laboratory study, (iii) environmental survey, and (iv) animal survey.

(i) Descriptive study: A descriptive cross-sectional study was conducted. We reviewed a medical record of the index case, interviewed the index case's relatives and conducted contact tracing. Active case finding was carried out in her household and among residents who lived nearby the index case's house. A suspected case was defined as a person who had a body temperature ≥ 38 °C or a history of high-grade fever and at least one of the following symptoms: (1) vomiting/diarrhea, (2) confusion/seizure/coma/stiff neck (3) hematemesis/hematochezia/ecchymosis; and had at least one of the exposure histories: (1) returned from an endemic area including Mainland China, Japan, South Korea (2) tick bite (3) contact with blood or secretion of a confirmed case during September 1 - October 14, 2019. A suspected case was tested positive using at least one of the following diagnostic tests: (1) RT-PCR for SFTSV; (2) ELISA for SFTSV IgG; (3) Indirect fluorescence assay (IFA) IgG and IgM.

For the definition of contacts, a household contact was a person who lived in the same house or visited the index case's house from September 17–30, 2019. A health care worker (HCW) contact was defined as a health care personnel who had direct contact with blood or secretion from a confirmed case and close contact within one-meter distance of a confirmed case while the case had a cough, was vomiting or bleeding, or had diarrhea. For precaution regarding contact and droplet transmission, a high-risk contact was defined as a contact who did not wear appropriate personal protective equipment (PPE).

(ii) Laboratory study: For the index case, blood samples were collected at day 10 and three months after the onset date, and were tested for SFTSV by real-time RT-PCR and fourfold rising of IgG ELISA assay. Blood samples were collected from all household contacts on October 13, 2019, and tested for SFTSV by real-time RT-PCR and IgG ELISA assay at the KCMH laboratory. The human-positive sample was confirmed via IFA at the National Institute of Infectious Diseases (NIID), Japan.

(ii.a) RNA extraction and real-time RT-PCR detection: The serum or plasma sample was inactivated with lysis buffer before the nucleic acid extraction. RNA was extracted from 1 mL of plasma using the NucliSENS® Magnetic Extraction kit and the NucliSENS® miniMAG (bioMérieux, Marcy-l'Étoile, France) according to the manufacturer's protocol. The elution volume for RNA extraction was 50 µL. The real-time RT-PCR method was performed according to a previous report [56]. In brief, primers (5′-GGG TCC CTG AAG GAG TTG TAA A-3′ and 5′-TGC CTT CAC CAA GAC TAT CAA TGT-3′) and a TaqMan hydrolysis probe (FAM-TTC TGT CTT GCT GGC TCC GCG C-BHQ-1) were designed to target the conserved sequences in the S segment. The AgPath-ID one-step RT-PCR kit (Thermofisher, MA, USA) was performed according to the manufacturer's Rotor-Gene

