Spatio-temporal analysis of the relationship between climate and Hand, foot, and mouth disease in Shandong Province, China, 2008-2012

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Abstract

Background: Hand, foot, and mouth disease (HFMD) is the most common communicable disease in China. Shandong Province is one of the most seriously affected areas. The distribution of HFMD had spatial heterogeneity and seasonal characteristic in this setting. The aim of this study was to explore the associations between climate and HFMD by a Bayesian approach from spatio-temporal interactions perspective.

Methods: The HFMD data of Shandong Province during 2008-2012 were derived from the China National Disease Surveillance Reporting and Management System. And six climatic indicators considered in the analysis were obtained from the Meteorological Bureau of Shandong Province. The global spatial autocorrelation statistic (Moran’s I) was used to detect the spatial autocorrelation of HFMD cases in each year. Four Bayesian models were further adopted to estimate the relative risk of the occurrence of HFMD via Markov chain Monte Carlo.

Results: The annual average incidence rate of HFMD was 104.40 per 100,000 in Shandong Province. HFMD had positive spatial autocorrelation at county level (Moran’s I ≥0.30, P<0.001). The best fitting Spatio-temporal interactive model showed that Average temperature, Annual average pressure, Average relative humidity, Average wind speed and Annual sunshine hours were significantly positive related to the occurrence of HFMD. The estimated relative risk of 36, 87, 91, 79, 65 out of 140 counties for 2008-2012 respectively were significantly more than 1.

Conclusions: There were obvious spatio-temporal heterogeneity of HFMD in Shandong Province, and the climatic indicators played important roles in the epidemic of HFMD. Bayesian approach should be recommended to capture the spatial-temporal pattern of HFMD.
**Key words:** Hand, foot, and mouth disease (HFMD), Spatial epidemiology, Bayesian approach, Climatic indicator, China

**Background**

Hand, foot, and mouth disease (HFMD) is a common communicable disease usually affecting children, particularly those aged 5 years and younger [1]. It is most frequently caused by Coxsackievirus A16 and Enterovirus 71 [1,2], and is often characterized by a distinct clinical presentation of fever, or vesicular exanthema on their hands, feet, mouths, or buttocks [3,4].

Over the last decades, many large-scale outbreaks of HFMD were reported in East and Southeast Asia and have caused major public health concerns worldwide, especially in the affected countries [5-8]. In China, several outbreaks have also been reported, such as Linyi in Shandong (2007) [9], Fuyang in Anhui (2008) [10], Shanghai (2009) [11], Nanchang in Jiangxi (2010) [12], etc. Since its beginning in Fuyang, large-scale epidemic have resulted in the deaths of many children, HFMD was classified as a class C notifiable infectious disease by the Ministry of Health in China on 2 May 2008 [13]. So far, HFMD is still one of the leading causes of child death and a serious public health issue in China.

Currently, there are still no available effective vaccines or antiviral treatments specifically for HFMD. Thus, it is quite important for its prevention and control based on possible influencing factors. In recent years, many epidemiological studies have been conducted to explore an individual person’s risk factors (e.g., demographic factors, socio-economic determinants, behavioral factors) [14-20]. Although these individual factors may play a role in HFMD incidence, population-level factors are...
more important for public health intervention. Considering the spatial distribution
characteristics of HFMD, several researches have been conducted at population-level
(e.g., county, community, city) based on spatial analysis methods (e.g., spatial
regression model, spatial paneled model, etc.), which should be more helpful to
understand the emerging trend of HFMD in certain area and explore the causes of
disease incidence (population-level factors) [21], and can guide us to take the correct
and timely public health interventions to prevent the outbreak. Among these, some
studies found that the incidence of HFMD was associated with some climatic
indicators (e.g., average temperature, relative humidity, annual sunshine hours, etc
[22-26]. Therefore, the effects of climatic indicators on HFMD should be paid more
attention on, especially in the context of climate change. In addition, the occurrence of
HFMD presents significant seasonality, i.e., temporal characteristic [23,27-31].
Therefore, spatio-temporal model should be considered, which can not only help to
recognize the spatial and temporal trend of disease, but also make prediction, then
guide us to formulate and implement appropriate regional public health intervention
strategies to prevent and control this disease.
However, few studies from spatio-temporal interactions perspective, have
attempted to explore this relationship and to assess how climate affect HFMD
incidence. On the other hand, Bayesian methods can take into account possible
correlations and covariate effects, take full use of the related information of disease
and prior knowledge, and allow to readily incorporating errors that may arise from
mean or median estimates of the independent variables, it has been recognized as a
powerful means to provide more robust estimates [32-35].
Thus, the goal of this study is to investigate the relationships between HFMD
incidence and climatic indicators based on Bayesian approaches. We used the data of
new cases of HFMD reported during 2008-2012 in Shandong Province, and Bayesian models were further adopted to model the effects of six key climatic indicators, with the aim of increasing our knowledge of the true underlying geographic distribution of HFMD rates and improving prediction indicators.

