ARTICLE IN PRESS

Ticks and Tick-borne Diseases xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Ticks and Tick-borne Diseases

journal homepage: www.elsevier.com/locate/ttbdis

Spatiotemporal patterns of severe fever with thrombocytopenia syndrome in China, 2011–2016

Jimin Sun[a,b], Liang Lu[a], Haixia Wu[a], Jun Yang[a], Keke Liu[a], Qiyong Liu[a,*]

[a] State Key Laboratory of Infectious Disease Prevention and Control, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China

[b] Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, China

ARTICLE INFO

Keywords:
Severe fever with thrombocytopenia syndrome
Spatiotemporal pattern
ARIMA
Prediction

ABSTRACT

Severe fever with thrombocytopenia syndrome (SFTS) is emerging and the number of SFTS cases have increased year by year in China. However, spatiotemporal patterns and trends of SFTS are less clear up to date. In order to explore spatiotemporal patterns and predict SFTS incidences, we analyzed temporal trends of SFTS using autoregressive integrated moving average (ARIMA) model, spatial patterns, and spatiotemporal clusters of SFTS cases at the county level based on SFTS data in China during 2011–2016. We determined the optimal time series model was ARIMA $(2, 0, 1) \times (0, 0, 1)_{12}$ which fitted the SFTS cases reasonably well during the training process and forecast process. In the spatial clustering analysis, the global autocorrelation suggested that SFTS cases were not of random distribution. Local spatial autocorrelation analysis of SFTS identified foci mainly concentrated in Hubei Province, Henan Province, Anhui Province, Shandong Province, Liaoning Province, and Zhejiang Province. A most likely cluster including 21 counties in Henan Province and Hubei Province was observed in the central region of China from April 2015 to August 2016. Our results will provide a sound evidence base for future prevention and control programs of SFTS such as allocation of the health resources, surveillance in high-risk regions, health education, improvement of diagnosis and so on.

1. Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease caused by severe fever with thrombocytopenia syndrome virus (SFTSV) which was firstly identified in 2009 (Yu et al., 2011). It is classified in the order Bunyavirales, family *Phenuiviridae*, genus *Phlebovirus* and consists of three segments of negative or ambisense polarity RNA, designated L, M and S segments (Xu et al., 2011). The clinical symptoms of SFTS including fever, fatigue, chill, headache, lymphadenopathy, anorexia, nausea, myalgia, diarrhea, vomiting, abdominal pain, gingival hemorrhage, conjunctival congestion are less specific (Ding et al., 2013). Some SFTS patients experienced a self-limiting clinical course, while some patients deceased due to multiple organ failure (Liu et al., 2014a; Liu et al., 2015). Of note, the case fatality rate of SFTS was about 30% when it was firstly identified (Yu et al., 2011).

Since the identification of SFTSV, SFTS or SFTS-like patients have been reported in China, South Korea, Japan, United Arab Emirates, and United States (Takahashi et al., 2014; McMullan et al., 2012; Shin et al., 2013; Denic et al., 2011). In China, 2750 SFTS-confirmed cases were reported from 16 provinces and the annual number of reported cases have increased year by year (Li et al., 2015). Epidemiological characteristics of SFTS including age distribution, gender distribution, occupation distribution, seasonal distribution, geographic distribution have been analyzed (Ding et al., 2013; Li et al., 2015; Sun et al., 2014). However, spatiotemporal patterns and trends of SFTS are less clear up to date. Spatiotemporal analysis methods have been widely used in some infectious diseases such as hand, foot, and mouth disease, dengue fever, malaria, Japanese encephalitis, scrub typhus, rabies, hepatitis E, tuberculosis, *Shigella*, etc. (Wang et al., 2016; Li et al., 2012; Clements et al., 2009; Wang et al., 2013; Wu et al., 2016; Yao et al., 2015; Liu et al., 2016; Gomez-Barroso et al., 2013; Tang et al., 2014). Here, we analyze temporal trends of SFTS using autoregressive integrated moving average (ARIMA) model, spatial patterns, and spatiotemporal clusters of SFTS cases at the county level which will provide evidence-based suggestions for the control and prevention of SFTS in future.

* Corresponding Author.
E-mail address: liuqiyong@icdc.cn (Q. Liu).

https://doi.org/10.1016/j.ttbdis.2018.03.026
Received 17 October 2017; Received in revised form 5 March 2018; Accepted 23 March 2018

Please cite this article as: Sun, J., Ticks and Tick-borne Diseases (2018), https://doi.org/10.1016/j.ttbdis.2018.03.026

2. Materials and methods

2.1. Data collection

The real-time notifiable communicable disease reporting system was put into use in China in 2004, realizing the timely online monitoring of individual cases. SFTS-confirmed cases should be reported to China information system for diseases control and prevention within 24 h after diagnosis according to the report guidelines of category B notifiable disease. All SFTS cases in this study were confirmed according to the national guideline for prevention and control for SFTS issued by the Chinese Ministry of Health in 2010 (www.moh.gov.cn/mohwsyjbgs/s8348/201010/49272.shtml). An acutely ill person 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 two weeks before illness onset) and laboratory data consisting of thrombocytopenia and leukocytopenia was defined as a probable case. A probable case with one or more of the following criteria: (1) detection of SFTSV RNA, (2) seroconversion or 4-fold increase in antibody titers between paired serum samples collected at least two weeks apart, and (3) isolation of SFTSV in cell culture was defined as a confirmed case. Surveillance data on SFTS-confirmed cases from January 2011 to December 2016 were obtained from the China information system for diseases control and prevention. Information of SFTS cases included gender, age, occupation, residential address, date of illness onset, date of confirmation. The demographic information for each county were collected from the China population and employment statistics yearbook 2013 of the National Bureau of Statistics of China. A county-level base map was acquired from data center for geographic sciences and natural sources research, Chinese Academy of Sciences (CAS) for the spatial analysis (http://www.resdc.cn/).

