

Spatial-temporal analysis and visualization of scarlet fever in mainland China from 2004 to 2017

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Abstract

This study analysed retrospectively the spatio-temporal distribution and spatial clustering of scarlet fever in mainland China from 2004 to 2017. The incidence of scarlet fever has been increasing in recent years. Previous studies on the spatial distribution of scarlet fever in China have mainly focused at the provincial and municipal levels, and there are few systematic reports on the spatial and temporal distribution characteristics of scarlet fever at the national level. Based on information obtained from the China's Centre for Disease Control (China CDC) on the incidence of scarlet fever, we explored systematically the spatial-temporal distribution of this disease by three methods: spatial autocorrelation analysis, spatial-temporal scanning analysis and trend surface analysis. The results demonstrate that the incidence of scarlet fever varies by season, generating one peak from May to June and a second from November to December, with February and August

show a comparatively low number of cases. Trend surface analysis indicates that the incidence of scarlet fever in northern China is higher than in the South, slightly higher in the West compared to the East and lower in the central part. Additionally, the results show that there are regions with clusters of scarlet fever distributed in the Centre, Northeast, Northwest, and North as well as in some eastern provinces, such as Zhejiang, Shanghai, Shandong and Jiangsu.

Introduction

Scarlet fever, an acute respiratory infectious disease caused by the group A *Streptococcus* bacterium, is common in children, especially at ages between 5 and 15 (Liu *et al.*, 2014; Ning *et al.*, 2018). The clinical symptoms include sore throat, high fever or skin infection and the characteristic red rash. A small number of patients have also heart, kidney and joint damage due to an allergic reaction. Scarlet fever is mainly transmitted through respiratory droplets or direct contact with mucus, saliva or skin, and some outbreaks can also be transmitted by food (Yang *et al.*, 2007). So far, there is no effective vaccine (You *et al.*, 2011). After the 20th century, the mortality rate of scarlet fever has declined considerably thanks to improvement of health care level, but outbreaks at different scales continue to be reported. Examples include Australia, Hong Kong, Vietnam, U.K. and U.S.A. (Lau *et al.*, 2012; Wong *et al.*, 2012; Andrey *et al.*, 2016; Wong *et al.*, 2018). In China, the incidence per 100,000 people has risen from 1.46 in 2004 to 5.68 in 2018. Scarlet fever epidemic and outbreaks have occurred in many areas of China, even with several death cases in Beijing and Shanghai (Wu *et al.*, 2017; Kong *et al.*, 2017).

Geographic Information System (GIS), a comprehensive, computerized system capable of collecting, saving, managing, calculating, displaying and analysing spatial-temporal data effectively, is widely used to describe the epidemic characteristics of infectious diseases and analyse their spatial distributions (Tang, 2011; Tami *et al.*, 2016; Kirby *et al.*, 2017; Zhang *et al.*, 2019). GIS also provides opportunities for understanding diseases from different perspectives. While current Chinese papers about the spatial and temporal distribution of scarlet fever rarely apply a perspective of the disease dealing with the national level, they rather focus at the provincial and municipal levels. We therefore studied spatial-temporal distribution characteristics of scarlet fever in mainland China at the provincial and national levels. Based on GIS technology and spatial statistics, we explored areas and periods at high risk to provide a reference for targeted, comprehensive prevention and control of scarlet fever in China.

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Materials and Methods

Study area and data sources

This study concerns mainland China, which includes 31 administrative regions (23 provinces, 5 autonomous regions, 4 municipalities, and 2 special administrative regions) covering an area of approximately 9.6 million km², is located in eastern Asia on the western border of the Pacific Ocean (Figure 1). According to the 6th census data (National Bureau of Statistics of China - <http://www.stats.gov.cn/>), the total population of the mainland is 133.28 billion, including 23.93 billion children aged 0-15 (18%). The incidence data of scarlet fever in mainland China from 2004 to 2017 were obtained from China Public Health Science Data Centre and the China Centre for Disease Control (China CDC), (<http://www.chinacdc.cn/>).

Thematic map of incidence of scarlet fever

Firstly, we divided the incidence of scarlet fever into 6 levels and used colour shades to indicate changes in morbidity: the darker the colour, the higher the incidence. Afterwards, we used the ArcGIS, v. 10.2.2 software (ESRI, Redlands, CA, USA) to produce the thematic provincial maps of the incidence of scarlet fever from 2004 to 2017.

Spatial autocorrelation analysis

Spatial autocorrelation analysis (Moran, 1950; Tsai *et al.*, 2009; Jiang *et al.*, 2011) is a common method to analyse the similarity of spatial data and quantitatively analyse the characteristics of spatial distribution in spatial units. Moran's *I* cannot only be calculated to analyse the spatial correlation of the entire research area (global autocorrelation), but also the spatial clustering in some specific areas (local autocorrelation). This index ranges from -1 to +1 indicating a positive correlation when the value is >0 at a statisti-

cally significant level; negative correlations are treated in a similar manner when the index is <0. Local Moran's *I* coefficient represents four different spatial clustering modes: High-High (HH) (hotspots), Low-Low (LL) (coldspots), High-Low (HL) and Low-High (LH). Spatial autocorrelation analysis was performed using the univariate (local) Moran's *I* tool in the GeoDa software (<http://geodacenter.asu.edu>). The significance level was set at $p < 0.05$ and 95% confidence level with the number of simulations at 999.