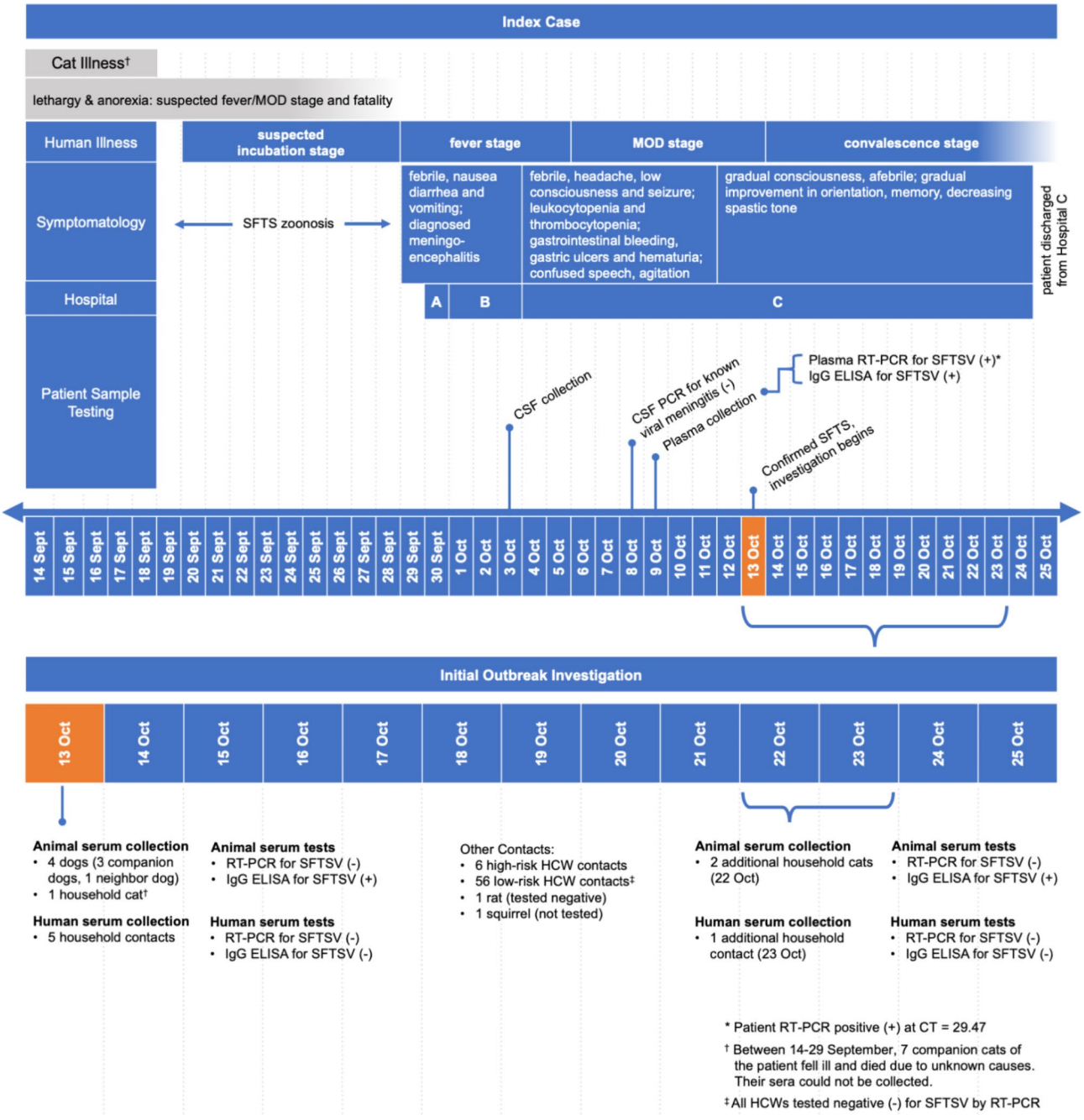

Fig. 2 Timeline of events and investigation from September 14, 2019, to October 25, 2019. On September 29, 2019, the index case had a high-grade fever, nausea, and vomiting. She went to a clinic and was given supportive medication. On September 30, 2019, she went to a private hospital in Bangkok (Hospital A). A doctor treated her as an outpatient department case. On October 1, 2019, family relatives took the patient to a private hospital in Samut Sakhon Province (Hospital B). She developed diarrhea and confusion. Her plasma was negative for Dengue NS1 and IgM but positive for IgG. Her cerebrospinal fluid revealed a viral infection profile, but the AllPlexTM Meningitis Panel Assay (multiplex one-step real-time RT-PCR for 18 meningitis pathogens including 6 bacteria and 12 viruses) was negative. Brain magnetic resonance imaging depicted no leptomeningeal enhancement. A doctor diagnosed meningoencephalitis and treated the patient with Meropenem, Doxycycline, Ampicillin, and Acyclovir. On October 4, 2019, the patient became more confused. The doctor referred her to a private hospital in Bangkok (Hospital C). A doctor further investigated the cause of meningitis. Her saliva, hair roots, and urine were negative for Rabies virus via RT-PCR. Her plasma at day 10 after the onset was sent by Hospital C for RT-PCR for SFTSV diagnosis at the KCMH laboratory, and it tested positive [15]. The patient was treated in an intensive care unit with the continuation of Doxycycline for 10 days. On October 12, 2019, the patient was transferred to the internal medicine ward, rehabilitated with breathing and walking exercises, and discharged from the hospital on October 25, 2019. Of 62 contacts, six household contacts, six high-risk HCW contacts, and 56 low-risk HCW contacts were identified. All contacts were followed up for 14 days. None developed symptoms. In active case finding, a total of 54 villagers in 20 households were interviewed. None met the case definition