Ethical approval for the study was obtained from the Chinese Center for Disease Control and Prevention Ethics Committee (No. 201214). Human research was carried out in compliance with the Helsinki Declaration.

2.2. Time-series analysis

ARIMA model, a frequently used time series model, is known to have better veracity and practicability in forecasting disease incidence. An ARIMA (p, d, q) model is decided by components p, the order of autoregression; d, the degree of difference; and q, the order of moving average. As the monthly incidences on SFTS presented seasonal fluctuations, a 12-step finite difference method was initially applied to smooth the temporal sequence. These parameters (p, d, q) were decided by an autocorrelation function (ACF) and a partial autocorrelation function (PACF). The Lung-Box tests for white noise test was used to verify the goodness-of-fit of the models and Akaike information criterion (AIC) were performed to determine the ultimate model. R 3.2.3 and SPSS Statistics 20.0 (SPSS Inc, Chicago, USA) were used for the establishment of the optimal model of ARIMA. Monthly incidences of SFTS from January 2011 to December 2015 were used for the establishment of ARIMA model and monthly incidences from January 2016 to December 2016 were used to compare with the predicted values calculated through the optimal ARIMA model.

2.3. Spatial variation analysis

Spatial analysis was conducted to detect geographic variation in relation to SFTS incidence and to explore the potential clustering regions. Global spatial autocorrelation analysis and local spatial autocorrelation analysis were carried out to analyze the spatial patterns of SFTS incidence clusters on the county level during the study period through use of Geographic Information System (GIS, ArcGIS software, version 10.2 ESRI, Redlands, CA, USA). Global spatial autocorrelation used global Moran's I Index which ranged from −1 to 1. Moran's Index = 0 a random spatial distribution, Moran's Index < 0 dispersing in the spatial distribution, and Moran's I > 0 implied clustering in the spatial distribution. Local spatial autocorrelation was used to explore significant hot spots (High-High), cold spots (Low-Low), and spatial outliers (High-Low and Low-High) by calculating local Moran's I between a given location and the average of neighboring values in the surrounding locations.

Temporal clustering of SFTS incidence was identified using SaTScan software version 9.4.4 (www.satscan.org). Discrete Poisson model and Kulldorff's space-time scan statistics were conducted to identify temporal clusters and space-time clusters. The maximum spatial cluster size and maximum temporal cluster size were all set to 25%. Log-likelihood Ratio (LLR) was employed to identify the special clusters by comparing the observed incidence with expected value. Monte Carlo simulation, generating 999 random simulations, was used to obtain P-values. The null hypothesis of a spatiotemporally random distribution was rejected when the P value < 0.05.

3. Results

From 2011–2016, a total of 5360 laboratory-confirmed SFTS cases were reported and annual incidences were 0.034 per 100,000, 0.043 per 100,000, 0.050 per 100,000, 0.076 per 100,000, 0.095 per 100,000, 0.095 per 100,000, respectively. As shown in Fig. 1, monthly incidences of SFTS presented significant seasonal fluctuations. Most cases were reported in May, June, July and seasonal index of the three months were 0.8404, 0.7401, and 0.6363, respectively in the seasonal difference analysis (Fig. 2). According to the results of ACF, PACF, and AIC, ARIMA $(2, 0, 1) \times (0, 0, 1)_{12}$ was established as the final model. Based on the established ARIMA model, we predicted monthly incidences from January to December 2016 (Table 1). When compared with the observed data, the majority of predicted data agreed closely with the observed data (Fig. 2).

The numbers of affected counties increased year by year and the numbers from 2011 to 2016 were 98, 99, 113, 140, 153, and 167, respectively. The cumulative number of counties where SFTS cases were ever reported between 2011 and 2016 was 289 (Fig. 3). In the spatial clustering analysis, the global autocorrelation suggested that SFTS cases were not of random distribution (Table 2). Local spatial autocorrelation analysis of SFTS identified foci mainly concentrated in Hubei Province, Henan Province, Anhui Province, Shandong Province, Liaoning Province, and Zhejiang Province (Fig. 4). The shift of hot spots (High-High) can be observed from 2011 to 2016 (Fig. 4). Hot spots were observed in Liaoning Province from 2011 to 2013, while no hot spots were observed in the province from 2014 to 2016.

Spatiotemporal cluster analysis was applied to detect the incidences of SFTS from 2011 to 2016 in China. Incidences were aggregated through space and time. Three clusters were observed and the most likely cluster was observed in the central region of China. The cluster consisted of 21 counties in Henan Province and Hubei Province including Cengdu District, Tongbai County, Queshan County, Runan County, Pingyu County, Xincai County, Huaibin County, Huangchuan County, Shangcheng County, Macheng County, Hong'an County, Xiaochang County, Guangshui County, Shihe District, Pingqiao District, Zhengyang County, Xi County, Guangshan County, Xin County, Dawu County, and Luoshan County (Fig. 5). There were 13,936,345 individuals in the cluster with a radius of 109.94 km. Most importantly, the expected number of SFTS was 27.74, but the observed number was 1659. The relative risk (RR) and the Log Likelihood Ratio for the analysis were 86.15 and 5435.3616, P = 0.000000 < 0.05 (Table 3). Cluster 2 was located in Jiaodong peninsula, Shangdong Province and consisted of 18 counties. Cluster 3 was located in and the central of Shandong Province and included 28 counties. Time frames of the three clusters were 2015/4-2016/8, 2015/5-2016/10, 2015/5-2016/9, respectively (Table 3).