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Original Article

Spatial and temporal analysis of severe fever with thrombocytopenia syndrome in Zhejiang Province, China, 2011 - 2015

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Abstract

Introduction: Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease first discovered in northeast and central China in 2009, and SFTS cases increased year by year in China. This study aimed to identify the spatial and temporal clusters of SFTS in Zhejiang Province, China.

Methodology: We analyzed the surveillance data of SFTS in Zhejiang Province during 2011 - 2015. Descriptive statistics were used to analyze the general characteristics and overall trend of SFTS. Circular statistic method was utilized to identify the seasonality. Space–time scan analysis was performed to explore the high risk spatio-temporal clusters of SFTS cases at county level.

Results: A total of 194 confirmed SFTS cases were reported in Zhejiang Province during 2011 - 2015. We found a significant increase in overall time trend since 2011. The seasonality was statistically significant ($P < 0.001$), with a mean date (95% CI) of 21st June (12th ~ 30th in June). Totally 21 (23%) counties reported the occurrence of SFTS, which gradually spread throughout Zhejiang. Three spatio-temporal clusters were detected, with one principle cluster (Daishan County, RR 234.48, June 2013 - November 2015) and two secondary clusters (6 counties, RR 30.73, April - October in 2015; Anji County, RR 373.26, May 2014).

Conclusions: Our results suggested that SFTS has increased and spatially expanded over the past years, with a remarkable seasonality. Three spatio-temporal clusters were identified. These findings are important for the improvement of SFTS surveillance and control strategies.

Key words: Severe fever, thrombocytopenia syndrome; epidemiological characteristic; seasonality; spatio-temporal analysis.

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Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease first discovered in northeast and central China in 2009 [1], and SFTS virus (SFTSV), a Phlebovirus in the family of *Bunyaviridae*, has been identified as the causative agent [2]. Ticks, especially *Haemaphysalis longicornis*, are suspected to be the potential vector, which have a broad animal host range [2,3]. Surveillance data [4] showed that incidence of SFTS is ascending in China, and a total of 5360 laboratory-confirmed SFTS cases have been reported until December 2016. Most cases occurred in individuals aged 40~80 years (91.57%), and the male-to-female ratio was 0.88. 98.00% of SFTS cases were reported from April to October with a peak in May to July. During 2011 - 2016, 99.53% of SFTS cases were limited to 7 provinces in China. In past few years, the disease also spread among several countries worldwide [5-7] with a case-fatality rate of 10 ~ 15% and the potential human-to-human transmission [8,9].

Since the occurrence, a number of studies were conducted to understand the epidemiology, etiology, diagnosis and therapy of this novel disease [1,10-14]. However, many knowledge gaps still exist, especially regarding the spatial and temporal pattern of the disease. Understanding when and where the SFTS clustering occurs is essential for effective disease surveillance and control.

Geographic Information System (GIS) and related technologies are useful tools for exploring the spatial and temporal characteristics of infectious diseases, making the epidemiological description more effective and accurate [15,16]. Therefore, it has been widely used in mapping the distribution and detecting potential clusters of emerging infectious diseases, such as severe acute respiratory syndrome (SARS) [17], influenza A (H1N1) [18] and avian influenza A (H7N9) [19].

Here, we utilized GIS methods to identify the spatial and temporal clusters of SFTS based on the surveillance data of Zhejiang Province. This study was expected to enhance the knowledge on the current features of SFTS epidemic, and provide scientific basis for the improvement of SFTS surveillance and control strategies.

Methodology

Case definition

The case definition was based on 'The diagnosis and treatment programs of severe fever with thrombocytopenia syndrome' issued by National Health and Family Planning Commission of the People's Republic of China [20], in which a suspected case of SFTS was defined as a patient with acute onset of fever (≥ 38.0 °C) and other symptoms (e.g., gastrointestinal symptoms, bleeding), epidemiological risk factors (being a farmer or being exposed to ticks 2 weeks before illness onset), and laboratory data showing thrombocytopenia and leukocytopenia. With the exception of laboratory confirmation, a patient should not only have met the criterion for a suspected case of SFTSV, but also at least one of the following criteria: (1) detection of SFTSV RNA by a molecular method, (2) sero-conversion or ≥ 4-fold increase in antibody titers between two serum samples collected at least 2 weeks apart, and (3) isolation of SFTSV in cell culture.

