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Pathogens and epidemiologic feature of severe fever with thrombocytopenia syndrome in Hubei province, China



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ABSTRACT

To evaluate the aetiological agents and epidemiologic features of severe fever with thrombocytopenia syndrome (SFTS) in Hubei province, China, sera from patients were collected from January to December 2011. All cases occurred from April to December, and the epidemic peaked from May to August. The ages of patients ranged from 10 to 86 years (median = 55 years), and the incidence of SFTS increased with age. The female:male ratio of cases was 1.008:1, and 54.6% (77/141) and 1.4% (2/141) of the cases were confirmed by qPCR to be SFTSV and Hantavirus (HV) infection, respectively. No case of simultaneous infection with two or more pathogens was found. The research in this paper showed that some suspected SFTS cases are confused with HV infection due to similar symptoms. The analysis showed that the distribution of SFTSV has a marked regional aggregation in Hubei province.

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1. Introduction

Beginning in March 2009, severe fever with thrombocytopenia syndrome (SFTS) was detected in the hilly region of Hubei province in central China. However, the cause of SFTS is unclear. The primary clinical manifestations of patients with SFTS were sudden-onset fever, thrombocytopenia, leukocytopenia, and gastrointestinal symptoms; these led to the disease being assigned the name SFTS. At first, the mortality rate of the infectious disease reached 30% (Yu et al., 2011). Subsequently, cases were reported in Henan, Shandong, Jiangsu, Liaoning, and other provinces of China, with clinical symptoms that were similar to those of human granulocytic anaplasmosis (HGA). Patients with such symptoms in Hubei

province were initially diagnosed with HGA (Yu et al., 2010; Xu et al., 2008), but in most cases the laboratory evidence was insufficient to verify the diagnosis. The Chinese Centers for Disease Control and Prevention (CDC) stated that such symptoms were not compatible with those of HGA, as described in the United States (Wellman et al., 1988). In March 2011, a new virus was isolated from a patient's blood by the Chinese CDC and named SFTS bunyavirus (SFTSV) (Li, 2011). An aetiological investigation of the disease was undertaken by the Hubei CDC. According to the above clinical characteristics and case definition, surveillance for SFTS was initiated in Hubei province. To evaluate the aetiology and epidemiology of SFTS, enhanced surveillance of acute febrile illness was carried out in Hubei province in 2011.

2. Materials and methods

2.1. Surveillance districts and blood collection

A surveillance network at town health centres and general hospitals was established in Hubei province (Fig. 1a). Cases were reported in the China Information System for Disease Control and Prevention. Acute-phase serum samples, clinical information and laboratory data of all patients with a diagnosis of SFTS in 2011 in Hubei province were obtained from the hospitals in the surveillance network.

Abbreviations: SFTS, severe fever with thrombocytopenia syndrome; SFTSV, severe fever with thrombocytopenia syndrome virus; HV, hantavirus; qPCR, quantitative real-time polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; CK, creatine kinase; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HTNV, Hantaan Virus; SARS, acute respiratory syndrome; HGA, human granulocytic anaplasmosis.

