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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1 Spatial-temporal mapping of hand, foot and mouth disease in relation to climate factors in Xinjiang, China from 2008 to
2 2016

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9 **[Objectives]:** The study mainly aims to depict the epidemiological characteristics of hand, foot and mouth disease (HFMD) in
10 Xinjiang, China and to evaluate the effects of meteorological factors on the incidence of HFMD and the spatial-temporal
11 heterogeneity of HFMD in Xinjiang under the influence of meteorological factors.

12 **[Methods]:** With the data from the national surveillance data of HFMD and meteorological parameters in the study area from 2008
13 to 2016. We first employed GeoDetector Model to examine the effects of meteorological factors on HFMD incidence in Xinjiang,
14 China and to test the spatial-temporal heterogeneity of HFMD risk, and then the spatial autocorrelation was applied to examine the
15 temporal-spatial pattern of HFMD.

16 **[Results]:** From 2008 to 2016, the HFMD distribution showed a distinct seasonal pattern and HFMD cases typically occurred
17 between May and July, peaking in June, in Xinjiang. The relative humidity, precipitation, air pressure and temperature had more
18 influence than other risk factors on HFMD incidence with explanatory powers of 0.30, 0.29, 0.29 and 0.21($p<0.000$), respectively.
19 The interactive effect of any two risk factors would enhance the risk of HFMD and there was a nonlinear enhancement between any
20 two risk factors interactive effect. The spatial relative risks in Northern Xinjiang were higher than in Southern Xinjiang. Global
21 spatial autocorrelation analysis showed a fluctuating trend over the years, the spatial dependency on the incidence of HFMD in 2008,
22 2010, 2012, 2014 and 2015, the negative spatial autocorrelation in 2009 and a random distribution pattern in 2011, 2013 and 2016.

23 **[Conclusion]:** Our findings show that the risk of HFMD in Xinjiang showed significant spatiotemporal heterogeneity. The monthly
24 average relative humidity, monthly average precipitation, monthly average air pressure and monthly average temperature factors
25 might have stronger relationships on the HFMD incidence in Xinjiang, China, compared with other factors. The differences in

climate and latitude between Southern and Northern Xinjiang and their arid and semi-arid geographical environment are part of the reasons why the distribution of HFMD in Xinjiang is different from other temperate continental climatic zones. These associations draw attention to climate-related health issues and will help in establishing accurate spatiotemporal prevention of HFMD in Xinjiang, China.

Keywords: HFMD, meteorological factors, spatial-temporal analysis, GeoDetector, Xinjiang Uygur Autonomous Region.

1. Background

Hand, foot and mouth disease (HFMD) is an infectious disease related to various enteroviruses that mostly affect children below 5 years old [1]. Its pathogens are typically coxsackieviruses (coxsackievirus A16 (CVA16)) and enteroviruses (enterovirus 71 (EV71)) [2-5]. Its clinical manifestations mainly include mouth ulcers, fever, and vesicles on the hands, feet, and mouth[6]. Most HFMD patients can fully recover since HFMD is a self-limited disease, but some patients may develop severe life-threatening complications and even death[3]. HFMD is transmitted through direct contact with feces, respiratory droplets, and blister fluid of infective patients or the contaminated environment[5].

In recent years, HFMD outbreaks have been reported frequently in Asian countries such as Vietnam, Thailand, Singapore, Malaysia and China [7-8], causing widespread public health concerns. In 2014, China had an unprecedented number of large-scale outbreaks of HFMD, with the cumulative number of cases reaching 2,778,861[9]. In May 2008, HFMD was added to Category C of notifiable diseases for disease surveillance in China[10]. Thus, HFMD is increasingly widely concerned.