Data collection

The surveillance data of SFTS in Zhejiang Province during 2011 - 2015 was obtained from China Information System for Disease Control and Prevention, a national surveillance system of infectious disease reported by medical institutions where a patient first attend. For each case, we collected the following data from the system: gender, age, occupation, place of residence, the date of symptom onset, the date of diagnosed and, in case of fatal outcome, the date of death. In addition, the background population for each county was obtained by the year for further analysis.

Under the mandate of the 'Law on Prevention and Control of Infectious Diseases' of The People's Republic of China, the short investigations on SFTS patients, which are conducted by medical institutions, are exempt from ethical approval and informed consent.

The GIS data was collected from National Earth System Science Data Sharing Infrastructure, National Science & Technology Infrastructure of China (http://www.geodata.cn).

Statistical analysis

Descriptive statistics were applied to illustrate the general characteristics of the SFTS cases. The number of confirmed SFTS cases by month, 2011 - 2015, was presented as a figure. The figure also showed a centered 12-month moving average [21] to present the overall trend (seasonal and random variation have been largely smoothed out). Circular statistic method [22] was used to identify the possibility of seasonal clustering, and estimate the peak of incidence of SFTS with corresponding 95% confidence interval (CI).

A retrospective space–time scan statistic with a Poisson model [23] was performed to explore the high risk spatio-temporal clusters of SFTS cases, using SaTScan software (version 9.3, https://www.satscan.org). Cases are assumed to be Poisson distributed with constant risk over space and time under the null hypothesis, and with different risk inside and outside at least one of the cylinders under the alternative hypothesis. The method is defined by a cylindrical window with a circular geographic base and with height corresponding to time. It involves a flexible scanning window which gradually moves across time and space. In this study, the spatial size of scan window was limited to 50% of the total population, and the time aggregation length was set to one month. Therefore, numerous overlapping cylinders of different sizes are generated, which cover the entire study area and time duration. Each cylinder is considered a possible candidate cluster. The statistical significance of each identified cluster was based on the log likelihood ratio (LLR) against a null distribution obtained through Monte Carlo simulation, with the number of replications set to 999 and the significance level defined as 0.05.

For each cylinder the numbers of cases inside and outside the cylinder are noted, together with the expected number of cases reflecting the population at risk [24]. The numbers of observed cases divided by the numbers of expected cases within and outside cylinder are proportional to the incidence ratios within and outside the cylinder, respectively [25]. Thus, this approach estimates the relative risk (RR) as the observed divided by the expected within the cluster divided by the observed divided by the expected outside the cluster [26]. In mathematical notation [26], it is:

$$RR = \frac{c/E[c]}{(C-c)/(E[C]-E[c])} = \frac{c/E[c]}{(C-c)/(C-E[c])}$$

Where c is the number of observed cases within the cluster and C is the total observed number of cases in the study. E(c) is the expected number of cases within the cluster under the null hypothesis, which equals C multiplied the population in the cluster divided by the total population [27]. E(C) is the total expected number of cases in the study. Since the analysis is conditioned on the total number of cases observed, E[C] = C.

Results

General characteristics

By applying the criteria stated above, a total of 194 confirmed cases of SFTS were reported in Zhejiang Province until 31st December 2015. The general characteristics of SFTS cases are presented in Table 1. The median age of the patients was 65 years (ranged from 0.5 to 88 years), and the majority cases (86.1%) aged 50 years and older. In total, 58.8% (114/194) were female, with a male-to-female ratio of 0.70:1. Moreover, the most common occupation was 'farmer' (57.7%). Additionally, 13.4% (26/194) died from the disease, and the case-fatality rate remained steady except the year 2011 with none death. The location and population of Zhejiang Province was shown in Figure 1.