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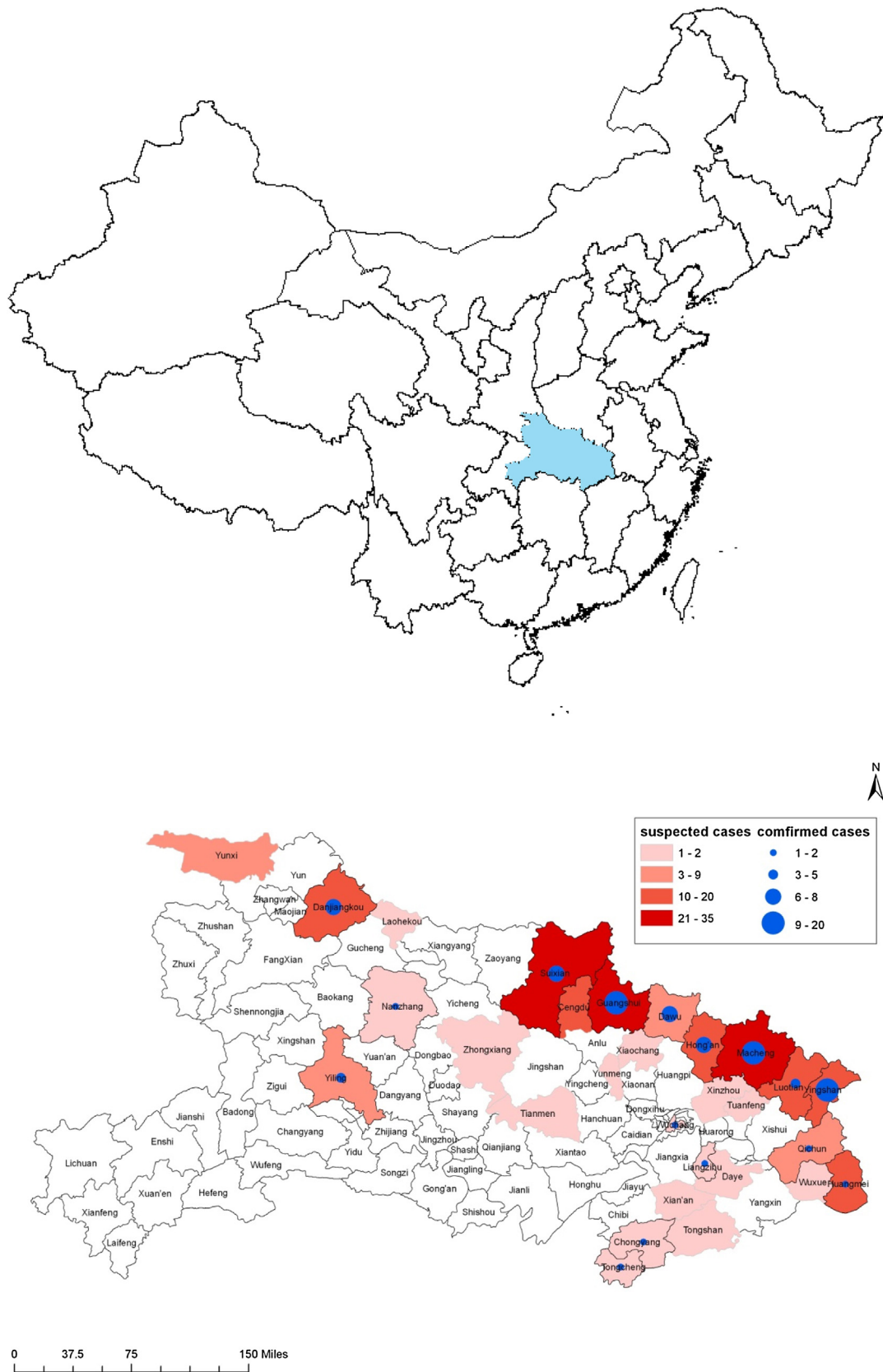


Fig. 1. a. Hubei Province, China (color area) where severe fever with thrombocytopenia syndrome was studied, 2011. b. Geographic distribution of reported cases with SFTS and confirmed cases infected with SFTSV in Hubei province in 2011.

Table 1
The Primers for RT-PCR for Hantavirus(HV)and genotyping.

Detection of object	Primer name	Sequence, 5'→3'	position	bp
HV	YF-Hanta-P	FAM-TTATCATCTGGTCWACAATGTCATG-BHQ-1	156–132	87
	YF-Hanta-F	CATGGATTACTTDGATAG	98–105	
	YF-Hanta-R	CTGTCTTTATTRTCWGAC	184–167	
Hantaan Virus	YF-Hv-P	FAM-CATCCCTCACCTTCTGCC-BHQ-1	118–101	155
	YF-Hv-F	GCTACTAKAACAAAYGATG	22–39	
	YF-Hv-R	CTGTCTGYAATGTTYTC	176–159	
Seoul Virus	YF-Sv-P	FAM-ATCCCTAACCTTCTGGCTGCTAT-BHQ-1	123–100	103
	YF-Sv-F	ATGGCAACTATGGAAGAA	43–60	
	YF-Sv-R	CTTCTCATACTGYTTTTC	145–127	

