Spatial-temporal mapping of hand, foot and mouth disease in relation to climate factors in Xinjiang, China from 2008 to 2016

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Research article

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Abstract

[Objectives]: The study mainly aims to depict the epidemiological characteristics of hand, foot and mouth disease (HFMD) in Xinjiang, China and evaluate the effects of meteorological factors (temperature & precipitation) on its dynamics through spatiotemporal analysis. This study provides substantial evidences for disease HFMD control and prevention. [Methods]: With the data from the national surveillance data of HFMD and meteorological parameters in the study area from 2008 to 2016, the correlation between meteorological factors and HFMD incidence was explored through kernel density analysis. Furthermore, the spatial autocorrelation of HFMD in each year was analyzed by the Spatial Autocorrelation (Global Moran's I) tool. [Results]: The relationship between monthly mean temperature (T) and HFMD cases fit best in the following logarithmic equation: $y=4.8176\ln(T)-19.773$, ($R^2 = 0.5194$). The relationship between monthly mean precipitation (P) and HFMD fit best in the following quadratic equation, $y=-1E-06 \times P^2 + 0.0108 \times P + 5.9867$, ($R^2 = 0.5319$). HFMD was mainly distributed in northern Xinjiang. Global spatial autocorrelation analysis indicated the spatial dependency on the incidence of HFMD in 2008, 2010, 2012, 2014 and 2015. The spatial dependency is the negative spatial autocorrelation in 2009. The incidence of HFMD in Xinjiang presented a random distribution pattern in 2011 and 2016. [Conclusion]: Our findings show that meteorological (air temperature & precipitation) variables had important effects on HFMD occurrence and transmission. This study provides a basis for the early warning of HFMD.

Introduction

Hand, foot and mouth disease (HFMD) is an infectious disease related to various [enteroviruses](#) that mostly affect children below 5 years old(Chen et al. 2019). Its pathogens are typically coxsackieviruses (coxsackievirus A16 (CVA16)) and enteroviruses (enterovirus 71 (EV71))(Chen et al. 2019; Ma et al. 2010; Nguyen et al. 2017; Yien Ling Hii et al. 2011). Its clinical manifestations mainly include mouth ulcers, fever, and vesicles on the hands, feet, and mouth(Onozuka and Hashizume 2011). Most HFMD patients can recover fully since HFMD is a self-limited disease, but some patients may develop severe life-threatening complications and even death(Ma et al. 2010). HFMD is transmitted through direct contact with feces, respiratory droplets, and blister fluid of infective patients or through contact with the contaminated environment(Yien Ling Hii et al. 2011).

Recent epidemics of HFMD have tended to be located in the Asian Pacific regions. In 2008, wide HFMD epidemics occurred in Vietnam, Thailand, Singapore, Malaysia, and China(Wang et al. 2011). Large outbreaks of HFMD were reported in China 2008 and 2009 and the cumulative number of cases in China in 2008 and 2009 respectively reached 489,540 and 1,155,575, indicating unprecedented large-scale outbreaks. In May 2008, HFMD was added to Category C of notifiable diseases for disease surveillance in China(Qunying Mao et al. 2014). Thus, HFMD is increasingly widely concerned.

At present, the correlation between HFMD incidence and meteorological factors, especially temperature and humidity, has been extensively explored, but these previous results were not consistent with each other(Chen et al. 2014; Chen et al. 2019). For instance, a regression model was established to predict