Temporal characteristics

The overall trend in the number of reported SFTS cases showed a significant increase since 2011, the first year with the occurrence of SFTS in Zhejiang. The distribution of reported SFTS cases followed a clear seasonal pattern, with cases increasing during the summer months (May–August) and decreasing until December. No case was observed in winter period (January and February). (Figure 2)

Figure 1. The location and population of Zhejiang Province.

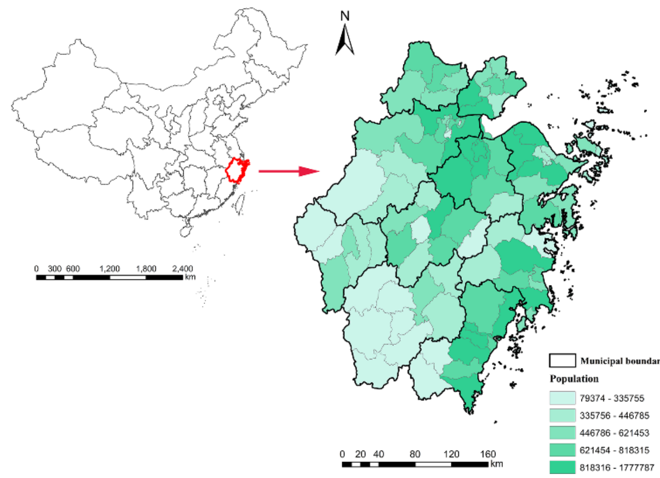


Figure 2. Trend of confirmed SFTS cases reported in Zhejiang Province, China, 2011 -2015.

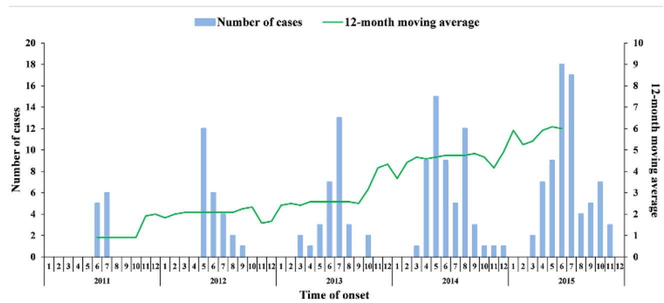


Table 1. General characteristics of 194 SFTS cases reported in Zhejiang, 2011 - 2015.

General characteristics	Confirmed SFTS cases					
	Overall (N = 194)	**2011 (N = 9)**	**2012 (N = 25)**	**2013 (N = 31)**	**2014 (N = 57)**	**2015 (N = 72)**
Age (years, N, %)						
Median(QI)	65.0 (56.0-73.0)	70.0 (62.0-73.5)	69.0 (56.5-77.0)	62.0 (55.0-75.0)	63.0 (50.5-69.0)	64.5 (56.3-74.8)
< 50	27 (13.9)	1 (11.1)	1 (4.0)	3 (9.7)	13 (22.8)	9 (12.5)
50–64	66 (34.0)	1 (11.1)	9 (36.0)	13 (41.9)	16 (28.1)	27 (37.5)
65–79	83 (42.8)	6 (66.7)	11 (44.0)	12 (38.7)	27 (47.4)	27 (37.5)
≥ 80	18 (9.3)	1 (11.1)	4 (16.0)	3 (9.7)	1 (1.8)	9 (12.5)
Gender (N, %)						
Male	80 (41.2)	3 (33.3)	12 (48.0)	19 (61.3)	24 (42.1)	22 (30.6)
Female	114 (58.8)	6 (66.7)	13 (52.0)	12 (38.7)	33 (57.9)	50 (69.4)
Occupation (N, %)						
Farmer	112 (57.7)	3 (33.3)	14 (56.0)	16 (51.6)	31 (54.4)	48 (66.7)
House worker or retired	58 (29.9)	5 (55.6)	8 (32.0)	9 (29.0)	15 (26.3)	21 (29.2)
Other	24 (12.4)	1 (11.1)	3 (12.0)	6 (19.4)	11 (19.3)	3 (4.2)
Outcome (N, %)						
Death	26 (13.4)	0 (0.0)	4 (16.0)	4 (12.9)	10 (17.5)	8 (11.1)
Survival	168 (86.6)	9 (100.0)	21 (84.0)	27 (87.1)	47 (82.5)	64 (88.9)

SFTS: severe fever with thrombocytopenia; QI: quartile interval.