**Method**

**Study area**

We performed this ecological spatial study of HFMD in Shandong Province, which was a coastal province in Eastern China with a population of approximately 98 million (Figure 1). Its area of 156,700 square kilometers was divided into 17 municipal districts which including 140 subdistricts (counties). And the county administrative level was often used for the HFMD-decision making process in China. Thus, county was used as the spatial unit of analysis in this study (Figure 1).

**Data sources**

**HFMD data**

Data concerning to the reported cases of HFMD were obtained from the China Information System for Disease Control and Prevention, a national system which included information on all disease of compulsory notification. The data contained the basic demographic and incidence information for 497,876 HFMD cases during 2008 to 2012.

**Demographic and climatic data**

The climatic indicators utilized in the present study were average temperature (AT), average pressure (AP), average relative humidity (ARH), average wind speed (AWS), annual sunshine hours (ASH) and annual rainfall (AR), which were obtained from the Meteorological Bureau of Shandong Province. And the corresponding demographic data of each county over the study period referred to Shandong Statistical Yearbook.
Statistical analysis

The frequencies of HFMD were summarized monthly and annually by geographic area (i.e., county), and the incidence rate of HFMD (per 100,000 population) in each county was calculated by HFMD counts divided by the corresponding population. We analyzed the temporal distribution characteristic of HFMD over the study period firstly. Then, the autocorrelation statistic (Moran’s I) [36] was used to detect the global spatial autocorrelation of HFMD cases in the study area and disclose the spatial pattern of HFMD with Z score at county level. The significance of Moran’s I was assessed by employing Monte Carlo randomization. A statistically significant (Z score ≥ 1.96) estimate of I indicated that neighboring counties had a similar prevalence rate of HFMD and cases were likely to cluster at county level. The software GeoDa™ 0.9.5-i was used to conduct the analysis.

Considering the epidemic pattern of HFMD, a Bayesian approach [32-35,37] was utilized to explore the relationship between HFMD and climatic indicators by constructing four separate models including/excluding spatial or temporal effects. The first Bayesian model was a conventional model with non-spatial random effects only (Non-spatial model); the second considered spatial random effects (Spatial model); the third took spatial and temporal random effects into account simultaneously (Spatio-temporal model); While the fourth added spatio-temporal interactive effects on the basis of spatio-temporal model (Spatio-temporal interactive model).

We adopted Markov chain Monte Carlo method to estimate the parameters of Bayesian models, including the relative risk (RR) of the occurrence of HFMD by the public domain software package WinBUGS 1.4.3 (http://www.mrc-bsu.cam.ac.uk/bugs). In the fit of all models, 100,000 samples for each parameter of interested were generated, with a burn-in of 20,000 iterations to
avoid the influence of the initial values. The Deviance Information Criterion (DIC) was used to assess the goodness-of-fit of models, smaller values of DIC indicated a more appropriate model [25].

**Results**

3.1 Prevalence of HFMD

From January 1, 2008 to December 31, 2012, there were 497,876 cases of HFMD reported in Shandong Province representing an average rate of 104.40 per 100,000. By county, the rates ranged between 18.65 and 328.44 per 100,000. Table 1 showed the demographic characteristics of HFMD cases in detail. Of the 497,876 cases, a majority of patients (473,183; 95.04%) were children younger than 6 years, the left (24,693; 4.96%) belonged to other age groups; 312,791 were male patients and 185,085 were female patients, with an average male-to-female ratio 1.69:1. Also it can be seen that most of HFMD cases were preschoolers (71.38% scattered children and 25.48% nursery children), the rest (3.14%) were students and others.