Spatial-temporal cluster analysis

In this study, the monthly incidence was taken as the clustering unit and the province as the minimum spatial unit; The maximum scanning radius was set as 30% of the total population and the maximum scanning time was set as 30% of the total research time. The Log Likelihood Ratio (LLR) was calculated on the basis of the Poisson distribution model. The *p*-value of LLR was obtained by the Monte Carlo method with the simulation time 999. The analysis process was carried out using the software SatScan9.4 (<http://www.satscan.org>) and the scanning results were visualized by ArcGIS, v.10.2.2.

Trend Surface Analysis (TSA)

Trend surface analysis (Xue *et al.*, 2004), which is based on the theory of multiple regression analysis and least square method, fits mathematical surfaces according to sample data and uses trend-surface equation models of different orders to explore the spatial distribution of diseases and find the local variation. According to previous studies (Xue *et al.*, 2004), we selected a 2-order trend surface model to analyse the overall trend of the incidence of scarlet fever and establish a three-dimensional view by ArcGIS, v.10.2.2.

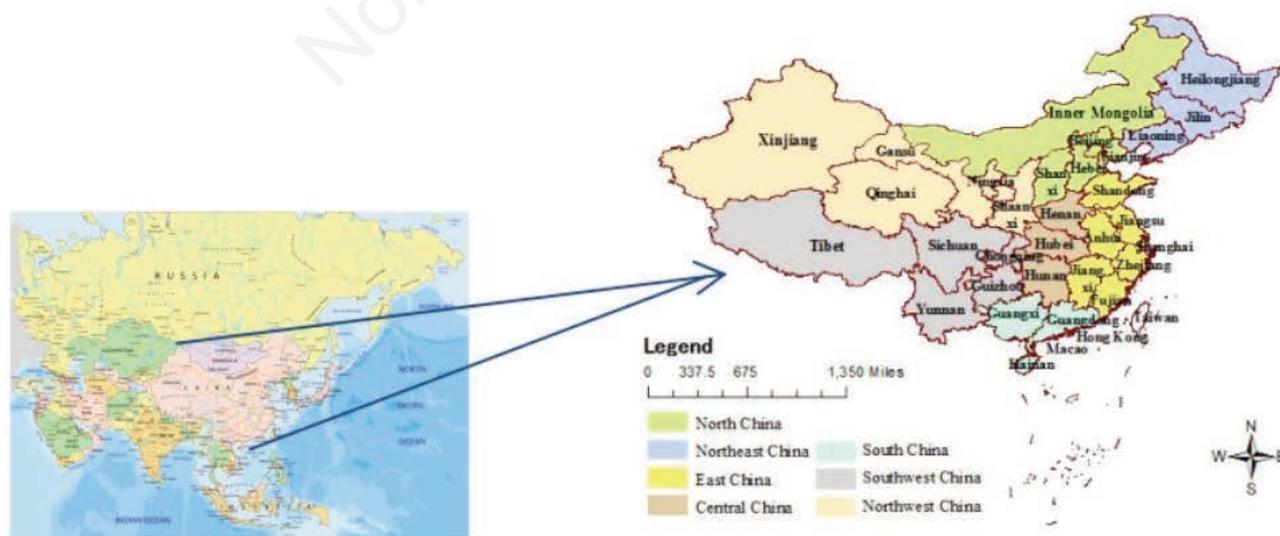


Figure 1. Geographic location of China and its provinces (municipalities, autonomous regions).

Results

The temporal distribution of scarlet fever

From 2004 to 2017, a total of 576,532 cases of scarlet fever were reported nationwide accumulatively, with an average annual incidence of 3.06 per 100,000 people. The incidence of scarlet fever in China increased per 100,000 people from 1.46 in 2004 to 5.39 in 2017, showing an overall upward trend ($\chi^2 = 8.785$, $p < 0.01$), (Figure 2). The monthly incidence of scarlet fever in China from 2004 to 2017 is shown in Figure 3. The incidence of scarlet fever has an obvious seasonal increase, with a double-peak distribution. The first peak occurring from May to June, and the second from November to December, while February and August have the lowest number of cases each year.

Thematic map of incidence of scarlet fever

The spatial distribution of scarlet fever in mainland China from 2004 to 2017 is shown in Figure 4. We can see that the disease struck

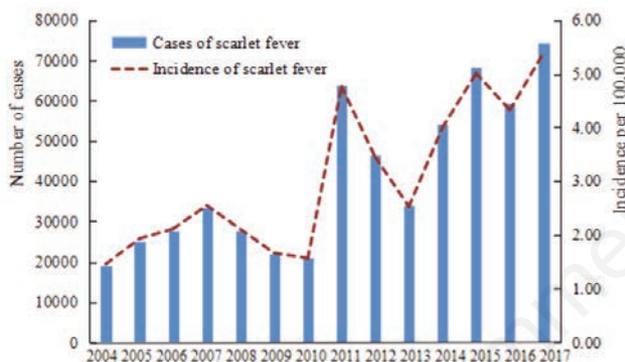


Figure 2. Annual trend of scarlet fever in China 2004-2017.