Circular statistic method was applied to assess for seasonality. The result of Rayleigh test suggested that the seasonal pattern was statistically significant ($Z = 83.21$; $P < 0.001$). The mean angle (95% CI) was 172.06 (162.87 ~ 181.24) degree, and the corresponding date (95% CI) of seasonal cluster of SFTS was 21st June (12th ~ 30th in June).

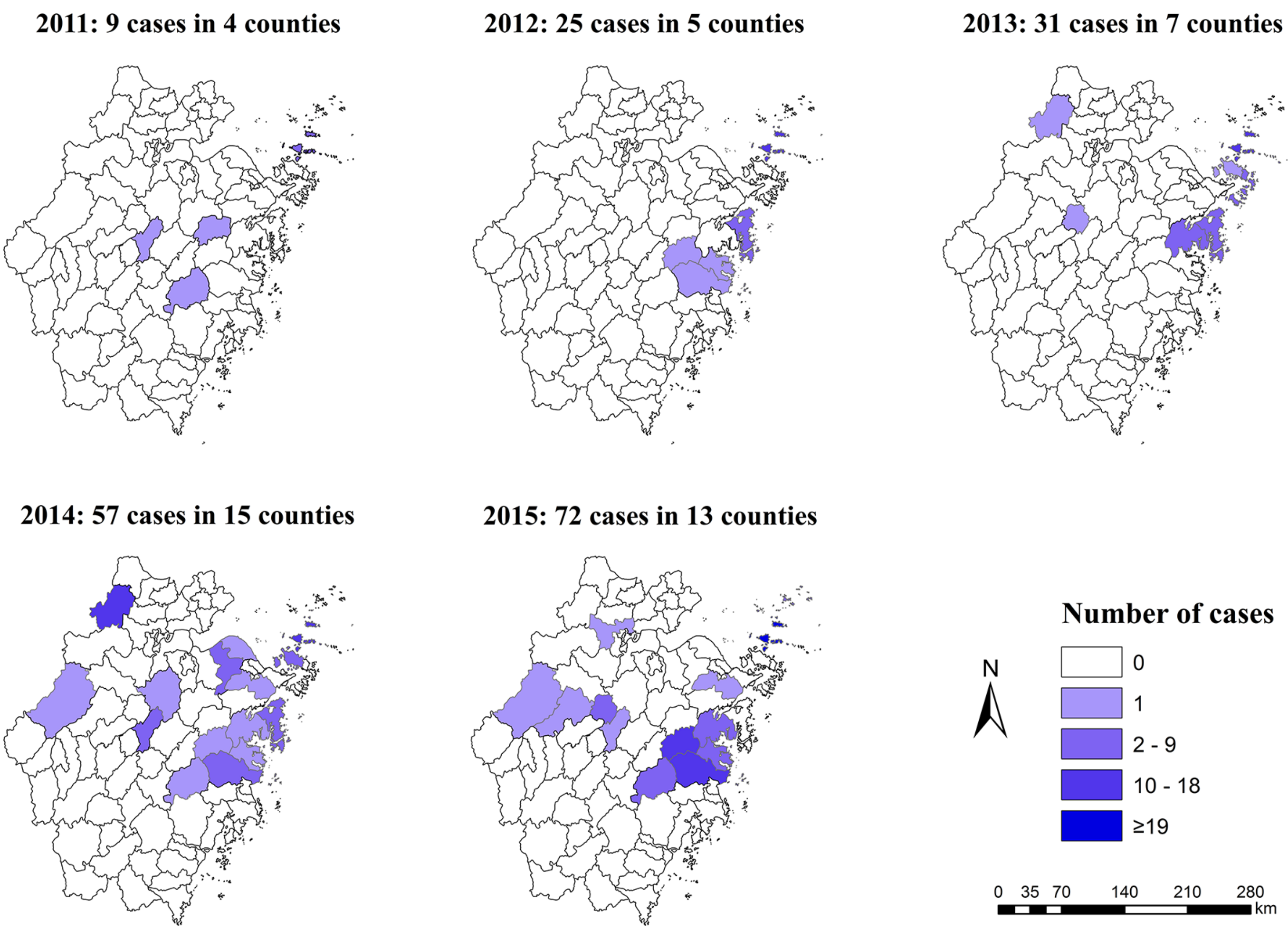
Spatial characteristics

In the study period, 21 counties reported the occurrence of SFTS, accounting for approximately 23% (21/90) of the total number of counties in Zhejiang Province. Among these 21 counties, 17 (81%) counties reported less than 10 cases. Of the rest 4 counties reporting more than 10 cases, 3 counties (Daishan, Linhai and Tiantai) located along east coast. More than 44% (87/194) cases occurred in Daishan County, which was the first county reporting SFTS in Zhejiang. The number of counties where SFTS was reported kept increasing from 2011 to 2015, indicating that SFTS gradually spread throughout Zhejiang. A geographical distribution map is presented in Figure 3.

Spatio-temporal analysis

Figure 4 and Table 2 shows the results of the space–time scan statistical analysis in Zhejiang Province, 2011 - 2015. Three significant clusters, including one principal and two secondary clusters, were detected, which accounted for 53.61% of total SFTS cases with only 6.61% of the total population in Zhejiang. The principal cluster, with a relative risk (RR) of 234.48, was detected in Daishan County during June 2013 to November 2015 (LLR 256.03, $P < 0.001$). One of the secondary clusters covered 6 counties (Linhai, Tiantai, Ninghai, Sanmen, Xinchang and Pan'an), lasting from April to October in the year of 2015 (LLR 75.88, RR 30.73, $P < 0.001$). Another secondary cluster occurred in Anji County in May 2014 (LLR 48.98, RR 373.26, $P < 0.001$).