HFMD consultation rates in Hong Kong and its prediction result showed that HFMD was mostly affected by relative humidity and least affected by wind speed(Ma et al. 2010). In Singapore, the relative risks of weekly HFMD cases under the variations of temperature and rainfall were estimated with time-series Poisson regression models(Yien Ling Hii et al. 2011). According to risk estimations, an increase of 1°C in maximum temperature above 32°C elevated the risk of HFMD incidence by 36% and an increase of 1 mm in weekly cumulative rainfall below 75 mm increased the risk of HFMD by 0.3%. Time-series analyses were performed to assess the relationship between pediatric HFMD cases and weather variability in Japan(Onozuka and Hashizume 2011) and Vietnam(Nguyen et al. 2017; Phung et al. 2018). According to the assessment results, the numbers of weekly HFMD cases in Japan and Vietnam were respectively increased by 11.2% and 5.6% with an increase of 1°C in average temperature and the numbers were respectively increased by 4.7% and 1.7% with an increase of 1% in relative humidity. With a generalized additive model, the effects of meteorological factors on HFMD occurrence in Guangzhou and South Korea were estimated and the estimation results indicated that the incidence of HFMD lagged behind the changes in temperature and precipitation(Chen et al. 2014; Munderloh et al. 2016). The relationships between HFMD and meteorological variables were explored with a negative binomial multivariable regression model (Li et al. 2014; Wang et al. 2016)and the variations in the number of HFMD cases with each unit increase in temperature, humidity, wind speed and air pressure were accurately calculated. The correlation between HFMD incidence and meteorological factors in Shandong was explored with spatial panel data models, indicating the high spatial auto-correlation on HFMD(Wang et al. 2015). The relationship between the meteorological variables and HFMD was identified and quantified with correlation analyses and Seasonal Auto-regressive Integrated Moving Average (SARIMA) models. The result indicated temperature rise led to the increase in the number of HFMD cases(Wei et al. 2015). A mixed generalized additive model(Xu et al. 2016), the distributed lag non-linear model(Zhang et al. 2016), was employed to estimate the effects of meteorological factors on pediatric HFMD and the estimation results indicated that relative humidity and daily average temperature had non-linear delayed effects(Xiao et al. 2017) on pediatric HFMD, but the effects were different between different regions. The correlation between climate variables and the annual HFMD incidence rate in Sichuan were analyzed with the hierarchical Bayesian spatial temporal interactive models and the analysis result indicated that the HFMD incidence showed a heterogeneous spatial-temporal distribution(Liao et al. 2016). HFMD case spatiotemporal patterns were identified with the empirical orthogonal function and GeoDetector was used to quantify the determinant powers of driving factors of HFMD(Xu et al. 2019). To our knowledge, previous studies adopted different methods from different perspectives to explore the relationship between HFMD incidence and meteorological factors. Most studies indicated that the relationship between meteorological factors and HFMD incidence were the non-linear relationship and the incidence of HFMD lagged behind the changes in meteorological factors. Furthermore, the change in HFMD incidence corresponding to per unit increase (or decrease) in typical meteorological factors was accurately calculated. However, the spatial-temporal distribution of HFMD and the long-term effects of corresponding meteorological factors in typical arid regions in Northwest China were seldom reported. The spatial dimension combined with temporal dimension could be used to comprehensively analyze the spatiotemporal heterogeneity of HFMD

in the whole region with long time series from 2008 to 2016 in Xinjiang. The spatial and temporal distribution patterns of HFMD incidence in different geographic areas were explored.

Inspired by the seasonal patterns of HFMD outbreaks, we hypothesized that the weather changes might influence the transmission of HFMD in Xinjiang. This study aims to establish a relationship between temperature, precipitation and the incidence of HFMD outbreaks in Xinjiang. Firstly, the epidemiological characteristics of HFMD from 2008 to 2016 in Xinjiang, China were obtained. Secondly, the raster data of monthly [average](#) temperature and precipitation were matched with the raster data of HFMD case. Thirdly, the correlations between meteorological factors variables and HFMD incidence were explored. Fourthly, the spatial aggregation of HFMD in Xinjiang from 2008 to 2016 was investigated. The study provides countermeasures and suggestions for further public health interventions.