2.2. Clinical case definition and surveillance methods

2.2.1. Suspected cases

The symptoms included primarily acute fever ($\geq 38^\circ\text{C}$) and thrombocytopenia (platelet count, $<100,000/\text{mm}^3$ of unknown cause) or fever with bleeding tendency, including melena, bleeding gums, skin point spots, or congestion of the conjunctiva (Liu et al., 2012). We collected blood samples from hospitalised patients whose symptoms met the criteria for the case definition and excluded patients whose symptoms met the criteria but who had another clinical- or laboratory–confirmed diagnosis.

2.2.2. Confirmed cases

Suspected cases exhibited one of the following symptoms: isolation of virus from serum; viral RNA in acute-phase serum; at least a four-fold increase in immunoglobulin G (IgG) titre in paired sera (convalescent and acute phases; detected by ELISA); and immunoglobulin M (IgM) in serum.

2.3. Detection of viral RNA in acute-phase serum samples by qPCR

Viral RNA was extracted from serum using a QIAamp Viral RNA Mini Kit (52904; Qiagen). The cut-off cycle threshold for a positive sample was 35 cycles. The extracted RNA was used as a template for RT-PCR to amplify SFTSV RNA using primers derived from the small RNA (sRNA) segments of the virus (Wen et al., 2014); RT-PCR was performed using the One-Step PCR Kit (TaKaRa), and PCR products were sequenced to confirm the presence of SFTSV.

2.4. Serologic testing by ELISA

A his-tagged affinity chromatography-purified recombinant nucleocapsid protein (NP) of SFTS V (strain HB29) expressed in *Escherichia coli* was used as the antigen (Niu et al., 2013). A Mac-ELISA was used to detect specific IgM/G (ELISA-IgM/G Kit; Key Laboratory for Medical Virology CDC).

2.5. Detection of other pathogens

IgM against Hantavirus (HV) was detected by ELISA (Beijing Wantai Company), and confirmed by qPCR (Shanghai Zhijiang Company) (Table 1). Infection with HGA was detected by qPCR (Dana Gene Company). Brucella was detected by the plate agglutination test (PAT) and confirmed by the standard tube agglutination test (SAT).

3. Results

3.1. Epidemiology of SFTSV

In 2011, 241 cases of SFTS were reported from 29 counties and districts in Hubei province (Fig. 1b); the morbidity and case fatality rates were 0.42/100,000 and 11.2%, respectively. The annual incidence of SFTS increased with age ($\chi^2 = 125.64, P < 0.001$). Patients 50–90 years of age accounted for 73.86% (178/241) of the total number of cases, while farmers accounted for 94.61% (228/241) (Fig. 2), and the female:male ratio was 1.008:1. We confirmed 77 cases of SFTSV infection in Hubei province in 2011. All of the cases

Table 2
Clinical Symptoms of patients with Laboratory-confirmed and unconfirmed.

Clinical Symptoms	Confirmed SFTSV N = 68. (%)	Unconfirmed SFTSV N = 40. (%)	Confirmed HV N = 2. (%)
Sign or symptom			
Fever	68(100)	40(100)	2(100)
Malaise	49(72)	31(78)	2(100)
Fatigue	48(71)	23(58)	2(100)
Anorexia	39(57)	21(53)	2(100)
Nausea	21(31)	16(40)	2(100)
Diarrhea	19(28)	6(15)	1(50)
Vomiting	17(25)	13(33)	2(100)
Dizziness	16(24)	5(13)	1(50)
Headache	13(19)	10(25)	2(100)
Throat congestion	13(19)	4(10)	2(100)
Cough	12(18)	6(15)	2(100)
Myalgia	8(12)	3(8)	1(50)
Chill	7(10)	5(13)	1(50)
Lymphadenopathy	7(10)	2(5)	0(0)
Body pain	5(7)	8(20)	1(50)
Arthralgia	5(7)	5(13)	1(50)
Sputum production	4(6)	6(15)	1(50)
Skin rash	2(3)	1(3)	0(0)
Laboratory test	68(100)	21(53)	2(100)
Thrombocytopenia	68(100)	15(38)	2(100)
Leukopenia			