Q instrument (QIAGEN, Hiden, Germany) protocol. Each 25-μL reaction contained 5 μL of RNA, 12.5 μL of 2X RT-PCR Buffer, 1 μL of RT-PCR enzyme mix, and 3 μL of 10 μM primer/probe mix. The cycling conditions were as follows: 50 °C for 30 min, 95 °C for 10 min, then 40 cycles of 95 °C for 15 s, 60 °C for 45 s. The threshold was set at 0.02. The amplification curve of any samples showing a typical S-shaped with a cycle threshold (Ct) < 40 was considered to be detected. If positive via real-time RT-PCR, the sample subsequently undergoes PCR and sequencing for confirmation and viral characterization.

(ii.b) IgG Enzyme-linked immunosorbent assay (ELISA): The IgG ELISA was performed at the Thai Red Cross Emerging Infectious Diseases Clinical Center, KCMH. It has been designed to screen human or animal sera using cell lysates as antigens which was provided from NIID, Japan. A Nunc-Immuno Plate (Thermo Fisher Scientific Inc., MA, USA) was coated with 100 μL per well of a predetermined optimal quantity of Huh7 cell lysates prepared from inactivated SFTSV-infected or uninfected cells (in most cases, 1:800 dilution in PBS), and incubated at 4 degrees Celsius overnight. Then, each well of the plate was inoculated with 200 μL of PBS containing 5% skim milk and 0.05% Tween 20 (PBST-M), followed by incubation for 1 hour for blocking. The plates were washed three times with PBS containing 0.05% Tween 20 (PBST) and then inoculated with the test samples (100 μl/well), which were heat-inactivated at 56°C for 30 minutes and diluted fourfold from 1:100 to 1:6,400 with PBST-M. After a 1-hr incubation period, the plates were washed three times with PBST, and then the plates were inoculated with goat anti-human IgG antibody labeled with HRPO (PerkinElmer, MA. USA) diluted 1:1000 with PBST-M, which was added to each well and incubated for 1 hour at room temperature. In testing the animal sera, 1:1000 dilution of the Recombinant Protein A/G peroxidase conjugated (Pierce™, Thermofisher, MA, USA) was used as a secondary antibody. After a additional 1 hour incubation period, the plates were washed, and 100 μL of ABTS [2,2'-azinobis (3-ethylbenzthiazoline sulfonic acid)] substrate solution (Roche Diagnostics, Maaheim, Germany) were added and incubated for 30 min at room temperature. The optical density at 405 nm (OD405) was measured against a reference of 490 nm using a microplate reader (Model Varioskan™ LUX multimode Microplate Reader; Thermo Fisher Scientific Inc., MA, USA). The adjusted OD405 value was calculated by subtracting the OD405 value of the negative antigen-coated wells from that of the corresponding wells. The cut-off value was determined as the average value of the control sera (healthy donor sera) plus three times the standard deviation (SD; mean + 3xSD). The sample was considered positive if it yielded an adjusted OD405 value above the cut-off value.

(iii) Environmental survey: An environmental survey was carried out in the index case's house and neighborhood area in a community to assess sanitation and identify possible reservoirs of SFTSV. We also investigated areas which could serve as shelters and sources of food for animals. These areas included construction sites, temples, markets, municipal solid waste-collecting sites, orchards, and paddy fields.