Figure 2 displayed the monthly distribution of HFMD cases during the study period, which indicated that the occurrence of HFMD presented significant seasonality. Obviously, the incidence peak appeared between April and August in the study years, which accounted for 83.00% of all reported cases.

3.2 Spatial autocorrelation of HFMD cases

The results of the spatial autocorrelation test were listed in Table 2, which demonstrated that high global spatial autocorrelation of HFMD existed at county level in Shandong Province within each epidemic year during 2008 to 2012 (Moran’s $I \geq 0.30, P<0.001$).

3.3 Relationship between HFMD incidence and climatic indicators

Table 3 and Table 4 showed the results of four separate Bayesian models. On the
basis of DIC (Table 3), Spatio-temporal model and Spatial model were quite similar
and superior to Non-spatial model obviously, which indicated that effect of spatial
heterogeneity was distinct, while temporal effect not. However, Spatio-temporal
interactive model had the lowest DIC, which may be caused by considering the
Spatio-temporal interaction. Thus, further analysis should be focused on
Spatio-temporal interactive model.

In Table 4, the parameter estimates for association and respective confidence
interval (CI) were presented, for all covariates in Spatio-temporal interactive model.
The results indicated that all variables except AR were significantly positive related to
the risk of HFMD. Among them, AP was most important variable with parameter
estimate 0.1054 (95% CI: 0.1014 to 0.1078), followed by AT with parameter estimate
0.0956 (95% CI: 0.0827 to 0.1076).

From Spatio-temporal interactive model, the neighbourhood RR ranged from
0.0072 to 29.6827 for 2008, 0.0139 to 37.7516 for 2009, 0.0168 to 63.6974 for 2010,
0.0162 to 58.7585 for 2011, 0.0634 to 30.4432 for 2012. Figure 3 displayed the
spatial distribution of the estimated RR, where 36, 87, 91, 79, 65 out of 140 counties
for 2008-2012 respectively, scattered throughout the study area, have RR > 1.

Discussion

Shandong Province had been one of the most serious HFMD epidemic areas, with
annual average incidence rate 104.40 per 100,000 during 2008 to 2012. Most HFMD
cases (95.04%) were aged less than 6 years old, with an average male-to-female sex
ratio 1.69 (see Table 1). Obvious single seasonal peaks were found between April and
July during the study period (see Figure 2), which were different from other districts
of China. For example, in Jiangsu Province, double peaks (the highest occurrence
between April and June and the second occurring in November) appeared [38]; in
Hong Kong, warmer seasonal peak (May-July) and winter peak (October-December) were detected [17]; in Guangdong Province, HFMD incidence peaked in April/May and September/October [19]. These differences might be partly due to climatic, geographic, social factors, etc [15,19]. In addition, spatial autocorrelation test indicated that HFMD had positive spatial autocorrelation at medium spatial scale level (county level) in Shandong Province (Table 2). This also confirmed that the occurrence of HFMD might be closely related to certain factors in the area.

Considering the goodness-of-fit as estimated by the DIC, the model including the spatial and temporal interactive effects was better fitted (DIC value = 6938.09, Table 3), which demonstrated a strong Spatio-temporal heterogeneity in HFMD risk at the county scale, with clusters of high risk areas, as previously reported [27]. And the HFMD incidence rate was correlated with average temperature, average pressure, average relative humidity, average wind speed, and annual sunshine hours (Table 4), which were partly compatible with previous ecological analyses from the literature [20,22,39], inferring that HFMD continued to be a disease strongly related to climate.

In this study, much more precise estimates of $RR$ were obtained from Spatio-temporal interactive model (see Figure 3), confirming the hypothesis that the risk of occurrence of the disease was related to what was occurring in the neighbourhood of each spatial unit. Figure 3 clearly displayed the spatio-temporal characteristic of $RR$, the epidemic of HFMD extended continuously over time, and the spatial pattern changed from concentrating on minority counties to expanding to more areas (especially in 2009 and 2010). Also, many high risk counties were located in areas for which HFMD clusters have been detected [27]. Therefore, objective decisions are required concerning the active detection, for prevention and control of HFMD in these areas.