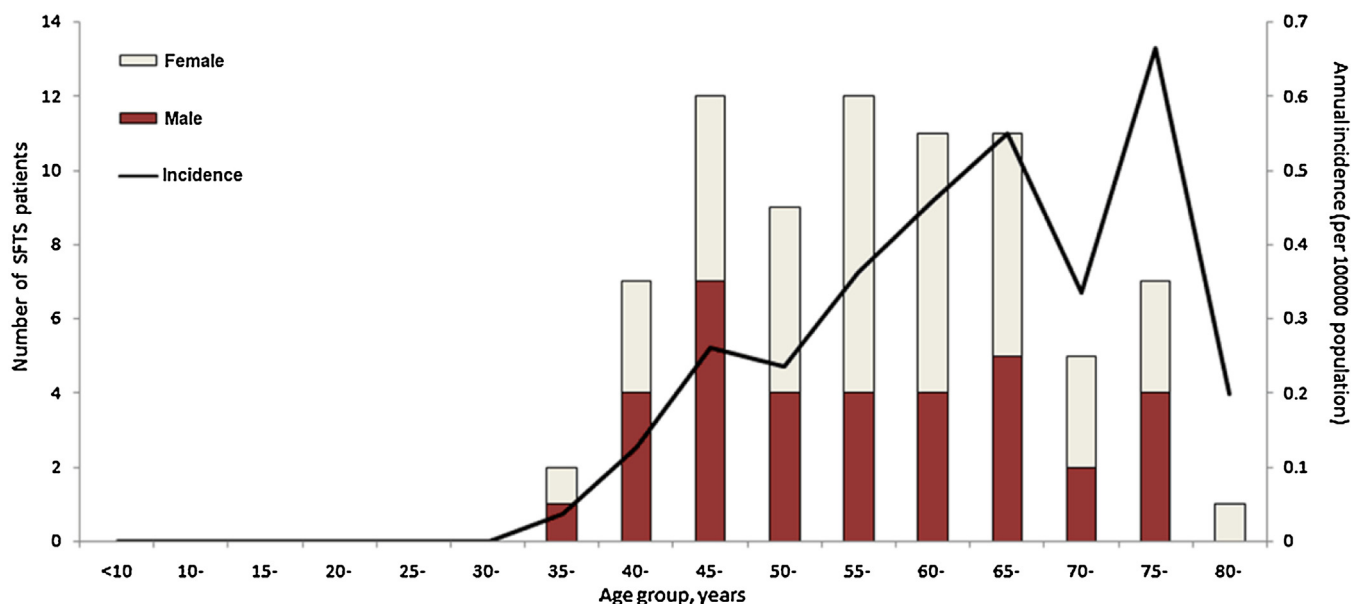


Fig. 2. Gender and age distribution of the SFTS cases in Hubei province, 2011. The black histogram represents the number of male cases and the white histogram represents the number of female cases over 5-year age groups. The line represents the annual average incidence(1/100000) over age groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

occurred from April to December (Fig. 3), and the epidemic peaked from April to August (58.4%, 45/77). In total, 77 SFTS cases from 16 counties and districts in Hubei province in 2011 were laboratory-confirmed. Of the confirmed cases, 81.8% (63 of 77) were in the Dabie mountainous area, adjacent to Henan and Anhui provinces.

3.2. Clinical features of SFTSV cases

The major clinical features of patients with confirmed SFTSV infection were sudden-onset

severe fever, of 7–10 days duration, accompanied by malaise and fatigue. Elderly patients who were in poor health and had high blood pressure, diabetes, and high blood lipid levels tended to have a poorer outcome. Clinical and laboratory manifestations included fever (100%), malaise (72%), thrombocytopenia (79%), and leucopenia (67%) (Tables 2 and 3). The creatine kinase (CK) and lactate

dehydrogenase (LDH) levels of the majority of cases were higher, which, together with haematuria and proteinuria, suggested rapid progression to multiple organ failure. The major clinical symptoms of patients were fever, leukocytopenia, and thrombocytopenia, together with abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST), calcium and LDH levels (Table 3).