(iv) Animal survey: A direct observation of animals was conducted to identify potential reservoir populations roaming around the study area. The potential animal reservoir was defined as a synanthropic animal (including cats, dogs, rodents, and birds) living in proximity to the index case's house from September 1 - October 14, 2019. A suspected animal reservoir was classified as an asymptomatic reservoir that was apparently healthy; otherwise, a symptomatic reservoir was classified by a fever and at least one of the following symptoms: (1) weight loss, (2) jaundice, (3) depression, or (4) anorexia. A probable and confirmed animal reservoir was a suspected animal with positive IgG ELISA and RT-PCR for SFTSV, respectively. We asked the owners to collect the health history of any domestic animals and did an empirical physical examination. We reviewed an animal case record to see if any relevant animal cases were brought to an animal clinic/hospital.

Rodent traps were placed at the buildings surrounding the index case's house, one at each building. Other traps were placed under the food and produce stalls in a nearby market. Bird coop with bait was set to capture free-ranging birds outside the index case' house and the market. Blood samples were collected from cats and dogs in the index case's house as well as rats and birds. Ticks found from animals were sent to the laboratory of the Department of Parasitology, Faculty of Veterinary Science, Chulalongkorn University for species identification. All animal samples were tested for SFTSV by real-time RT-PCR at the KCMH laboratory.

IRB/IACUC approval was not required because this was an outbreak investigation performed by the Joint Investigation Team (JIT), Division of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand.

One health approach investigation

a) **Description of the index case**, **2019**: The index case was a 70-year-old Thai female owning a grocery store in Sam Phran District, Nakhon Pathom Province. Her underlying medical condition was dyslipidemia. She had fed cats and dogs in her house for five years and preferred to get rid of their ticks (*Rhipicephalus sanguineus)* with her bare hands—she regularly had wounds under her fingernails from this activity. We

Table 1 SFTSV RNA, IgM, and IgG antibody detection results of the human samples

Patient ID	Host type	Specimen type	Collection date	Laboratory results				
				RT-PCR (Ct)	Serology	IgG ELISA**	IgG-IFA	IgM-IFA
P-01/1*	patient	Plasma	9-Oct-2019	Positive (29.47)	Positive	400	320	< 10
P-01/2*	patient	Serum	8-Jan-2020	Negative	Positive	≥ 6400	Not done	Not done
C-01	contact	Serum	13-Oct-2019	Negative	Negative	< 100	< 10	< 10
C-02	contact	Serum	13-Oct-2019	Negative	Positive	≥ 100	< 10	< 10
C-03	contact	Serum	13-Oct-2019	Negative	Negative	< 100	< 10	< 10
C-04	contact	Serum	13-Oct-2019	Negative	Negative	< 100	< 10	< 10
C-05	contact	Serum	13-Oct-2019	Negative	Negative	< 100	< 10	< 10
C-06	contact	Serum	13-Oct-2019	Negative	Negative	< 100	< 10	< 10
C-07	contact	Serum	13-Oct-2019	Negative	Positive	≥ 100	< 10	< 10
C-08	contact	Serum	23-Oct-2019	Negative	Negative	< 100	< 10	< 10

*The same patient but collected samples at different time points

**The mean of 10 healthy human control sera = 0.00, SD = 0.013; cutoff for human sample = 0.039 (Supplemental Table 1)

Table 2 SFTSV RNA, IgM, and IgG antibody detection results of the animal samples

Animal ID	Host	Specimen type	Collection date	Laboratory results		
				RT-PCR	IgG ELISA	IgG ELISA Titer
D-01	Dog	Serum	13-Oct-2019	Negative	Positive	≥ 6400
D-02	Dog	Serum	13-Oct-2019	Negative	Positive	≥ 6400
D-03	Dog	Serum	13-Oct-2019	Negative	Positive	≥ 6400
D-04	Dog	Serum	13-Oct-2019	Negative	Positive	≥ 6400
C-01	Cat	Serum	13-Oct-2019	Negative	Positive	≥ 6400
C-02	Cat	Serum	22-Oct-2019	Negative	Positive	≥ 6400
C-03	Cat	Serum	22-Oct-2019	Negative	Positive	≥ 6400
R-01	Rat	Serum	23-Oct-2019	Negative	Negative	< 100
Control*D1-10	Dog	Serum	April 2022	Negative	Negative	< 100
Control*C1-10	Cat	Serum	April 2022	Negative	Negative	< 100