Method And Materials

2.1 Study area

[Xinjiang Uygur Autonomous Region](#) is the largest provincial administrative region in China. Its area is $166 \times 10^4 \text{ km}^2$ and its population is 2486.76 million in 2018. Xinjiang locates in the geographical center of Eurasia ($34.3^\circ\text{--}49.5^\circ\text{N}$, $73.5^\circ\text{--}96.3^\circ\text{E}$) and neighbors Russia, Kazakhstan, [Kyrgyzstan](#), Tajikistan, Pakistan, Mongolia, India, Afghanistan from north to south. The mountains border Xinjiang on three sides and the Tianshan Mountains cuts across northern Xinjiang. As a typical arid and semi-arid area, Xinjiang has a temperate continental climate. The annual mean temperature ranges from 9°C to 12°C and the annual precipitations in northern and southern Xinjiang are respectively 210 mm and less than 100 mm, displaying an uneven spatial distribution pattern. The Tianshan Mountains has a higher precipitation, whereas southern Xinjiang suffers the severe water stress. The dominant wind throughout a year is northwest wind (Wei et al. 2019). Fig. 1 shows the geographical location of Xinjiang.

2.2 Data sources

The data of daily HFMD cases in Xinjiang from January 1, 2008 to December 31, 2016 were from China Information System for Disease Control and Prevention. The collected patient's data include gender, age, living address, types of patients, the onset date of symptom and confirmation time of symptom. The raster data of monthly average temperature and precipitation from 2008 to 2016 were retrieved from the Science Database of Resource Discipline Innovation Platform (<http://www.data.ac.cn>). The meteorological data grid size is $0.49^\circ \times 0.49^\circ$. According to the encoded national standard addresses, the first six bits of encoded addresses were used to extract the longitude and latitude information of patients and visualize the spatial information of patients.

2.3 Methods

The demographic characteristics of HFMD cases were firstly obtained through the descriptive analysis performed with monthly data. Then the seasonal and cyclical patterns of HFMD were displayed in the

graphs of the monthly data of HFMD cases.

Through Spearman correlation analysis, the correlation between the monthly incidence of HFMD and the monthly mean values of meteorological factors were analyzed. A comprehensive model of meteorological factors(Guo et al. 2016) and HFMD was established by ordinary least squares (OLS) regressions in SPSSTM v17.0.

Kernel density (KD) analysis(Rybnikova et al. 2018) was carried out with the kernel density tool in ArcGISTM v10.2 (ArcGIS, 2017 a) to portray the temporal evolution and spatial distribution of the HFMD. The KD analysis of point elements was based on Silverman quadratic kernel function to calculate the density of point elements around each output raster pixel(Yang Li 2019). The parameter 'Population' was set to NONE. The search radius of kernel density analysis in this study was set as $0.49^{\circ} \times 0.49^{\circ}$.

In order to reveal the spatial dependence of variables, HFMD incidences were firstly annualized according to 14 states or territories and then the global spatial autocorrelation test (Moran's I) was performed for every year. The global spatial autocorrelation analysis was performed with the help of GeoDa v1.2.0 software in this study.

Global spatial autocorrelation is a well-known measure to evaluate spatial patterns(Wang et al. 2015) based on Eq. (1). If the calculation results showed statistically significant differences, spatial-autocorrelation exists in explored regions. (see Formula 1 in the Supplementary Materials)

The range of Moran's I value is $[-1, 1]$ and the Moran scatter diagram represents the spatial agglomeration between a unit and its surrounding units. When $I > 0$, there is a positive spatial autocorrelation between space units within the range. In other words, the difference in attribute values between adjacent space units is small. The distribution patterns of "low-low" clustering and "high-high" clustering of attribute values are presented. Moreover, the closer the I value is to 1, the closer the relation between spatial units is or the smaller the difference between attribute values is. When $I < 0$, there is negative spatial autocorrelation between spatial units within the range. In other words, there is a significant difference in the attribute values of adjacent spatial units and the closer the I value is to -1, the less concentrated the distribution between spatial units is or the more significant the difference in attribute values is. When $I = 0$, there is no spatial autocorrelation between spatial units within the range and spatial variables present a random distribution pattern

Results

3.1 Descriptive analysis

In total, 64,330 HFMD cases were reported from 2008 to 2016, with a daily mean of 19.8. Fig. 2 shows the monthly distributions of mean temperature, precipitation and HFMD cases in Xinjiang from 2008 and 2016. The monthly HFMD distribution showed a distinct seasonal pattern over the period and HFMD cases typically occurred between May and July, peaking in June (Fig. 2a). The conclusion is consistent

with previous studies(Munderloh et al. 2016). The mean temperature (Fig. 2b) and precipitation (Fig. 2c) were coupled with the incidence peak of HFMD and similar findings had been reported in Hefei, China(Wei et al. 2019; Zhang et al. 2019) and in Japan(Onozuka and Hashizume 2011). The annual morbidity among males was about 1.5 times of that among females. Children under 5 years old were at the highest risk of HFMD. Most cases (86.2%) were dispersed children who did not go to kindergarten or school.