Figure 3. Spatial distribution of confirmed SFTS cases reported in Zhejiang Province, China, 2011 - 2015.



Discussion

In this study, we explored the spatial and temporal characteristics of SFTS in Zhejiang Province, during the period 2011 - 2015. The results of our study suggested that SFTS cases displayed a consistent marked seasonality from 2011 to 2015, with most cases reported during May - August. In addition, three spatio-temporal clusters of SFTS cases were detected, indicating that the disease was not randomly distributed over space and time in Zhejiang Province.

The epidemic season of SFTS started from early spring to late autumn, with a significant peak observed in summer. Our finding of the seasonality was in agreement with the previous studies [28-30], which indicated that the climatic conditions might be associated with the incidence of SFTS. It was found that the activity of ticks (considered as the major potential vector to transmit the SFTS virus) and tick–pathogen interactions could be affected by climatic conditions, such as temperature and relative humidity [31-33]. The climate in eastern China is cold between December and January, and temperatures begin to rise in late February. It is usually pleasant in March and April, and starts to get warm from May. The density of ticks is relatively higher in spring, summer and autumn [34,35], which is consistent with the incidence of SFTS. Additionally, seasonal pattern may also be ascribed to the increased outdoor activity of the farmers or house workers such as harvesting tea and cutting grasses [2], subsequently resulting the higher possibility of exposure to the potential arthropod vectors and mammalian hosts. More attention need to be paid as there can be a potential outbreak in the same period (May - August) in future.