Cutoff calculation = mean of control sera + 3 × SD

*The mean of 20 control sera = 0.00, SD = 0.013; cutoff for animal sample = 0.034 (Supplemental Table 1)

identified 10–20 ticks per suspected animal reservoir. The index case did not travel to other provinces one month prior to the onset of her symptoms, and she had never traveled abroad.

b) **Real-time RT-PCR detection of SFTSV in humans and animals**: The result of the SFTSV RNA fragments of S gene was detected in the plasma sample of the patient (Ct = 29.47) by real-time RT-PCR for the partial small (S) segment. However, a conventional PCR test at the nucleoprotein gene was negative (data not shown). Then, 19 samples from the at-risk groups who had been in contact with the patients were collected: 8 household contacts, 4 dogs, 3 cats and 1 rat. The results of real-time RT-PCR for these samples were all negative (Tables 1 and 2).

c) **SFTSV IgG antibody detection in humans and animals**: A blood specimen was collected from the patient, and eight serum samples were collected from household contacts: persons who lived in the same house or visited the index case's house, and a healthcare worker who had had direct contact with the blood or secretions of the patient. Viral antibody detection by IgG ELISA was conducted to diagnose SFTS. Serum samples obtained from 10 healthy donors were used to establish the cut-off value of the IgG ELISA, and the cut-off OD was 0.009 (Table 1). The patient samples collected during the symptomatic phase (P-01/1, October 9, 2019) and 3 months after symptom onset (P-01/2, January 8, 2020) were IgG-ELISA positive at 400 and ≥ 6400, respectively. The first plasma sample of the patient was confirmed positive by IgG-IFA at titer 320 but not by IgM-IFA. Notably, the IgM-IFA is less sensitive than IgG-IFA [10], which is likely the reason for the negative result. Our study did not involve IgM capturing, which significantly reduces the sensitivity of the assays. Even though the IgM-IFA of the patient's first serum was negative, a fourfold increase of IgG titer by ELISA in two consecutive patient sera was mandatory to conclude true SFTSV infection. Two serum samples from contacts (C-02 and C-07) were weakly positive for IgG-ELISA antibodies to SFTSV at 1:100 dilution with OD 0.028 and 0.067, respectively, but negative by IgG-IFA and IgM-IFA, as shown in Table 1 and Supplemental Fig. 1. IgG ELISA generally has low specificity [17],

so we performed an additional experiment, IgG IFA. Sera showing positive in both ELISA and IFA would be true antibody-positive against the SFTSV.

d) **Environmental investigation**: The index case's home was a single-story house (Fig. 3). In front of the house was the local road next to the irrigation canal, while behind the house was a banana plantation. The house was located near the famous floating market in the metropolitan area with convenient public transportation. During weekends and holidays, many Thai and foreigner tourists visited there to purchase Thai food and souvenirs. Some tourists also visit a local Buddhist temple to participate in religious rituals. Despite a regular waste collection by the local government, the markets and large number of people generated a high amount of solid waste. The temple nearby served as a good roosting site for feral pigeons and other generalist birds. Agricultural areas such as banana plantations and rice fields, along with construction sites and garbage collecting points, provided shelter and food sources for free-roaming dogs and cats, plus rodents. Additionally, shaded areas under the buildings could potentially serve as resting and questing grounds for ticks, mites, and fleas.

e) **Animal investigation**: There were three dogs, twelve cats, and one squirrel (*Callosciurus finlaysoni*) kept at the index case's house. All animals in the house were not sick. Almost all the pets were indigenously born except some cats with unknown history were adopted from other people. The squirrel was confined in a small cage. Both the dogs and cats were kept within the home area. However, at least three stray cats were found on the roof of her house. All dogs and cats in the house were reportedly vaccinated against feline parvovirus and rabies but there was no vaccination record. The dogs suffered from skin diseases and many ticks (10–20 each) were found on their bodies. In early September 2019, seven cats became lethargic and anorexic and gradually died of feline distemper within one week. Unfortunately, they were not tested for SFTSV infection during the outbreak investigation.