3.2 Spearman correlation analysis

The meteorological factors (mean monthly temperature (Fig. 3(a) and mean monthly precipitation (Fig. 3(b)) and HFMD cases in Xinjiang were respectively plotted as scatter plots (Fig. 3). We found a monotonic relationship between the two variables and the HFMD incidence. Therefore, Spearman rank correlation coefficient was calculated (Table 1).

Table 1 Spearman’s rank correlation analysis between HFMD incidence and meteorological factors (n=108).

	HFMD cases	precipitation	temperature
Spearman’s rho of HFMD	1.000	0.686**	0.772**
Spearman’s rho of mean precipitation	0.686**	1.000	0.665**
Spearman’s rho of mean temperature	0.772**	0.665**	1.000

***. P*(2-tailed) <0.001. The correlation is significant.

Mean monthly precipitation and mean monthly temperature were positively correlated with HFMD incidence (Table 1). The correlations between monthly HFMD incidence and monthly average air temperature (*rs*=0.772, *P*<0.001) and between HFMD monthly incidence and monthly average precipitation (*rs*=0.686, *P*<0.001) were found. Based on these correlations, the relationships between meteorological variables and the number of HFMD cases were further analyzed through partial correlations. Monthly HFMD incidence was positively correlated with the average monthly air temperature (95% confidence interval (CI): 4.3-8.7) and monthly HFMD incidence was positively correlated with the average monthly precipitation (95% confidence interval (CI): 9.7-12.38). The difference was statistically significant.

The average monthly air temperature increased with the incidence of HFMD. The relationship between monthly mean temperature and HFMD cases is a logarithmic relationship (Fig. 3(a)): (see Formula 2 in the Supplementary Materials)

Among the two meteorological factors, precipitation was highly correlated with the number of HFMD cases and the correlation was not the same with that between temperature(Wei et al. 2015) and HFMD

cases. The relationship between monthly mean precipitation and HFMD is a quadratic relationship (Fig. 3(b)): (see Formula 3 in the Supplementary Materials)

Table 1 shows the correlation between meteorological factors (temperature and precipitation) and HFMD incidence. The models between meteorological factors (temperature and precipitation) and HFMD incidence were respectively established above. However, a combined model of HFMD and two meteorological factors should be established. Therefore, OLS model was used to estimate the relationship between HFMD incidence, temperature, and precipitation as follows: (see Formula 4 in the Supplementary Materials)

3.3 Temporal and spatial variations

The annual average temperature, annual average precipitation and annual kernel density maps of HFMD are shown in Fig. 4. The maps depict the spatial and temporal variations of HFMD cases in Xinjiang from 2008 to 2016. As shown in Fig. 4 (Population set as NONE), the distribution of HFMD is uneven. HFMD cases in northern Xinjiang were significantly more than those in southern Xinjiang. Kernel density analysis showed that HFMD mainly distribute along the Tianshan Mountains and its major tributaries. Urumqi, Ili Kazak Autonomous Prefecture, Changji Prefecture, Tacheng Prefecture and Bayingolin Mongolian Autonomous Prefecture are the high-density areas of HFMD. It may be ascribed to the sufficient precipitation in the above areas. These areas are suitable for the growth and transmission of HFMD virus. In 2012 and 2016, the density of HFMD exceeded 7000 cases in a single grid of focal area. These high-density areas are mainly concentrated in Urumqi and Ili Kazak Autonomous Prefecture.