At present, several studies have extensively explored the correlation between HFMD and meteorological factors such as relative humidity [1,11-12], precipitation [12] and temperature [12-13]. The occurrence of HFMD showed apparent different characteristics in countries or regions with distinct climate conditions [14]. In Vietnam[15], HFMD increased 7% (RR:1.07; 95%CI: 1.052–1.088) and 3.1% (RR: 1.031, 95%CI: 1.024–1.039) for 1 °C increase in monthly temperature above 26 °C and 1% increase in monthly humidity above 76%.Whereas HFMD decreased 3.1% associated with a 1mm increase in monthly cumulative rainfalls. In South Korea[16], at an average temperature below 18°C, the HFMD rate increased by 10.3% for every 1°C rise in average temperature (95% CI: 8.4, 12.3%). We also saw a 6.6% increase in HFMD rate (95% CI: 3.6, 9.7%) with every 1% increase in relative humidity under 65%, with a 1.5% decrease in HFMD rate observed (95% CI: 0.4, 2.7%) with each 1% humidity increase above 65%. Annual

50 HFMD incidence of counties was positively associated with the average annual temperature (RR: 1.171, 95% CI: 1.0435 –1.3134)
51 in Sichuan, China [17]. The climatic types of arid and semi-arid regions in Northwest China are obviously different from the above
52 research areas. The basic quantitative study on meteorological factors and HFMD in Xinjiang is to explore the determinants of
53 meteorological driving factors of HFMD in Xinjiang.

54 To our knowledge, previous studies adopted different methods from different perspectives to explore the relationship between
55 HFMD incidence and meteorological factors. In summary, it can be divided into four categories: Establish a mathematical model
56 to predict the incidence of HFMD, for example, seasonal auto-regressive integrated moving average (SARIMA) models[3], SIR
57 model[18]. The risk model of HFMD was estimated by the variation of meteorological factors: time-series Poisson regression
58 models[5]. Meteorological factor changes and time lag model of HFMD: the generalized additive model [19], the negative binomial
59 multivariable regression model [20], the distributed lag non-linear model[21]. Determinants of the drivers of HFMD: spatial panel
60 data models [22], GeoDetector models [14]. To quantify the determinants powers of driving factors of HFMD in Xinjiang, the
61 Geographical detector is an appropriate model for this study. It is a set of statistical methods for detecting spatial differentiation and
62 good at revealing the driving forces behind it.

63 Most of the previous studies concentrated in areas with high HFMD incidence, which are often characterized by high population
64 density. The climate in high incidence areas is often temperate to humid, such as Hong Kong[20], Guangdong[13], Guangxi[23]
65 and Jiangsu [24] provinces. However, the spatiotemporal heterogeneity of HFMD under the influence of meteorological factors in
66 Northwest China was seldom studied. In general, the study on HFMD in arid and semi-arid regions is still limited; more research
67 on such climates would potentially make the mechanism of HFMD transmission clearer under different climate conditions.

68 It was reported that the HFMD ranks the first in the number of class C infectious diseases in Xinjiang, 2019 [25], and the
69 number of cases increases gradually each year, but the relationship between HFMD and meteorological factors in Xinjiang has not
70 been proved. In this study, we analyze the spatial-temporal heterogeneity of HFMD and its relationship with meteorological factors
71 in Xinjiang at the county scale, which is located in Northwest China having a semi-arid climate to shed more light on the mechanisms
72 of HFMD transmission in those regions. The objectives of this study are: Firstly, to understand the spatiotemporal distribution
73 characteristics of HFMD from 2008 to 2016 in Xinjiang, as well as the global spatial autocorrelation and the incidence of HFMD

among different years. Secondly, factor detectors were used to quantify the determinants of meteorological drivers of HFMD, and risk detectors were used to detect the relative risks of HFMD under different meteorological elements. This study aims to provide countermeasures and suggestions for further public health interventions.

2. Methods

2.1 Study area

Xinjiang Uygur Autonomous Region is the largest provincial administrative region in China. The area is $166 \times 10^4 \text{ km}^2$ and the population was 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 and Afghan 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 210mm and less than 100mm, displaying an uneven spatial distribution pattern. The Tianshan Mountains have a higher level of precipitation, whereas Southern Xinjiang suffers severe water stress. The dominant wind throughout the year is northwest wind. Fig. 1 shows the geographical location of Xinjiang.