The blood specimens were collected from suspected animals living at the index case's house, including 4 dogs and 3 cats, totaling 7 serum samples. All seven serum samples from suspected dogs and cats showed positive IgG antibodies against SFTSV with a high titer of ≥6400, as shown in Table 2. Twenty healthy animal samples from the non-effect area (from Bangkok, >50 km far from Nakhon Pathom) were used to establish the cut-off value of the IgG ELISA; all showed an OD≤0.00. Supplemental Table 1 shows raw data of IgG ELISA OD. Unfortunately, the animal samples were not confirmed by IFA due to the strict regulations on shipping animal samples to Japan.

A survey of animals raised in the neighboring area found dogs, cats, rabbits, pet birds, chickens, and geese. Livestock including goats, sheep, cattle, or horses were not found in the area. One sick dog was found in a house next to the index case's house, but the owner denied our request to collect a specimen. Only one Pacific rat (*Rattus exulans*) was captured as the relative abundance of rats was very low (2.1 rats per 100 trap-nights). There was

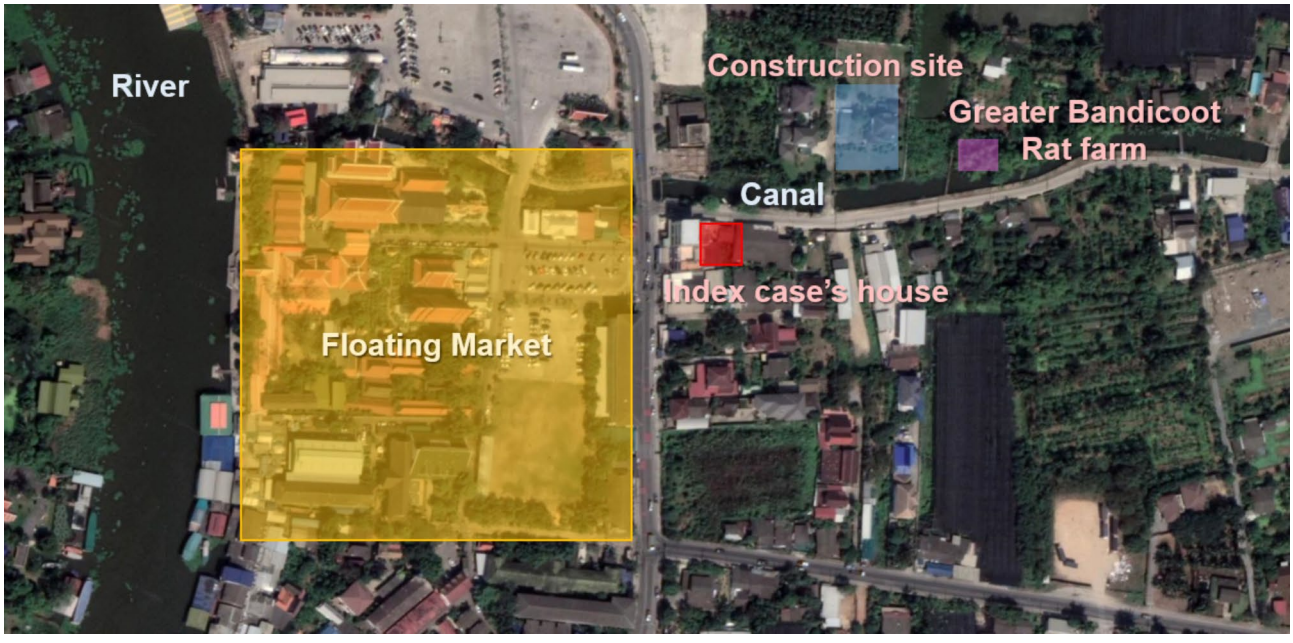

Fig. 3 Map of the index case's house and nearby environment

Greater Bandicoot Rat (*Bandicota indica*) farming near the index case's house, but the farmer denied specimen collection. Rat farmers usually collect the animals from multiple middlemen in rural areas from different provinces, keep the rats for propagation and fattening, and slaughter and sell them as food delicacies when an order is placed. The most abundant birds from point counts were feral pigeons (*Columba livia domestica*) which live in flocks, roost on temples, and feed on swill around the area. The RT-PCR for SFTSV negative results for cat and dog samples in the index case's house, as well as the rat sample, are shown in Table 2. Birds ($n=10$) in a neighborhood area all tested negative for SFTSV (data not shown). Ticks ($n=10$) on the dogs were identified as *Rhipicephalus sanguineus* and their RT-PCR for SFTSV results were also negative (data not shown).