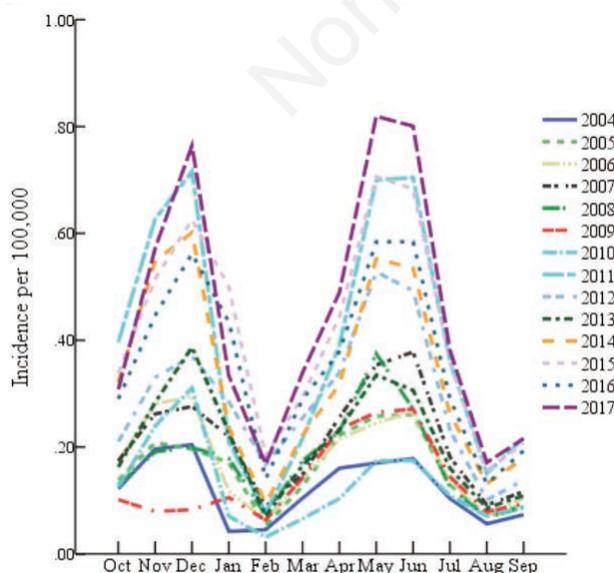


Figure 3. Monthly incidence of scarlet fever in China 2004-2017.

in all parts of the country, with a higher number of cases in the north-eastern, northern and north-western part of the country, especially in Liaoning, Jilin, Heilongjiang, Beijing, Tianjin, Xinjiang and Inner Mongolia, while Hunan, Hubei, Jiangxi, Anhui, Guangxi, Guangdong, Hainan, Fujian and other southern regions (Shanghai excepted) had a low incidence. Overall, however, the incidence of scarlet fever had a tendency to spread in the southern direction.

Spatial autocorrelation analysis

The results of global spatial autocorrelation analysis showed that the annual Moran's I of scarlet fever in mainland China ranged from 0.2892 to 0.4975 between 2004 and 2017, with a statistical significance of $p < 0.05$ (Table 1). The results indicate that there was an evident spatial positive correlation binding the cases of scarlet fever together, each year showing up as high levels of spatial clustering and dependence. However, the annual change of the Moran index was not statistically significant ($\chi^2 = 0.173$, $p > 0.05$), which means that the spatial autocorrelation of scarlet fever did not increase. The local spatial autocorrelation analysis showed that the incidence of scarlet fever in mainland China had an obvious clustering. The HH and LL cluster regions showed little difference between the different years. The HH cluster regions, indicating hotspots, were mainly concentrated in Inner Mongolia and areas in the Northeast, while the LL cluster regions, indicating coldspots, were mainly concentrated in more southern and south-eastern provinces. As seen in Table 2 and Figure 5, Shandong was a HL cluster region in 2016.

Spatial-temporal clustering scanning analysis

The purely spatial scanning results showed that large cluster region existed every year from 2004 to 2017, while there were 6-10 provinces with clusters, all of which had a high risk of incidence, Relative Risk (RR) ranged from 2.51 to 6.74. From 2004 to 2015, the spatial clustering of scarlet fever was centred in Heilongjiang (47.8613N, 127.7630E) and mainly distributed in 6 provinces situated in the north-eastern and northern parts of China.

Table 1. Global spatial autocorrelation analysis of scarlet fever incidence in China, 2004-2017.

Year	Moran's I	Means	SD	Z-value	p-value
2004	0.3673	-0.036	0.1081	3.732	0.001
2005	0.2892	-0.0319	0.1063	3.0203	0.006
2006	0.3753	-0.0381	0.1076	3.8408	0.003
2007	0.4673	-0.0392	0.1076	4.706	0.001
2008	0.4919	-0.037	0.1116	4.7396	0.001
2009	0.4555	-0.0337	0.1173	4.1709	0.002
2010	0.4975	-0.038	0.1098	4.8759	0.001
2011	0.4063	-0.0365	0.1082	4.0917	0.001
2012	0.4411	-0.0352	0.1168	4.0766	0.001
2013	0.309	-0.036	0.1065	3.2391	0.005
2014	0.4542	-0.0358	0.1164	4.2111	0.002
2015	0.3471	-0.037	0.1152	3.3342	0.004
2016	0.4009	-0.0371	0.118	3.7102	0.002
2017	0.313	-0.0366	0.1159	3.0156	0.004

Moran's I : coefficient that allows the analysis of spatial autocorrelation. SD: Standard Deviation. Z: Statistics for Hypothesis Testing on the Overall Moran's I .