This study has identified a steadily increasing overall time trend for SFTS in all counties combined during the study period, suggesting that SFTS has in fact increased year by year in the overall region. Moreover, the geographical distribution map illustrated that the disease increased in area over the years and expanded outwards from Daishan County in 2011 towards several directions in subsequent years. This phenomenon could be attributed to several corresponding factors. The winter months of each year was gradually warmer and more humid from 2011 to 2015 in Zhejiang Province [36]. It is likely that climatic conditions have favored a higher population growth and the proliferation of pathogens [37]. Likewise, arthropod vectors (e.g. ticks) may have extended activity period due to relatively warmer weather during winter [38], which may affect arthropod vectors' population dynamics and distribution over space as well [37,39]. Beside climate–change, the effect of gradually

Figure 4. Spatio-temporal clusters of confirmed SFTS cases reported in Zhejiang Province, China, 2011 - 2015.

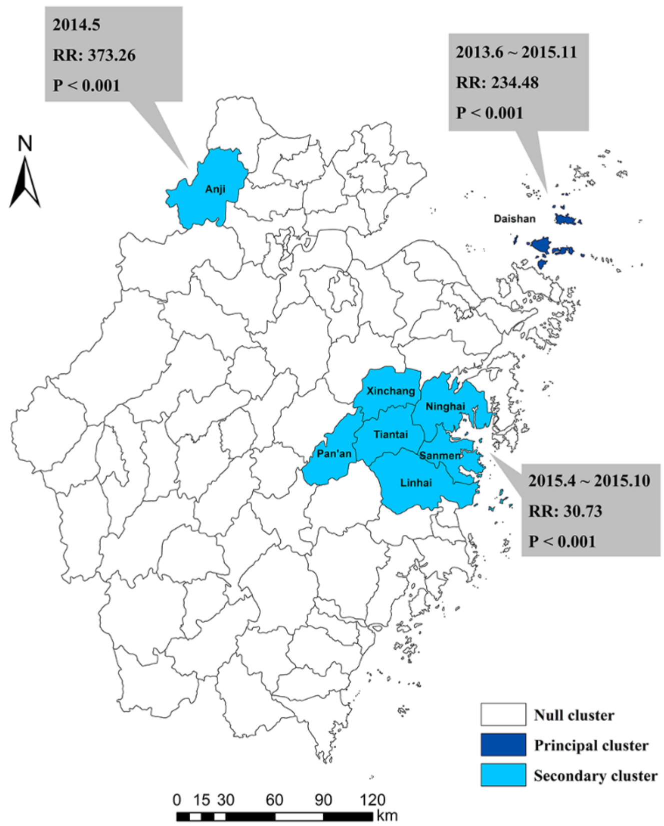


Table 2. Detailed information on spatio-temporal clusters of confirmed SFTS cases reported in Zhejiang Province, China, 2011 - 2015.

Clusters	Principal cluster	Secondary cluster 1	Secondary cluster 2
Time frame	2013.6 – 2015.11	2015.4 – 2015.10	2014.5
Counties included	Daishan	Linhai, Tiantai, Ninghai, Sanmen, Xinchang, Pan'an	Anji
Number of population[a]	206055	2966274	469036
Number of observed cases	60	32	12
Number of expected cases	0.37	1.24	0.028
Annual incidence (/100,000)	11.5	1.8	25.1
RR	234.48	30.37	373.26
LLR	256.03	75.88	48.98
P-value	< 0.001	< 0.001	< 0.001

SFTS: severe fever with thrombocytopenia; RR: relative risk; LLR: log likelihood ratio; [a] Background population within the cluster.

improving awareness of diagnose and increasing interest in case reporting cannot be excluded when we considered the causes of the disease trend in Zhejiang. Our findings have implications for prevention and management strategies of SFTS.