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Fig. 1 Geographical location of the study area in China

2.2 Data sources

Data on HFMD were provided by the Chinese Centre for Disease Control and Prevention (CDC). HFMD incidence in China

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was reported to the CDC via the China Information System for Disease Control and Prevention, the national disease report system, by the physicians treating the disease and public health personnel. 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. Meteorological data were obtained from the China Meteorological Data Sharing Service System [25], including daily average temperature (TEM), daily average relative humidity (RHU), daily average barometric pressure (PRS), daily cumulative precipitation (PRE), daily average evaporation (EVP), daily average wind speed (WIN) and daily sunshine duration (SSD). Monthly average temperature, relative humidity, barometric pressure, precipitation, evaporation, wind speed and sunshine duration were computed or aggregated from daily weather data. The monthly county-level meteorological variables were estimated by using ordinary spatial kriging methods based on 66 meteorological surveillance stations within Xinjiang conducted by ArcGIS10.1. The 66 meteorological surveillance stations are mapped in Figure 1.

2.3 Methods

GeoDetector is a statistical method to detect the temporal-spatial heterogeneity, which quantitatively expresses the spatial stratified heterogeneity of the research object by analyzing the differences and similarities of intra-layer and inter-layer variance (<http://www.geodetector.cn/>). This tool has been widely used in land use, disease risk factor detection and other fields[27-28].

Factor detector:

In this study, the q-statistic in GeoDetector was used to quantify the spatiotemporal heterogeneity of HFMD and detect the interaction relationship between spatial effect and temporal effect [29]. GeoDetector was adopted to identify the risk factors from the 7 candidate meteorological factors that caused the temporal-spatial stratified heterogeneity of HFMD in Xinjiang from 2008 to 2016. The q-statistic was specified as follows Eq.1 (The q-statistic for heterogeneity analysis regarding covariates was provided by the R Geodetector software):

$$q = 1 - \frac{1}{N\sigma^2} \sum_{h=1}^L N_h \sigma_h^2 = 1 - \frac{SSW}{SST} \quad SSW = \sum_{k=1}^L N_k \sigma_k^2, SST = N\sigma^2 \quad (1)$$

where q denotes the level of spatiotemporal heterogeneity; the value of the statistic is required to be within [0, 1]. If the value

approaches 1, it indicates a strong heterogeneity and if the value approaches 0, it indicates a random distribution. N was the number of all units, which could be divided into L strata. Stratum h was composed of N_h units. SSW and SST are represented within the sum of squares and the total sum of squares, σ^2 and σ_h^2 are the variance over all the units and within stratum h ($h = 1, \dots, L$), respectively.

Interaction detector:

By identifying the interactions between different risk factors X_1 and X_2 , the interaction detector shows whether the interaction will increase or decrease the explanatory power of the dependent variable Y, or the effect of these factors on Y is independent of each other. The relationship between the two factors can be divided into the following categories [30]:

Enhance: if $q(X_1 \cap X_2) > q(X_1)$ or $q(X_2)$

Enhance, bivariate: if $q(X_1 \cap X_2) > q(X_1)$ and $q(X_2)$

Enhance, nonlinear: if $q(X_1 \cap X_2) > q(X_1) + q(X_2)$

Weaken: if $q(X_1 \cap X_2) < q(X_1) + q(X_2)$

Weaken, univariate: if $q(X_1 \cap X_2) < q(X_1)$ or $q(X_2)$

Weaken, nonlinear: if $q(X_1 \cap X_2) < q(X_1)$ and $q(X_2)$

Independent: if $q(X_1 \cap X_2) = q(X_1) + q(X_2)$

Risk detector:

The risk detector is used to identify significant differences in the average incidence of HFMD between sub-regions. The study area is divided into sub-regions according to the classification of each risk factor. The t statistics were used to determine whether there is a significant difference in the average incidence of HFMD between two sub-regions. The t statistic is shown in Eq 2:

$$t_{\bar{y}_{h=1} - \bar{y}_{h=2}} = \frac{\bar{Y}_{h=1} - \bar{Y}_{h=2}}{\left[\frac{Var(\bar{Y}_{h=1})}{n_{h=1}} + \frac{Var(\bar{Y}_{h=2})}{n_{h=2}} \right]^{1/2}} \quad (2)$$

$\bar{Y}_h$ represents the mean value of attributes within sub-region h, such as incidence of HFMD; n_h is the number of cases in sub-region h, and Var is the variance.