After 2015, a large cluster was centred in Inner Mongolia (44.0861N, 113.9101E) and distributed in the Northeast, North and Northwest, with the number of provinces with clusters had increased to 10. Jilin, Liaoning, Inner Mongolia, Beijing and Tianjin were the largest cluster regions of scarlet fever every year (Figure 5). The spatial-temporal scan for the period 2004-2017 showed 6 high-risk, spatial-temporal cluster regions which con-

tained one most likely cluster areas (that consisted of 9 cluster provinces), 5 secondary cluster areas (that consisted of 11 cluster provinces) and 1 low-risk region. The low-risk spatial-temporal clusters were mainly in Hunan, Hubei, Jiangxi, Chongqing, Guizhou, Guangdong, Guangxi, Fujian, Anhui, Henan and Zhejiang provinces from January 2004 to December 2010 (Table 3, Figure 6).

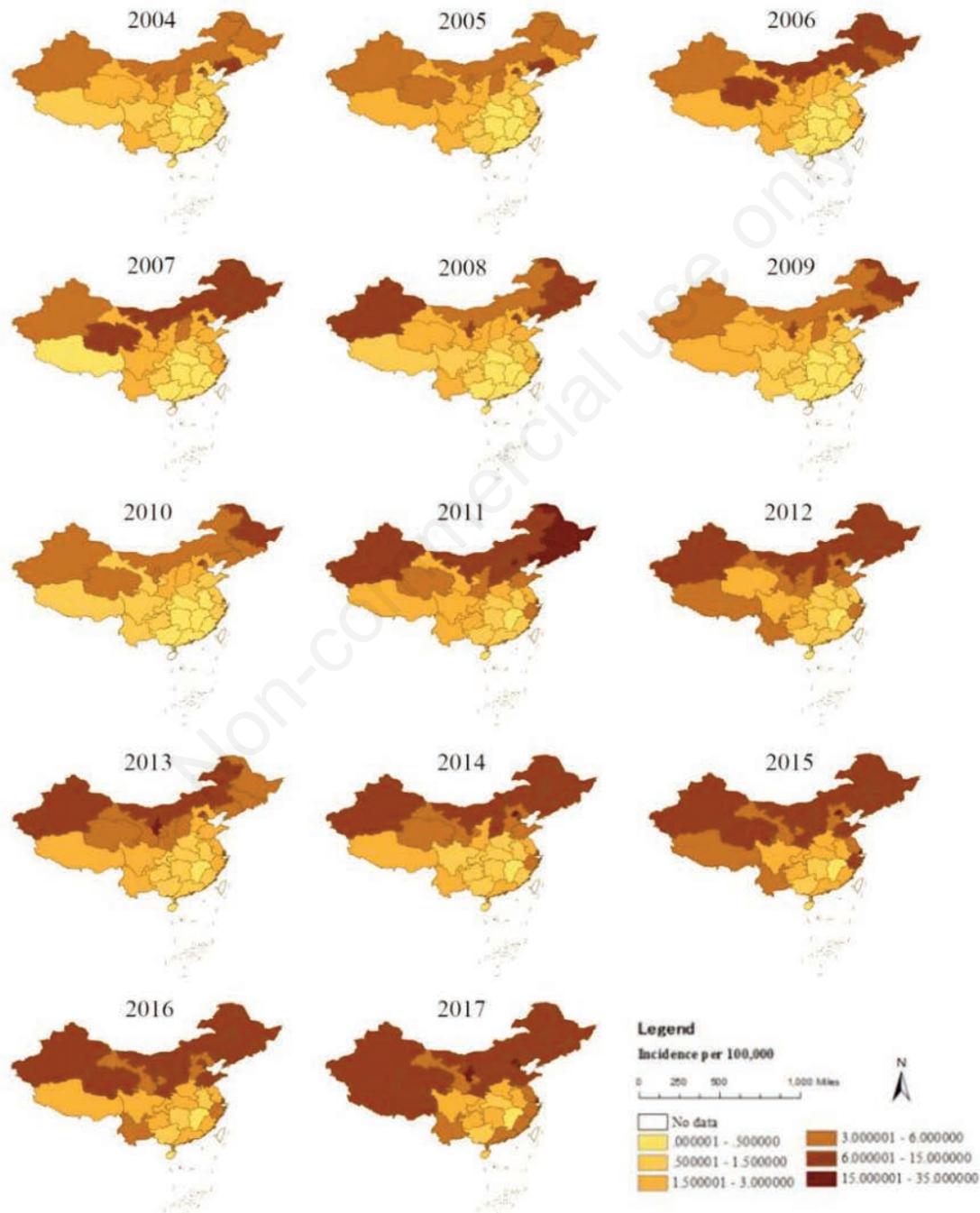


Figure 4. National thematic maps of scarlet fever incidence from 2004 to 2017.

Trend surface analysis

The incidence of scarlet fever was taken as the dependent variable and the geographic position of each province as the independent variable to establish a 2-order trend surface model. From 2004 to 2017, the incidence of scarlet fever showed an obvious 'U' distribution, which means low in the middle and two high sides from

an east-west direction; on the other hand, the north-south distribution showed that the incidence in the northern region was significantly higher than in the southern region (Figure 7). The trend surface analysis showed that the incidence of scarlet fever was high in the northern part of China, slightly higher in the western than in the eastern part, and lower in the central part. This phenomenon indicates an evidence of high and low scarlet fever cluster areas.