3.3. qPCR and ELISA analysis

A total of 141 of SFTS cases was analysed by qPCR. The positivity rate of PCR amplification of the S segment was 54.6% (77/141). PCR products were confirmed to be SFTSV RNA by sequencing. The consistency of detection by qPCR and ELISA-IgM was 51.2% (42/82) (Table 4). Sensitivities were calculated by combining the qPCR and ELISA results of acute-phase serum samples as the denominator. The sensitivity of ELISA was 63.08% (41/65) and that of qPCR was

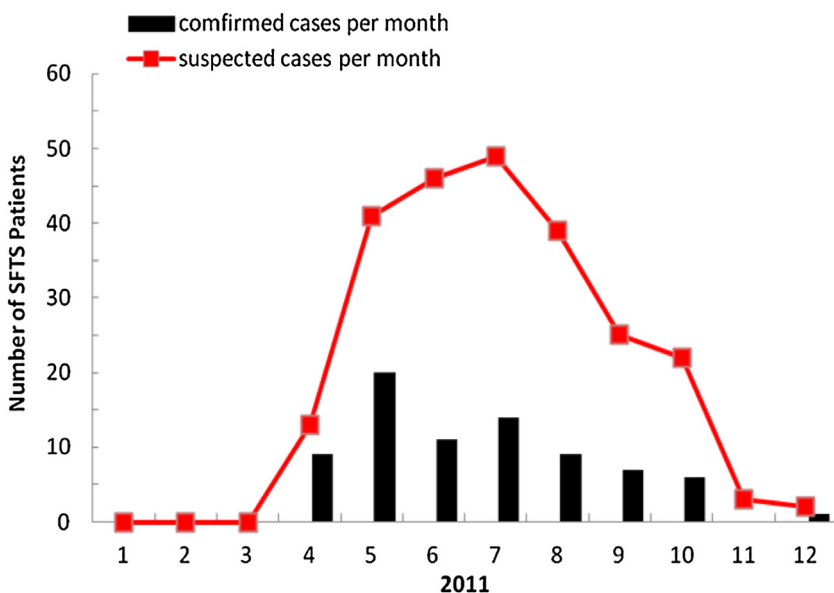


Fig. 3. Cases of severe fever with thrombocytopenia syndrome by month of illness onset, Hubei Province, China, 2011.

Table 3
Laboratory clinical findings in patients with SFTS.

Category	Reference value	Elevated level	Low level no./total no. (%)	Normal level
Platelet count	(100–300)×10 ⁹ /L	1/63(2)	50/63(79)	12/63(19)
White-cell count	(4–10) ×10 ⁹ /L	1/63(2)	42/63(67)	20/63(32)
Calcium	(2.3–2.7)mmol/L	0	59/61(97)	2/61(3)
ALT	(0–40)u/L	39/56(70)	0/56	17/56(30)
AST	(0–40)u/l	48/57(84)	0/57	9/57(16)
Proteinuria	Negative	27/38 ^P (71)	0/38	11/38 ^N (29)
LDH	(135–225)u/L	23/26(88)	0/26	3/26(12)
CK	(0–75)u/L	14/54(26)	0/54	40/54(74)
Hematuria	Negative	14/40 ^P (35)	0/40	26/40 ^N (65)
Neutrophil count	(2–7.7) × 10 ⁹ /L	1/61(2)	32/61(52)	28/61(46)
Sodium	(135–145)mmol/L	2/64(3)	16/64(25)	46/64(72)
Albumin	(35–50)g/L	0/66	17/66(26)	49/66(74)
Blood sugar	(3.9–6.1)mmol/L	4/65(6)	0/65	61/65(94)
Ratio of albumin to globulin	1–2.5	1/66(2)	4/66(6)	61/66(93)

① Abbreviations:P,positive;N,negative. ②“1/63” (1), the percentage of cases whose level of platelet count increased; “1”, the cases whose platelet count was in elevated level; “63”, the cases whose result of platelet count were available. The meaning of the following data is similar to the above.