Spatial autocorrelation analysis

Spatial autocorrelation analysis [31-32] including global spatial autocorrelation and local spatial autocorrelation, in this study, we applied global spatial autocorrelation methods and the global Moran's I statistic to describe the spatial clusters of HFMD distribution in Xinjiang by GeoDa v1.2.0 software (<http://geoda.uiuc.edu/downloadin.php>). The Moran's I statistic is calculated by Eq. (3)

$$I = \left[n \sum_{i=1}^n \sum_{j=1}^n \omega_{ij} (X_i - \bar{X})(X_j - \bar{X}) \right] / \left[\sum_{i=1}^n \sum_{j=1}^n \omega_{ij} \sum_{i=1}^n (X_i - \bar{X})^2 \right] \quad (3)$$

where n denotes the number of observed values, X_i represents the incidence rate in the region i , X_j represents the incidence rate in the region j , $\bar{X}$ indicates the mean value, and ω_{ij} represents a spatial weight matrix of the systematic binomial distribution, which represents neighboring relations between geographical units with n representing the total number of those units. In the present study, the data were based on regions. The value ω_{ij} is 1 if region i and region j are adjacent. Otherwise, the value is 0.

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 I value is to 1, the closer relationship between space units is and the smaller 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 I value is to -1, the less concentrated distribution between spatial units is and the more significant 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.

3. Results

3.1 Descriptive analysis

Fig. 2 Time series of monthly data of HFMD cases and meteorological variables in Xinjiang, China from 2008 to 2016

In total, 56,379 HFMD cases were reported from 2008 to 2016 in Xinjiang, with a daily average of 17.2 cases and the annual average incidence was 25.27/10,000. Fig. 2 shows the monthly distributions of HFMD cases and meteorological variables in Xinjiang from 2008 to 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. The annual morbidity among males was about 1.5 times higher than that of 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. A descriptive summary of the meteorological and socioeconomic variables is shown in Table 1.

Table 1 Descriptive statistics of meteorological variables

Covariates	Minimum	25% Percentile	Median	75% Percentile	Maximum
Average relative humidity (%)	32.35	41.64	51.52	61.11	70.69
Average temperature (°C)	0.01	4.42	8.82	13.23	17.63
Cumulative precipitation (mm)	0.02	0.49	0.95	1.42	1.91
Sunshine duration (hour)	5.72	6.8	7.89	8.97	10.05
Average wind speed (m/s)	0.84	1.68	2.53	3.37	4.21
Average barometric pressure(hPa)	699.42	777.75	856.08	934.41	1012.74
Average evaporation (mm)	0.16	1.92	3.68	5.44	7.2

3.2.1 Factor detector analysis

As shown in Table 2, the determinant power of the average relative humidity was obviously associated with the incidence of HFMD ($q = 0.30$), indicating that the average relative humidity mainly explains the spatial heterogeneity of the incidence of HFMD. Precipitation, barometric pressure, temperature and sunshine duration were also associated with the incidence of HFMD in Xinjiang, having explanatory powers q of 0.29, 0.29, 0.21 and 0.20, respectively. The study reveals that humidity, precipitation and barometric pressure were three dominant factors influencing the transmission of HFMD in the semi-arid regions.

Table 2 Explanatory power of each impact factor on the incidence of HFMD in Xinjiang

	EVP	PRE	PRS	RHU	SSD	TEM	WIN
q statistic	0.11	0.29	0.29	0.30	0.20	0.21	0.07
p value	0.000	0.000	0.000	0.000	0.005	0.000	0.005

3.2.2 Interaction detector:

The study found that the interaction of any two risk factors has greater explanatory power than any single metrological factor. Compared with their individual impact, they most presented the effect of “nonlinear enhance” or “bivariate enhance”. As shown in Table 3, the q statistics of average relative humidity was 0.3, which increased to 0.5 after accounting for the interactive effect of average barometric pressure on the HFMD incidence. As 0.5 is significantly higher than 0.3 (q statistics of average relative humidity) and 0.29 (q statistics of average barometric pressure), the result indicated that relative humidity and barometric pressure has a significantly bivariate enhanced interactive associations on the incidence rate of HFMD. The explanatory power of average relative humidity increased to 0.39 after considering the interactive effect of precipitation on HFMD incidence. The coupled impact of average relative humidity (q=0.3) and average wind speed (q=0.07) played an important role in HFMD, with an explanatory power of 0.43 (Table 3). High average relative humidity and high average wind speed were associated with a high incidence of HFMD. The interaction of these risk factors could effectively explain the spatial heterogeneity of the HFMD, and the selected risk factors had a tendency of strengthening interaction.