3.4 Spatial autocorrelation of HFMD incidence

Local Indicators of Spatial Association (LISA) was calculated by global spatial autocorrelation analysis. LISA aggregation chart (Fig. 5) shows the results of the spatial autocorrelation test, demonstrating a highly statistically significant spatial autocorrelation difference of HFMD at the state level in Xinjiang for each year from 2008 to 2016. The Moran’s I values (Table 2) ranged from -0.135 to 0.202 ($P < 0.05$), indicating the spatial dependency on the occurrence of HFMD in 2008, 2010, 2012, 2014 and 2015. Moran I value in 2009 was -0.135, indicating that there was a negative spatial autocorrelation of HFMD in Xinjiang. Moran I values in 2011 and 2016 were respectively -0.066 and -0.00018, indicating that the incidence of HFMD in Xinjiang presented a random distribution pattern. Bayingolin Mongolian Autonomous Prefecture showed the high-high spatial autocorrelation of HFMD incidence, whereas Kashgar, Hotan, Aksu and Kizilsu Kirghiz Autonomous Prefecture showed the low-low spatial autocorrelation of HFMD incidence in 2008 and 2010. From 2011 to 2016, Urumqi has always shown the high-high spatial autocorrelation of HFMD incidence.

Table 2 Results of the spatial autocorrelation test on HFMD cases in Xinjiang from 2008 to 2016.

Years	2008	2009	2010	2011	2012	2013	2014	2015	2016
Moran's I	0.144	-0.135	0.202	-0.066	0.120	0.056	0.134	0.146	-0.001
Z-score	1.904	-0.647	2.832	0.042	1.933	1.181	2.092	2.146	0.625
P values	$P<0.05$	$P<0.05$	$P<0.05$	$P<0.05$	$P<0.05$	$P<0.05$	$P<0.05$	$P<0.05$	$P<0.05$

Discussion

Although the correlation between climatic factors and HFMD incidence has been extensively explored(Munderloh et al. 2016; Onozuka and Hashizume 2011), the relationships between HFMD occurrence and meteorological factors in typical arid and semi-arid areas were interpreted with daily HFMD surveillance data for the first time in the study. The relationship interpretation can help the prevention and control of HFMD in this climate environment (Xinjiang and other central Asia regions).

In the study, the majority of HFMD cases were children less than 5 years old. Obvious seasonal peaks occurred between May and July. The results were similar to previous studies(Wang et al. 2015; Xu et al. 2019).

In order to further explore the relationship between meteorological factors and HFMD incidence, in this study, separate and synthetic models were used to simulate each climatic factor, respectively. Average temperature and average precipitation were related to the HFMD incidence in Xinjiang. In temperate regions, HFMD outbreaks occurred in summer or early fall(Yien Ling Hii et al. 2011) when air temperature rise and precipitation increase occurred lately. Therefore, HFMD incidence in temperate regions was different from that in tropical and subtropical regions(Xu et al. 2016; Zhang et al. 2019). Meteorological factors (monthly [average](#) air temperature and monthly [average](#) precipitation) were positively correlated with HFMD incidence. The results were the same to previous studies(Wang et al. 2015). Enteroviruses are resilient to the gastrointestinal environment, but their stability in the ambient environment depends on humidity and temperature(Wei et al. 2015). Moreover, moderate monthly cumulative precipitation partly maintained the HFMD epidemic in the study period. Precipitation might affect water sanitation and facilitate disease transmission due to the increased contact rate of droplets mainly carrying HFMD virus(Zhang et al. 2016). High precipitation promoted the attachment of HFMD virus and increased the exposure probability(Cheng et al. 2014). In a study in Japan, with the increase in temperature, Herpangina & HFMD incidence increased. In a warm environment, the transmission of HFMD virus was enhanced, but cold and hot climate limited the transmission(Liu W et al. 2015; Onozuka and Hashizume 2011; Yien Ling Hii et al. 2011). The above conclusions also supported a monotonic relationship between HFMD incidence and meteorological factors. In this study, the relationship between monthly mean temperature and HFMD cases was the logarithmic relationship and the relationship between monthly mean precipitation and HFMD was the quadratic relationship. Therefore, in the study, with HFMD cases in the spatial grid as the

study object, based on the annual average air temperature and precipitation spatial data of the same grid size, kernel density is a good option for the relationship analysis(Rybnikova et al. 2018).