Table 4
Test results for 82 patients infected severe fever with thrombocytopenia syndrome,Hubei Province,China,2011.

SFTSV-qPCR	SFTSV-ELISA		No. Patients
	+	-	
+	25	24	49
-	16	17	33
No.Patients	41	41	82

+, positive; -, negative.

Table 5
The results for 82 patients infected severe fever with thrombocytopenia syndrome,Hubei province,China,2011.

Acquisition time after illness onset,week	qPCR		ELISA		No. Patients
	+	-	+	-	
<1	29	13	20	22	42
1–2	20	20	21	19	40

+, positive; -, negative.

75.38% (49/65). Using the combination of the qPCR and ELISA results of acute-phase serum samples, 79.2% (65/82) of patients were diagnosed with SFTSV infection (Table 5); 19.5% (16/82) were positive for IgG against SFTSV by ELISA-IgG. Of the 82 patients infected with SFTS, acute-phase serum samples (obtained during the first week of illness) of 42 patients were available. Among these 42 serum samples, 29 (69%) were positive for SFTSV RNA by qPCR and 20 (47.6%) were positive for IgM against SFTSV by ELISA-IgM. Of the 40 patients with available acute- phase serum samples (obtained during the second week after onset of illness), 20 (50%) were positive for SFTSV by qPCR and 21 (52.5%) were positive for IgM against SFTSV by ELISA-IgM. There was no significant difference in assay performance for samples obtained one or two weeks after the initial illness ($X^2 = 0.974$, $p > 0.05$).

3.4. Detection of other pathogens

We also detected *Anaplasma phagocytophilum*, Hantavirus, and Brucella. Of the total number of cases, 54.6% (77/141) were diagnosed with SFTSV infection, while 1.4% (2/141) were diagnosed by IgM against Hantavirus (HV), and confirmed by qPCR as being HV infection. The further genotyping of HV is Hantaan Virus (HTNV). No case of simultaneous infection with two or more pathogens was found. Moreover, no evidence of HGA and Brucella infection was found in these patients. These results suggest that some cases

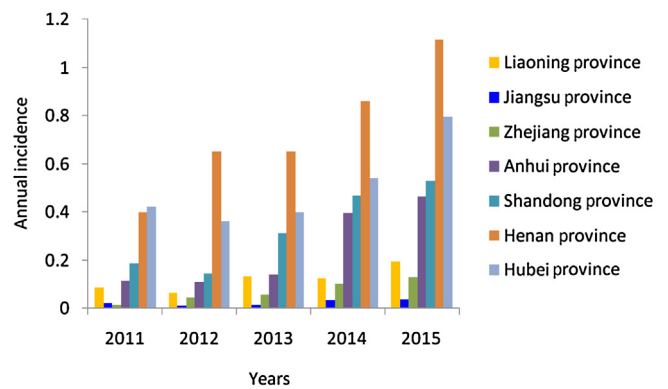


Fig. 4. The annual incidence of SFTS cases in China, 2011–2015. The color histogram represents the annual average incidence (1/100000).

with the symptoms of SFTS may be caused by HV; therefore, the underlying cause of SFTS should be diagnosed and interpreted with caution.

4. Discussion

Following the severe acute respiratory syndrome (SARS) epidemic in 2003, the Chinese government has focused on establishing an infectious disease surveillance and reporting system to facilitate identification of both known and unknown diseases. Among the 17 prefectural-level cities in Hubei province, 13 (including 29 counties and districts) reported SFTS cases. An investigation was performed to identify whether SFTS was caused by other pathogens. The clinical symptoms resembled those of human anaplasmosis, Brucellosis, and hemorrhagic fever (HFRS). Neither the specific nucleotide nor antibodies against those pathogens could be detected in blood samples from a majority of the patients. Instead, SFTSV and Hantavirus (HV) were detected from patients' blood. Because most SFTS cases in Hubei province were SFTSV infections, with few being HV and none being HGA, SFTSV was the major aetiological agent of SFTS in Hubei Province. However, the few cases of HV suggested that some suspected SFTS cases are confused with HV infection due to similar symptoms. There is no significant difference in the clinical symptoms between those patients with confirmed HV infection and those with confirmed SFTSV infection, but there are significant differences in clinical symptoms between laboratory-confirmed and unconfirmed cases ($X^2 = 12.45$, $p < 0.001$). Differences in symptoms between laboratory-confirmed SFTSV tests are thrombocytopenia (100%) and leukopenia (100%), and laboratory-unconfirmed SFTSV

tests were 53% and 38%, respectively (Table 2). These results are helpful for accurately diagnosing SFTS.