Table 3 The value of q for interactions between pairs of factors on the incidence of HFMD.

Covariates	EVP	PRE	PRS	RHU	SSD	TEM	WIN
EVP	0.11						
PRE	0.34EB	0.29					
PRS	0.35EB	0.37EB	0.29				
RHU	0.35EB	0.39EB	0.50EB	0.30			
SSD	0.21E	0.33EB	0.40EB	0.38EB	0.20		
TEM	0.34EN	0.33EB	0.41EB	0.37EB	0.34EB	0.21	
WIN	0.25EN	0.36ID	0.36ID	0.43EN	0.35EN	0.32EN	0.07

Note: EN: Enhance (nonlinear), EB: Enhance (bivariate), ID: Independent, E: Enhance

3.2.3 Risk detector analysis

Figure 3 shows the spatial distribution of HFMD cases in Xinjiang from 2008 to 2016, the number of HFMD cases was divided into four grades by natural breaks using ArcGIS. A deeper red color indicates a higher number of HFMD cases, most of them were concentrated in Northern Xinjiang.

Figure 4 showed the relative risk (RR) of HFMD with different meteorological factors from 2008 to 2016 in Xinjiang. Actually, the distribution of RR in space was not the same every year, and there were certain changes. Specifically, the spatial RRs in counties in Northern Xinjiang were higher than the counties in Southern Xinjiang, implying that these counties have relatively higher HFMD risk. Conversely, counties in Southern Xinjiang generally have lower RRs. This is consistent with the spatial distribution characteristics of the number of HFMD cases in Figure 3. The Northern Xinjiang had a higher average relative humidity, suitable temperature and precipitation level, resulting in a higher RR of HFMD. The southern regions were affected by the Taklimakan desert, high temperature, low relative humidity, precipitation and air pressure, and the risk of HFMD is relatively low. We found that the lowest RR of HFMD in Khotan, during the study period. According to the following meteorological risk factor charts, Urumqi, Tacheng Prefecture, Changji Prefecture and Ili Kazak Autonomous Prefecture are the high RR areas of HFMD in Northern Xinjiang. It may be ascribed to the higher average relative humidity and sufficient precipitation in the above areas. These areas are suitable for the growth and transmission of the HFMD virus.

Fig. 3 The spatial distribution of HFMD cases in Xinjiang

Fig. 4 The relative risk (RR) values of the spatiotemporal interaction effect

In Figure 5 we found that when the monthly average precipitation exceeded 0.94mm, the incidence of HFMD decreased. The monthly average precipitation of 0.02-0.94mm accounted for 82.5% of the total incidence of HFMD in Xinjiang. There was an inverted V-shape association between temperature and HFMD. A similar pattern was observed from the association between the monthly average relative humidity and HFMD, the monthly average sunshine duration and HFMD, the monthly average wind speed

218 and HFMD. When the monthly average relative humidity ranges from 51.52% to 70.69%, HFMD shows a higher incidence than
 219 other periods. 6.8 to 8.96 hours of sunshine duration are the sensitive monthly average sunshine duration for HFMD. When the
 220 monthly average temperature was 8.81 °C, the HFMD reached a peak. The incidence of HFMD was the most active during the
 221 temperature changed from 4.22°C to 13.22°C. The incidence of HFMD increased along with the monthly average relative humidity
 222 and the monthly average sunshine duration, reached a peak when the monthly average relative humidity was at 61.1% and the
 223 monthly average sunshine duration was at 7.78 hours and then decreased afterwards, respectively. Risk detector value presented a
 224 logarithmic relationship between the monthly average evaporation and HFMD, an exponential relationship between the monthly
 225 mean air pressure and HFMD. With regards to the association between the monthly average wind speed and HFMD, the incidence
 226 of HFMD was the highest when the monthly average wind speed was less than 2.52m/s. It should be noted that when a single
 227 meteorological factor mentioned above reaches the high incidence period of HFMD, it does not mean the outbreak period of HFMD,
 228 and it also requires the comprehensive action of other meteorological factors.