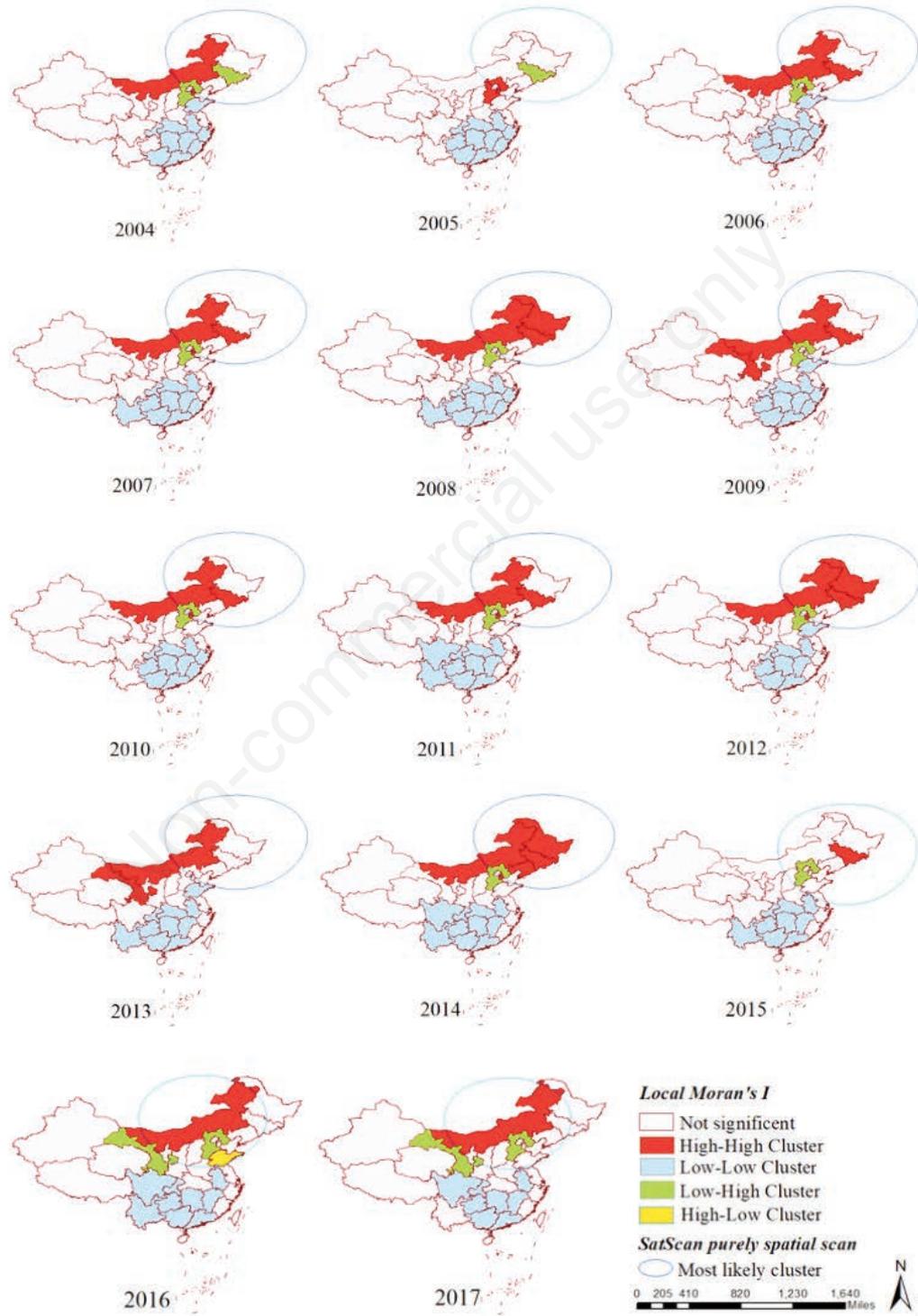


Figure 5. Visualization of Scarlet fever Spatial Clustering in China 2004-2017.