Space-time scan statistics analysis was applied to identify potential clusters of SFTS in both temporal and spatial dimension. Three clusters were detected, giving the statistical evidence that there were probable epidemics or outbreaks of SFTS in these areas. Daishan County was identified as the area of principal cluster, lasting for quite a long period (June 2013 to November 2015). It was the first region reporting the SFTS case in Zhejiang, with the occurrence of approximately half of total cases in the following years. Daishan consists of several island with considerable proportion of wooded and hilly lands [40] under the warm and humid climate, in accordance with the previous studies reporting the occurrence of SFTS cases in parallel environment [2,41,42]. Obviously, the presence of environmental or climatic linkages behind the epidemic is conceivable. Unfortunately, that could not be adequately evaluated in the present study due to the data limitation. On the other hand, Daishan consists of relatively isolated islands, where most of the residents mainly engage in fishing, and there are very few domesticated animals such as cattle and sheep. Considering the fact that the proportion of patients with definite bitten history by ticks is not very high, the evidence to confirm the main vector and host of the disease is insufficient. These suggest that Zhejiang Province, especially Daishan County, may have different characteristics from other provinces in terms of host and vector of the disease, an issue worth further study. Meanwhile, it is important to note that, as the most severely affected county in Zhejiang, Daishan has implemented SFTS interventions including promoting public awareness, laboratory capacity and clinicians' skills. These actions may result in more patients being diagnosed and reported. Furthermore, some SFTS cases may be missed diagnosis in other counties because less county-level Centre for Disease Control and Prevention (CDC) has the capacity to identify SFTSV infection except Daishan CDC during 2011-2013 [43].

One of the secondary clusters included 6 counties in east coast of Zhejiang, during the epidemic season of SFTS in the year of 2015. These counties shared similar environmental and climate conditions with Daishan, including warm and humid climate and hilly-forested landscape. These regions, together with Daishan, should be prioritized for interventions to control the disease. Furthermore, it is possible that there are some other areas with similar environmental and climatic conditions suitable for SFTSV transmission in Zhejiang, actually existing SFTS cases but reporting none due to lack of diagnostic awareness or laboratory capacity to identify SFTSV in local hospitals. Potential risk areas of SFTS in Zhejiang Province is necessary to be explored in future study. Meanwhile, more emphasis should be put on the further enhancement of a comprehensive surveillance system of SFTS in Zhejiang Province.

Another secondary cluster was in Anji County in May 2014. A total of 13 cases were identified during this outbreak. Index patient developed illness onset on April 23 and died on May 1, with the history of tea leaves collection 1 month before the illness onset. Secondary patients including 8 family members, 3 neighbors and 1 person who lived in the same village, developed illness onset subsequently. A retrospective cohort study of this outbreak demonstrated that 'direct contact with blood of the deceased' was an important risk factor [44]. In recent years, a quantity of clusters of SFTS cases have been reported in the provinces of Jiangsu, Shandong, Hubei, and Anhui, and virological investigations verified limited human-to-human transmission of SFTSV [8,9,45,46]. In addition, two family clusters were reported in Zhejiang before [43]. However, the index patient and secondary patients were considered to be infected from the same infectious source. The cluster of Anji County suggested that precaution should be taken for family members, neighbors and medical staff when looking after the patients with SFTSV infection.

There are several methodological issues and limitations. First, as an emerging infectious disease, the increasing number of reported cases in recent years may be partially associated with the improvement of knowledge and awareness to report. Second, no meteorological data was collected in this study. Therefore, no meteorological factors were studied for the seasonality of SFTS. Third, after the identification of SFTSV in 2009, the national guideline for prevention and control for SFTS was issued by the Chinese Ministry of Health in 2010 and SFTS patients should be reported by doctors to China Information System for Diseases Control and Prevention. According to the guideline, either of three techniques (molecular method, sero-conversion or cell culture) can be used for diagnosis. However, this detail was not collected in China Information System for Disease Control and Prevention, from which the study data was obtained.

Conclusion

In summary, this study showed that SFTS has increased and spatially expanded over the past years, with a remarkable seasonality. Three spatio-temporal clusters were identified using GIS methods. These findings provide reference of identifying prior areas for implementing public health intervention, and scientific basis for further improvement of SFTS surveillance and control strategies.

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Authors' Contributions

Study design: JJ, JL. Data collection: JS, YZ. Data analysis: FL, FH. Writing: FL, FH. Revising: JJ, JL, and FH. Interpretation of data: JL, JS.

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