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Fig. 5 Average incidence of HFMD according to the different risk factor strata. a. Evaporation; b. Precipitation; c. Relative humidity; d. Sunshine duration; e. Temperature; f. Wind speed; g. Pressure

3.3 Spatial autocorrelation of HFMD incidence

Moran's I value was calculated by global spatial autocorrelation analysis. From 2008 to 2016, the Moran's I value (Table 4) of HFMD in Xinjiang ranged from -0.135 to 0.202 ($P < 0.05$), showing a fluctuating trend over the years, indicating the spatial dependency on the occurrence of HFMD in 2008, 2010, 2012, 2014 and 2015. Moran's I value in 2009 was -0.135, indicating that there was a negative spatial autocorrelation of HFMD in Xinjiang. Moran's 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 Mongol 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 always showed the high-high spatial autocorrelation of HFMD incidence.

Table 4 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	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$

4. Discussion

In recent years, the HFMD has become increasingly recognized as a significant health problem[33,34]. Moreover, in areas with different regions, the HFMD risk has introduced a significant difference. The correlation between HFMD incidence and climatic factors has been extensively explored[6,15], the relationships between HFMD occurrence and various meteorological factors in Xinjiang where typical arid and semi-arid areas were interpreted with daily HFMD surveillance data for the first time in the study. More research in such climates would potentially make the mechanism of HFMD transmission clearer under different climate

conditions.

Previous studies have shown that the response of HFMD incidence with respect to climate change differs. In temperate regions, HFMD outbreaks usually occurred in summer or early fall [5] since temperature rise and precipitation increase occurred later than in tropical regions. Therefore, HFMD incidence in temperate regions was different from that in tropical and subtropical regions [19,34]. For example, a study conducted in Vietnam located in Southeast Asia showed that the peak of HFMD comes in April. However, a study of HFMD in Gansu, China, showed that the HFMD reached the peak in June [35]. The climate of the two places mentioned above differs markedly. The study on the response of meteorological factors to HFMD has some similarities and differences with the previous conclusions. For instance, a study conducted in Guangdong province located in South China, showed that there was a nonlinear relationship between temperature and HFMD [13]. The positive correlation between temperature increase and HFMD incidence are corroborated by other studies. For instance, a study in Japan, with the increase in temperature, Herpangina & HFMD incidence increased. In a warm environment, the transmission of the HFMD virus was enhanced, but cold and hot climate limited the transmission [5,6,24]. Similarly, a study was implemented in Ningxia which located in the upper reaches of the Yellow River in Western China, it demonstrated that average temperature, relative humidity, and wind speed played significant roles in the spatial-temporal distribution of HFMD risk [14]. In our research, the relationship between monthly average temperature and HFMD relative risk represents inverted V-shape, a similar pattern was observed for the association between the monthly average relative humidity and HFMD, the monthly average precipitation and HFMD, the monthly average sunshine duration and HFMD, the monthly average wind speed and HFMD. It indicates that there is a non-linear relationship between meteorological factors and the risk of HFMD in Xinjiang. Furthermore, another study in Guangdong which has a high incidence of HFMD in China, indicated that the risk of HFMD was significantly associated with monthly average relative humidity, monthly average temperature, and monthly average rainfall. In this study, from the results of GeoDetector, an increase in HFMD incidence was found to be associated with the monthly average relative humidity, monthly average precipitation, monthly average air pressure and monthly average temperature, which was similar to some other research studies. Other climate conditions may also have a threshold effect. It should be noted that the thresholds of meteorological factors corresponding to the incidence of HFMD in Xinjiang are significantly different from other study areas. A study conducted in mainland China showed that relative humidity between 80.59 to 82.55% would lead

to a higher risk of HFMD [37]. However, the monthly average relative humidity between 51.52 to 61.10%, which is the threshold of HFMD in Xinjiang. Ultimately, we analyzed the association between temperature, precipitation and the incidence of HFMD in Xinjiang Uygur Autonomous Region, China, from one previous study, which can be used to support our results [38]. It's worth noting that risk detector value presented a logarithmic relationship between the monthly average evaporation and HFMD, an exponential relationship between the monthly mean air pressure and HFMD. This is different from previous research results.