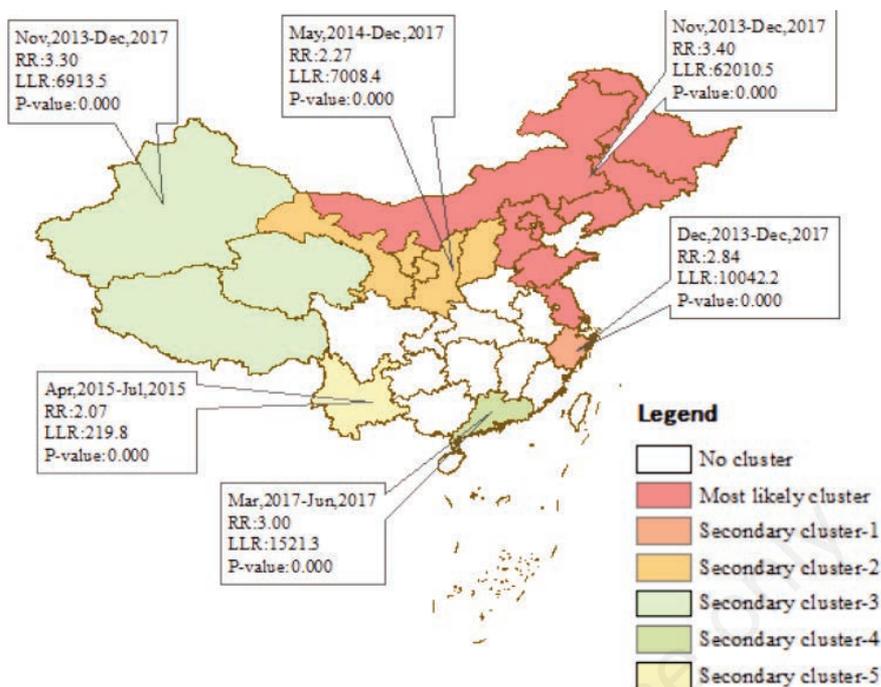


Figure 6. Distribution of spatiotemporal cluster regions of scarlet fever in China 2004-2017.

Table 2. Local spatial autocorrelation analysis of scarlet fever incidence in China, 2004-2017(LISA)

Years	High-high cluster	Low-low cluster	High-low cluster	Low-high cluster
2004	Inner Mongolia, Tianjin	Anhui, Hubei, Chongqing, Hunan, Guangxi, Guangdong, Jiangxi, Fujian, Shandong, Zhejiang	—	Jilin, Hebei Jilin
2005	Hebei, Tianjin	Anhui, Hubei, Chongqing, Guizhou, Guangxi, Guangdong, Fujian, Jiangxi, Hunan, Zhejiang	—	Jilin
2006	Inner Mongolia, Tianjin, Jilin	Anhui, Hubei, Chongqing, Guizhou, Guangxi, Guangdong, Fujian, Jiangxi, Hunan, Shandong, Zhejiang	—	Hebei
2007	Inner Mongolia, Tianjin, Jilin	Anhui, Hubei, Chongqing, Guizhou, Guangxi, Guangdong, Fujian, Jiangxi, Hunan, Yunnan	—	Hebei
2008	Inner Mongolia, Heilongjiang, Jilin	Anhui, Hubei, Chongqing, Guizhou, Guangxi, Guangdong, Fujian, Jiangxi, Hunan, Yunnan, Zhejiang	—	Hebei
2009	Inner Mongolia, Gansu, Jilin	Anhui, Hubei, Chongqing, Guizhou, Guangxi, Guangdong, Fujian, Jiangxi, Hunan, Shandong, Zhejiang	—	Hebei
2010	Inner Mongolia, Tianjin, Jilin	Anhui, Hubei, Chongqing, Guizhou, Guangxi, Guangdong, Fujian, Jiangxi, Hunan, Zhejiang	—	Hebei
2011	Inner Mongolia, Tianjin, Jilin	Anhui, Hubei, Chongqing, Guizhou, Guangxi, Guangdong, Jiangxi, Hunan, Sichuan, Yunnan	—	Hebei
2012	Inner Mongolia, Tianjin, Jilin, Heilongjiang	Anhui, Hubei, Chongqing, Guizhou, Guangxi, Guangdong, Jiangxi, Hunan, Shandong	—	Hebei
2013	Inner Mongolia, Gansu	Anhui, Hubei, Chongqing, Guizhou, Guangxi, Guangdong, Jiangxi, Hunan, Shandong, Yunnan	—	—
2014	Inner Mongolia, Heilongjiang, Jilin, Liaoning, Tianjin	Anhui, Hubei, Chongqing, Guizhou, Guangxi, Guangdong, Jiangxi, Hunan, Sichuan, Yunnan	—	Hebei
2015	Jilin	Anhui, Hubei, Chongqing, Guizhou, Guangxi, Guangdong, Jiangxi, Hunan, Yunnan	—	Hebei
2016	Inner Mongolia	Anhui, Hubei, Chongqing, Guizhou, Guangxi, Guangdong, Jiangxi, Hunan, Yunnan	Shandong	Gansu, Hebei
2017	Inner Mongolia	Anhui, Hubei, Chongqing, Guizhou, Guangxi, Guangdong, Jiangxi, Hunan	—	Gansu, Hebei

Table 3. Spatial-temporal scanning analysis of scarlet fever incidence in China, 2004-2017

Cluster areas	Cluster provinces	Cluster period	Cluster centre	Scanning radius	RR	LLR	p-value
Most likely cluster	Heilongjiang, Jilin, Liaoning, Inner Mongolia, Beijing, Tianjin, Hebei, Shandong, Jiangsu	2013/11-2017/12	43.6654N,126.1929E	1324.46km	3.40	62010.5	0.000
Secondary cluster-1	Zhejiang, Shanghai	2013/12-2017/12	29.1685N,120.0429E	249.83km	2.84	10042.2	0.000
Secondary cluster-2	Ningxia, Shaanxi, Gansu, Shanxi	2014/5-2017/12	37.2717N,106.1648E	541.71km	2.270	7008.4	0.000
Secondary cluster-3	Xizang, Qinghai, Xinjiang	2013/11-2017/12	31.4927N,88.4401E	1108.33km	3.30	6913.5	0.000
Secondary cluster-4	Guangdong	2017/3-2017/6	23.3518N,113.4229E	0.00km	3.00	1521.3	0.000
Secondary cluster-5	Yunnan	2015/4-2015/7	24.9758N,101.4877E	0.00km	2.07	219.8	0.000

RR: Relative Risk; LLR: Log Likelihood Ratio. p-value: Probability.