Bayesian spatio-temporal interactive model was a valuable tool for the spatial and
temporal interactive assessment of disease patterns that could help to identify county
differences, and explore possible risk factors simultaneously. This method could solve
most of the problems faced by traditional statistical methods, such as the spatial
autocorrelation and the potential dependence between the covariates [40]. In previous
studies, Scan statistics methods had been used to determine the spatial or
spatio-temporal distribution of HFMD [23,27-30]. These approaches might absorb the
surrounding regions and generate false-positives areas due to a lack of specificity,
since they encompassed many neighbourhoods and tended to detect larger clusters
than expected [41-42]. However, the scan statistics could be complementary to
Bayesian method. That was to say, the scan statistic detected general regions in which
the risk was significantly high and the Bayesian posterior distribution further helped
to identify the neighbourhoods contributing strongly to the scan statistic circle [43].
Thus, results for cluster analysis should be interpreted with knowledge of the spatial
rate distribution, such as spatial Bayesian rates in particular [44]. Furthermore, the
analysis unit (i.e., county) was also considered adequately given the disease and risk
factors information that was available and the spatial level at which policies were
taken. However, one must note that ecologic bias was inevitable in any ecological
study [45]. In addition, some results might be biased due to the artificial grouping of
observations and variables at the county level. Despite these limitations, this approach
used here was very useful to explore spatially aggregated data and to highlight the
most risky areas to conduct more accurate analysis.

Conclusions

Using a Bayesian approach to estimate the contribution of climatic indicators on the
spatial-temporal pattern of HFMD should be encouraged in epidemiology. Our results
confirmed the spatial-temporal heterogeneity of HFMD distribution, with high risk in
particular areas observed in Shandong Province, and the importance of climatic
covariate. The results may help public health authorities to set up priorities regarding
to be targeted for prevention or control measures.

Abbreviations

HFMD: Hand, foot, and mouth disease; AT: Average temperature; AP: Average
pressure; ARH: Average relative humidity; AWS: Average wind speed; ASH: Annual
sunshine hours; AR: Annual rainfall; RR: Relative risk; DIC: Deviance information
criterion; CI: Confidence interval.

Competing interests

The authors declare that they have no competing interests

Authors’ contributions

YL substantially contributed to the study design, analysis and interpretation of data,
and drafted the manuscript. XW contributed to the data collection and data sorting,
and critically revised the manuscript. CP participated in the data collection, and
critically revised the manuscript. ZY contributed to the interpretation of results and
critically revised the manuscript. HL participated in the statistical analyses and
critically revised the manuscript. FX conceived of the study, and participated in its
design and helped to revise the manuscript. All authors read and approved the final
manuscript.

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We are also pleased to acknowledge the Meteorological Bureau of Shandong Province for providing us with climatic data.

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Figure Legend

**Figure 1.** The location of study area, Shandong Province in China.

**Figure 2.** Monthly distribution of HFMD cases in Shandong Province, 2008–2012.

**Figure 3.** Estimated relative risk for HFMD by Bayesian Spatio-temporal interactive model across 140 counties in Shandong Province, 2008-2012.
Table 1. Demographic Characteristics of HFMD cases in Shandong Province, 2008-2012.