We concluded that SFTSV had long been epidemic in Hubei province because the clinical symptoms of our cases were identical to those of Anaplasma infection, which was found in *Haemaphysalis longicornis* in 2010 in Hubei province (Zhang et al., 2010). Reports from Henan province in China showed that only 8% of SFTS cases had evidence of HGA (Xu et al., 2011). Infection with *Anaplasma phagocytophilum* has been suggested as a cause, but the pathogen was not detected in laboratory testing of the majority of patients in 2011 in Hubei province. This suggests that SFTSV may cause sub-clinical infections in children and adults. Moreover, the cytopathic effects of SFTSV were modest in Vero cells, rendering detection problematic. Therefore, the distribution of SFTSV and HGA infections in Hubei province should be investigated further.

The number of cases increased gradually from April to September, when the tick density is highest (Tesh, 1988; Schmaljohn and Hjelle, 1997). Changes in tick density are associated with the number of confirmed SFTSV cases (Klompfen et al., 1996). Therefore, ticks may transmit the virus, rendering the disease more dangerous. SFTSV has been isolated from ticks by the Chinese CDC (Zhang et al., 2011). Moreover, person-to-person and blood transmission of SFTSV was reported (Bao et al., 2011; Gai et al., 2011; Jiang et al., 2015).

All SFTSV cases in Hubei province showed abnormal AST and ALT levels. The majority of cases exhibited elevated CK and LDH levels, which, combined with haematuria and proteinuria, indicated that multiple organs could be infected by SFTSV. We had understood it was caused by SFTSV, a novel bunyavirus found in 2011 in China, but the main cause of death in clinical practice is not yet clear. The mechanism of blood transmission is also unclear; possibilities include bleeding, virus replication rate, and a high viral load. Further research on this matter is warranted.

The SFTSV positivity rate by qPCR was higher in acute-phase blood samples obtained in the first week (35.36%) than in the second week (24.39%) (Table 5). However, the SFTSV IgM positivity rate showed the opposite result. These findings support use of qPCR of serum samples to confirm detection of SFTSV during the first week after illness onset, and serum ELISA for detection during the second week. The results also suggest that ELISA or qPCR alone is insufficiently sensitive for diagnosis of SFTSV infection in the early stage of SFTS. Combining qPCR and ELISA results can increase sensitivity markedly.

By the end of 2015, the cases of SFTS were mainly distributed in eastern and central China: Henan province, Hubei province, Anhui province, Shandong province, Jiangsu province, Liaoning province, and Zhejiang province. The highest incidence of SFTS was in Hubei (0.42/100000) compared with other provinces in 2011, and ranged from 0.42 per 100000–0.79 per 100000 from 2011 to 2015. However, the highest incidences of SFTS were in Henan and Hubei from 2011 to 2015 in China. Since 2012, the incidence of SFTS increased annually in Hubei, Henan, and Shandong, with the greatest incidence in Henan province, and the second highest in Hubei province in China (Fig. 4).

SFTS is a new acute infectious disease. Infections with SFTSV were distributed throughout Hubei province; however, the majority of qPCR-confirmed cases were in the Dabie mountainous area in Hubei province, which is adjacent to Henan province and Anhui province. The Dabie mountainous area is located in Hubei, Henan and Anhui provinces, suggesting a clustered distribution of SFTSV infection.

Conflict of interest

The authors declare no conflict of interest regarding the publication of this paper.

Ethics statement

This research was approved by the Ethics Committee of the Centers for Disease Control and Prevention of Hubei province, which uses international guidelines to ensure confidentiality, anonymity, and informed consent. Informed consent was obtained from all study participants.

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