One health approach for SFTS response

Our study demonstrates the use of the One Health approach to support outbreak investigations of SFTS as an emerging disease in Thailand. Overall, the prevalence of SFTSV in animals in Southeast Asia is unclear, particularly in Thailand. Upon a suspected SFTS outbreak, we conducted concurrent human-animal-environmental health studies aimed at revealing current prevalence of SFTS and routes of SFTSV transmission between species. As such, we propose integrating SFTS surveillance in Thailand along the human-animal-environmental interface in domestic and farming livestock and poultry, notably by including samples of wildlife which could serve as reservoirs of SFTSV as it spreads to humans both via tick bite and direct contact with animals or their secretions and droplets.

The first confirmed case of SFTSV infection in Thailand was reported in 2019 from two studies: one case in Nakhon Pathom (same case as our study) by RT-PCR without sequencing [15], and 3 cases in or near Bangkok by PCR and sequencing [16, 57]. In this outbreak investigation, SFTS case was confirmed (1) RT-PCR positive, (2) IgG-ELISA and IgG-IFA positive at 10 days after symptom onset, (3) the fourfold IgG antibody raising at 3 months after symptom onset, and (4) high titer IgG antibody positives from seven animals (4 dogs and 3 cats) living at the index case's house. It should be noted that the conventional PCR was negative such that sequencing could not be performed, which might be due to low viral copies (ct 29.47), while the IgM-IFA was negative from the same sample collected 10 days after onset. Therefore, the first SFTSV case in Thailand has been confirmed based on a combination of real-time PCR and IgG seroconversion results. We demonstrate that a combination of diagnostic tools is needed for SFTS confirmation. We note that index case and her family did not travel abroad for three months prior to the infection, highlighting that SFTSV has been prevalent in Thailand for longer than we presently know. Notably, IgG ELISA tests conducted among domestic animals in the village, both cats and dogs, yielded positive results with a high titer, confirming the local infection of SFTSV. Meanwhile, RT-PCR tests across all animal samples including ticks collected from these antibody-positive animals were negative. This finding may indicate that the animals were infected by SFTSV for a long period of time [41, 51] before patient onset and probably the source of infection. Continued One Health surveillance is essential to rule out if SFTS is endemic in this area or if this outbreak was a one-time event. Two household contacts had weak IgG-positive antibodies against SFTSV via IgG-ELISA, but they were found negative by IgG-IFA; in addition, they did not have any symptoms related to SFTS during the past 12 months. The weak positive IgG result may be caused by cross-reaction with other endemic diseases or the antibody wane from a long post-infection period. This emphasizes the need for a confirmation test for weak SFTS-positive results.

Ixodid ticks likely drive SFTSV transmission in domestic animals and wildlife alike, but we propose that conducting surveillance for synanthropic animals is much easier and more pertinent to public health. The first broad surveillance of SFTSV in East Asia for domesticated artiodactyls and other wild mammals was conducted in Taiwan about twenty months (from March 2021 to December 2022), the highest RNA prevalence of SFTSV being in sheep, cattle, and goats, while wildlife had a positive rate of 11.9% [58]. This surveillance program only elucidated one side of the epidemiology of SFTS, though, as the authors did not include human serologic samples in their study. Furthermore, a meta-analysis on the infection rate and susceptibility of animals to SFTSV in 2018 analyzed seroprevalence and found high prevalence among goats, sheep, cattle, and dogs (>29%), with low prevalence among chickens, rodents and pigs (<10%). The meta-analysis conducted by Chen et al., 2019, provides valuable insights into the epidemiology of SFTSV in animals, but also highlights a need for combining animal data with human data [24]. Indeed, a gap remains in understanding the true endemic range of SFTSV in both humans and animals, as well as in understanding links of *Ha. longicornis*, *R. sanguineus*, and other ticks as SFTSV vectors across the human-animal interface.