<table>
<thead>
<tr>
<th>Age</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-</td>
<td>5735</td>
<td>22983</td>
<td>18790</td>
<td>12272</td>
<td>10588</td>
<td>70368</td>
</tr>
<tr>
<td>1-</td>
<td>9447</td>
<td>43615</td>
<td>39586</td>
<td>25753</td>
<td>24090</td>
<td>142491</td>
</tr>
<tr>
<td>2-</td>
<td>7028</td>
<td>29746</td>
<td>31852</td>
<td>19636</td>
<td>18013</td>
<td>106275</td>
</tr>
<tr>
<td>3-</td>
<td>5244</td>
<td>19746</td>
<td>24920</td>
<td>17637</td>
<td>15978</td>
<td>83525</td>
</tr>
<tr>
<td>4-</td>
<td>2605</td>
<td>11724</td>
<td>13624</td>
<td>9954</td>
<td>10077</td>
<td>47984</td>
</tr>
<tr>
<td>5-</td>
<td>1245</td>
<td>5034</td>
<td>6586</td>
<td>5039</td>
<td>4636</td>
<td>22540</td>
</tr>
<tr>
<td>6-</td>
<td>617</td>
<td>2355</td>
<td>2436</td>
<td>2430</td>
<td>2088</td>
<td>9926</td>
</tr>
<tr>
<td>7-</td>
<td>316</td>
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<td>8-</td>
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<td>830</td>
<td>640</td>
<td>596</td>
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<tr>
<td>9-</td>
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<td>589</td>
<td>490</td>
<td>379</td>
<td>407</td>
<td>2009</td>
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<tr>
<td>10-14</td>
<td>285</td>
<td>1043</td>
<td>875</td>
<td>703</td>
<td>734</td>
<td>3640</td>
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<td>≥15</td>
<td>148</td>
<td>362</td>
<td>423</td>
<td>342</td>
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<table>
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<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>Total</th>
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<tbody>
<tr>
<td>Male</td>
<td>21213</td>
<td>86928</td>
<td>89302</td>
<td>59731</td>
<td>55617</td>
<td>312791</td>
</tr>
<tr>
<td>Female</td>
<td>11768</td>
<td>52229</td>
<td>51973</td>
<td>36005</td>
<td>33110</td>
<td>185085</td>
</tr>
<tr>
<td>Ratio of Male-to-Female</td>
<td>1.80</td>
<td>1.66</td>
<td>1.72</td>
<td>1.66</td>
<td>1.68</td>
<td>1.69</td>
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<table>
<thead>
<tr>
<th>Occupation</th>
<th>2008</th>
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<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>Total</th>
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<tr>
<td>scattered children</td>
<td>22608</td>
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<td>99463</td>
<td>66004</td>
<td>61715</td>
<td>355380</td>
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<tr>
<td>nursery children</td>
<td>9119</td>
<td>29259</td>
<td>38167</td>
<td>26619</td>
<td>23698</td>
<td>126862</td>
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<td>other</td>
<td>1254</td>
<td>4308</td>
<td>3645</td>
<td>3113</td>
<td>3314</td>
<td>15634</td>
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<tr>
<td>Total</td>
<td>32981</td>
<td>139157</td>
<td>141275</td>
<td>95736</td>
<td>88727</td>
<td>497876</td>
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</table>
**Table 2.** Results of the spatial autocorrelation test on HFMD cases in Shandong Province, 2008-2012

<table>
<thead>
<tr>
<th>Year</th>
<th>Moran's I</th>
<th>Z Score</th>
<th>P-value</th>
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<tr>
<td>2008</td>
<td>0.30</td>
<td>6.03</td>
<td>&lt;0.001</td>
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<tr>
<td>2009</td>
<td>0.37</td>
<td>7.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2010</td>
<td>0.30</td>
<td>5.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2011</td>
<td>0.45</td>
<td>8.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2012</td>
<td>0.35</td>
<td>6.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model specifications</td>
<td>DIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-spatial model</td>
<td>138655.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spatial model</td>
<td>81210.60</td>
<td></td>
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<tr>
<td>Spatio-temporal model</td>
<td>81215.80</td>
<td></td>
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<tr>
<td>Spatio-temporal interactive model</td>
<td>6938.09</td>
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</table>
Table 4  Estimated the effects of climatic indicators on HFMD by Spatio-temporal interactive model fitted, Shandong Province, China, 2008-2012

<table>
<thead>
<tr>
<th>Covariates</th>
<th>β</th>
<th>95% confidence interval</th>
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<tbody>
<tr>
<td>Intercept</td>
<td>-28.7500</td>
<td>-29.0100, -28.4100</td>
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<tr>
<td>Average temperature</td>
<td>0.0956</td>
<td>0.0827, 0.1076</td>
</tr>
<tr>
<td>Annual average pressure</td>
<td>0.1054</td>
<td>0.1014, 0.1078</td>
</tr>
<tr>
<td>Average relative humidity</td>
<td>0.0741</td>
<td>0.0551, 0.1034</td>
</tr>
<tr>
<td>Average wind speed</td>
<td>0.0705</td>
<td>0.0198, 0.1267</td>
</tr>
<tr>
<td>Annual sunshine hours</td>
<td>0.0557</td>
<td>0.0049, 0.1043</td>
</tr>
<tr>
<td>Annual precipitation</td>
<td>0.0473</td>
<td>-0.0125, 0.1393</td>
</tr>
</tbody>
</table>
Figure 2
Figure 3