This study mapped the spatial and temporal distributions of HFMD from 2008 to 2016 in Xinjiang. The results of kernel density analysis demonstrated that HFMD incidence showed obvious regional differentiation, displaying a dynamic spatial-temporal distribution. The distribution of HFMD was mainly concentrated in northern Xinjiang. The incidence of HFMD in southern Xinjiang might be ascribed to the precipitation stress. The incidence of HFMD in Urumqi, Changji Prefecture, Tacheng Prefecture and other areas in Northern Xinjiang was obviously worthy of in-depth investigation. In 2012 and 2016, the density of HFMD exceeded 7000 cases in a single grid of focal area. Spatially, the focal area of HFMD incidence was located in Urumqi and regional centers. These focal areas have a well-developed economy, the fast highway system, and the large heterogeneous migrant population, which increases the HFMD risk(Liao et al. 2016).

The global spatial autocorrelation analysis results demonstrated the area with the high HFMD incidence was different from the high spatial autocorrelation area of HFMD in Xinjiang. Urumqi has always shown the high spatial autocorrelation of HFMD incidence because the incidence of HFMD in Urumqi remained high over the years and the adjacent area is also a high incidence of HFMD. Multiple regions showed the low spatial autocorrelation because the incidence of HFMD had inter-annual variation in several regions, with a low incidence of HFMD in adjacent area, such as Aksu and Ili Kazak Autonomous Prefecture.

Due to the large area, complex climatic states, and [population density](#) in various parts of Xinjiang, it is difficult to grasp the influences of meteorological factors on HFMD transmission(Wei et al. 2015). In the study, we quantitatively proved that HFMD cases were correlated with precipitation and air temperature in Xinjiang Uygur Autonomous Region, Northwest China.

Threshold temperature and threshold humidity for HFMD outbreaks have been extensively studied. It has also been widely accepted by scholars that when meteorological factors change, HFMD outbreak shows hysteresis. However, the relationship between meteorological factors on the grid scale and the morbidity of HFMD was seldom reported. In this study, based on latitude and longitude information extraction of HFMD cases according to GB code addresses, the spatial expression of HFMD under temporal and spatial variations were obtained.

In the future, we will compare the resulted obtained via different investigation techniques, such as geographically weighted regression (GWR). With GWR, spatially changing relationships between variables can be explored(Gilbert and Chakraborty 2011; Rybnikova et al. 2018). GWR will be applied in our study on the relationship between HFMD incidence and meteorological factors.

The findings provide the basis for HFMD prevention. To decrease the climate change risk of HFMD epidemics, it is necessary to analyze HFMD cases in other geographic regions based on the consideration of meteorological factors and demography(Liu W et al. 2015).

Conclusions

Our study provides strong evidences that the prevalence of HFMD in Xinjiang had an obvious seasonal feature. The HFMD incidence exhibited the dynamic spatial-temporal distribution between various states of Xinjiang Uygur Autonomous Region. In brief, the spatial and temporal dynamics of HFMD and the influences of meteorological factors from 2008 to 2016 in Xinjiang, China were explored. Northern Xinjiang are the focus of HFMD prevention and control. The result can help to improve preventive measures of HFMD.

Declarations

Author statements

All authors declare that there are no conflicts of interest.

Ethical approval

This study was reviewed and approved by the Ethics Committee of the Xinjiang Center for Disease Control and Prevention, China. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees.

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Figures

Figure 1

Geographical location of the study area in China Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

Figure 2

Time series of monthly data of HFMD cases (a), temperature (b) and precipitation (c) in Xinjiang, China from 2008 to 2016 (unit: Temperature(°C), precipitation (mm))

Figure 3

Fitting curve of meteorological factors (mean monthly temperature (a) and mean monthly precipitation (b)) and HFMD cases (unit: temperature (°C), precipitation (mm)).

Figure 4

Raster data of mean annual temperature, precipitation and HFMD cases in the study area from 2008 to 2016.

Figure 5

Moran scatter diagram of Xinjiang HFMD from 2008 to 2016.

Supplementary Files

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