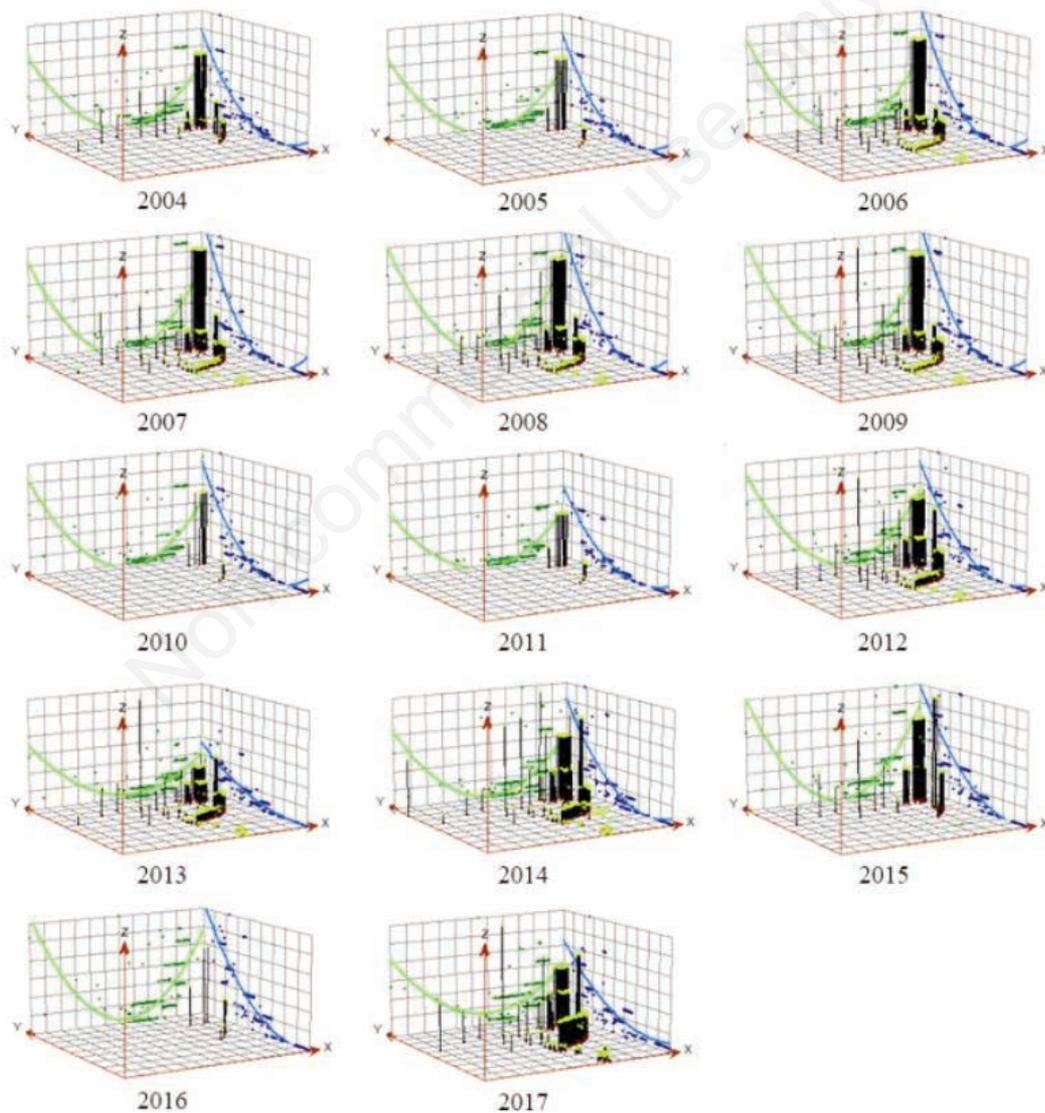


Figure 7. Trend surface analysis of scarlet fever in China from 2004 to 2017. The Z-axis represents incidence, the X-axis and Y-axis represent longitude and latitude respectively, the blue curve represents the change of the trend value in the north-south direction, and the green curve represents the change of the trend value in the east-west direction.