The possible reason of the relationship between HFMD and meteorological factors is the stability of the enterovirus that causes HFMD in the external environment, such as humidity and temperature [39]. Moderate monthly cumulative precipitation can sustain the prevalence of HFMD. Because precipitation might affect water sanitation, promote the attachment of HFMD virus and increase the risk of exposure, thus facilitating the spread of HFMD and previous studies also have strong support for this view[1,12].

In order to further explore the relationship between meteorological factors and HFMD incidence, in this study, GeoDetector was adopted to explore the spatial and temporal heterogeneity and its interactive effects on the HFMD incidence in Xinjiang and spatial autocorrelation analysis was applied to examine the spatial pattern of HFMD in Xinjiang. The results 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. We think the possible reason is these focal areas have a well-developed economy, the fast highway system, and the large heterogeneous migrant population, which increases the HFMD risk [17].

The global spatial autocorrelation analysis results demonstrated that 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 also had a high incidence of HFMD. Multiple regions showed low spatial autocorrelation because the incidence of HFMD had inter-annual variation in several regions, with a low incidence of HFMD in adjacent areas, such as Aksu and Ili Kazak Autonomous Prefecture.

The present study has some limitations. First, there were only 66 meteorological surveillance stations in Xinjiang; ordinary kriging interpolation results might not cover all variations of the meteorological variables at the county level. However, this was

more accurate than using the same meteorological data on all counties in each city. Second, we estimated spatiotemporal variations in HFMD at the scale of counties and months; we did not include the factors at an individual and pathogenic levels, such as personal hygiene, educational background, incomes of the children's parents, living conditions, and composition of major pathogens. Further studies should consider the potential impacts of these factors. Third, the result should be examined via different investigation techniques, such as geographically weighted regression (GWR). With GWR, spatially changing relationships between variables can be explored [41,42]. GWR will be applied in our study on the relationship between HFMD incidence and potential impact factors.

5. Conclusions

The findings of our study indicated that the spatial-temporal distribution of HFMD risk in Xinjiang, China, was non-homogeneous. The higher relative risk counties mainly gathered in Northern Xinjiang. Meteorological factors, such as monthly average relative humidity, monthly average precipitation, monthly average barometric pressure and monthly average temperature, might be the driving factors of HFMD in Xinjiang. The high relative risk areas and high spatial correlation areas of HFMD all point to the Northern Xinjiang. Therefore, in the high incidence of HFMD season and relative risk areas, we can reduce environmental exposure and contact transmission to decrease the spread of HFMD.

Abbreviations

HFMD: Hand, foot and mouth disease; CA16: coxsackievirus A16; EV71: enterovirus 71; RR: relative risk; CDC: Chinese Centre for Disease Control and Prevention; TEM: temperature; RHU: relative humidity; PRS: pressure, PRE: precipitation; EVP: evaporation; WIN: wind speed; SSD: sunshine duration; EN: Enhance (nonlinear); EB: Enhance (bivariate); ID: Independent; E: Enhance.

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Authors' Contributions

HW W were in charge of the conception, design of study and revised the manuscript. L X wrote the manuscript and revised it critically for intellectual content. ZQ X undertook in data analyzed and helped to revise the manuscript. RF H provided HFMD data. All authors read and approved the final manuscript.

Availability of data and materials

The meteorological data used in the study were available from National Meteorological Information Center (<http://data.cma.cn/>). The vector map data was applied from Resource and Environment Data Cloud(<http://www.resdc.cn/>) with official permission. The datasets of HFMD generated during and analyzed during the current study are not publicly available due to confidentiality requirements but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Consent to publish

Not applicable.

Ethics approval and consent to participate

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. We aggregated the HFMD for each day at the county level (excluding the Xinjiang production and construction corps), not referring to patient's privacy information.

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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.