The clear limitation of this study is the scarce number of samples to yield robust conclusions about how SFTSV had spread. Because this was the first One Health investigation for SFTS in Thailand, the Surveillance and Rapid Response Team (SRRT) from the Department of Disease Control (DDC), Ministry of Public Health collected samples only deemed relevant to the immediate need. This limits our understanding of true SFTSV prevalence in the area and necessitates further investigation. Despite

our limited sample size, SFTSV in domestic animals in Thailand is corroborated by a recent publication from Ishijima et al., 2023, who showed through RT-PCR and immunoassays that approximately 17% of dogs in multiple districts across central Thailand were infected with SFTSV, suggesting the widespread of SFTSV in the country [17].

Overall, our understanding of the maintenance and circulation of SFTSV in animals in Thailand remains to be explored, as further studies on other free-ranging animals such as rodents and exotic farmed animals like bandicoots have not yet been conducted. In addition, Thailand has competent tick vectors capable of transmitting SFTSV, and while the *R. sanguineus* dog ticks in this investigation tested negative for SFTSV by RT-PCR, it is plausible that we are presently blind to local transmission of SFTSV occurring through tick blood meals, as well as through transovarial and transstadial routes. In order to manage and mitigate the emerging threat of SFTSV among both human and animal populations, the DDC, alongside multisectoral partners from the Ministry of Agriculture and Cooperatives, Ministry of Natural Resources and Environment, and Universities, has implemented a collaborative One Health network. The aim is to establish a robust surveillance system for monitoring SFTS occurrences in both humans and animals. We are making concerted efforts to enhance the capacity of public health laboratories specifically dedicated to SFTSV diagnosis.

Actions taken post-study

We notified Thailand's national focal point for the International Health Regulations, provided health education to a family member regarding tick bite prevention, and removed ticks from the index case's house using a 6%w/v Flumethrin solution. We conducted follow-up with case contacts alongside local public health officers and infection control nurses from private hospitals. Additionally, we facilitated risk communication for the general population in the region.

Abbreviations

SFTSV	Severe fever with thrombocytopenia syndrome virus, formally recognized as *Dabie bandavirus*; also known as SFTS bunyavirus, SFTS *phlebovirus*, and *Huaiyangshan* banyangvirus
SFTS	Severe fever with thrombocytopenia syndrome
MOD	Multiple-organ dysfunction
IgM	Immunoglobulin type M
IgG	Immunoglobulin type G
ELISA	Enzyme-linked immunosorbent assay
RT-PCR	Reverse transcription polymerase chain reaction
DDC	Department of Disease Control
SRRT	Surveillance and Rapid Response Team of the Department of Disease Control

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

CS conducted the filed investigation and wrote the manuscript. RT conducted the filed investigation and wrote the manuscript. CSH wrote the manuscript. PL collected specimens and contributed to the manuscript. CC conducted the filed investigation and collected specimens. NT conducted laboratory tests. SP conducted laboratory tests. PT conducted laboratory tests. SW analyzed laboratory data, oversaw the study, and reviewed the final manuscript. RB oversaw the study and reviewed the final manuscript. TK conducted laboratory tests. TY conducted laboratory tests. MS oversaw the study and reviewed the final manuscript. SI oversaw the study and reviewed the final manuscript. OP oversaw the study and reviewed the final manuscript.

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Data availability

Supplementary Table 1: IgG ELISA Results. Supplementary Fig. 1: IgG-IFA and IgM-IFA Results. Other data used during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

IRB/IACUC approval was not required because this was an outbreak investigation performed by the Joint Investigation Team (JIT) at the Division of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand.

Consent for publication

The need for informed consent was waived due to the samples being collected for an outbreak investigation.

Competing interests

The authors declare no competing interests.

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