Discussion

Analysis of spatial-temporal distribution characteristics of scarlet fever in China showed that its incidence has been on the rise since 2004 in mainland China, which was consistent with the trend of other parts in the country (Pan *et al.*, 2016; Wu *et al.*, 2017; You *et al.*, 2018). Wong *et al.* (2018) also pointed out in the article that scarlet fever has reappeared in some countries in the past decade, and its incidence is on the rise. Our finding of a nationwide outbreak in 2011 has been corroborated in Hong Kong by Lau *et al.* (2012), in Jiangsu by Zhang (2018), in Changchun by Liu (2018) and in Beijing (Wang *et al.*, 2019). The increasing incidence in recent years may be attributed to the accumulation of susceptible people (Wong *et al.*, 2012). From 1995 to 2010, the incidence of scarlet fever was only sporadic without an outbreak or epidemic. Since then, the population has grown considerably, which may have added a large number of susceptible people. With the improvement of health conditions and prevention and control system of infectious disease, the increased rates of visits and diagnostic interventions might also have affected the report rate of scarlet fever to some extent (Andrey *et al.*, 2016; Wu *et al.*, 2017). Furthermore, Zeng *et al.* (1997) found that there was a typical ‘Z-D phenomenon’ in the epidemic of scarlet fever, that is, the skewness of the peak of the seasonal incidence curve was correlated to the rise and fall of the incidence in the following year, *i.e.* many factors that affected the first peak would continue to the next epidemic due to inertia.

The seasonal analysis showed that the incidence of scarlet fever in China has obvious seasonal variation, with a double-peak distribution, reaching the first peak in May-June and the second peak in November-December, which is similar to the results of other provincial and municipal studies in China (Li *et al.*, 2012; Wang *et al.*, 2016; Ning *et al.*, 2018). Remarkably, the two peaks occurred in the first semester or the second semester of each school year of the childcare institutions and the schools. Combined with previous studies, children aged 5-15 years (appropriate ages for kindergarten or primary or middle school in China) are the main susceptible populations of scarlet fever, thus it can be inferred that this is one of the reasons for the peak. In addition, we found that the incidence of scarlet fever was lowest in February and August each year, in which childcare facilities and schools are closed. Thus, the exposure of susceptible people decreases, reducing the incidence of the disease. We recommend that surveillance of scarlet fever in school-age children be strengthened during the two peak periods.

The analysis of this study shows that there is obvious spatial clustering of scarlet fever. The high incidence areas are mainly in north-eastern China (Heilongjiang, Jilin, Liaoning), the North (Beijing, Tianjin, Hebei, Inner Mongolia, Shanxi), north-western China (Ningxia, Shaanxi, Gansu, Qinghai, Xinjiang) and some eastern coastal areas (Zhejiang, Shanghai, Shandong, Jiangsu). Meteorological conditions are possible reasons for different spatial clustering of scarlet fever among areas. Scarlet fever is an acute respiratory infectious disease, and meteorological factors play an important role in the process of transmission (Li *et al.*, 2012). When the average temperature is low, group A *Streptococcus* bacterium can multiply in large numbers and spread effectively, while pathogens cannot easily spread the temperature is above 30 (Duan *et al.*, 2016). When the temperature variation is large, children have a weak respiratory defence function due to their incomplete immune system, which results in pathophysiological reac-

tions such as inflammation of the respiratory tract, which alleviates entrance of bacterial pathogens. At the same time, large temperature variations facilitate adsorption of pathogens to objects such as dust suspended in the air contributing to the risk for infection of susceptible people (Cheng *et al.*, 2014). Dry environments, on the other hand, increases the risk of the whirling up of settled pathogens thereby providing longer exposure times, which translates into a higher risk of infection (Lowen *et al.*, 2007; Duan *et al.*, 2016). In China, the North is characterized by lower temperature, lower relative humidity, drier air and larger temperature variation compared to the South, all of which will promote the high incidence of scarlet fever in northern regions to a certain extent. In addition, the eastern coastal areas of China have a more developed economy, higher population density mobility, more childcare institutions and schools, and more concentrated and frequent contact among the population. All these factors provide opportunities for susceptible populations to contact pathogens closely and accelerate the speed of transmission of the pathogen.

Currently, tertiary prevention is the main measure to prevent and control scarlet fever in China due to no effective vaccine against scarlet fever. Scarlet fever has been on the rise across the country in recent years, it is necessary for local health and medical institutions to strengthen the surveillance and management of the source of infection, carry out health education, and popularize the prevention and treatment of scarlet fever for the sake of treatment of this disease. In particular, the principle of ‘early detection, report, diagnosis, isolation, and treatment’ should be strictly followed in the beginning of the two peak periods. Measures like indoor ventilation, keeping the indoor air clean, can help to protect the vulnerable population in the high-incidence cluster regions.

The limitation of this study is that we lack access to information, such as drug resistance, health status, socioeconomic factors, etc. In further research, we will combine these factors to comprehensively explore the key factors of scarlet fever.

Conclusions

In summary, our research systematically explored the temporal and spatial variation of scarlet fever in mainland China from 2004 to 2017. The incidence of scarlet fever is generally on the rise and has significant seasonality and spatial regionality. The high-risk area is mainly distributed in parts of northeast China, north China, northwest and east coast, which will help to control the epidemic of scarlet fever more effectively. The health department should strengthen the monitoring and prevention of scarlet fever in the country, especially in high-risk areas and peak periods of scarlet fever.

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