Spatial clustering of severe Hand-Foot-Mouth disease cases in Hainan Island, China

Shao-Ming Chen, Li Qiu, Zhong-Hua Du, Yu-Ming Jin, Jian-Wei Du, Yan Chen, Chiho Watanabe, and Masahiro Umezaki

Received: September 14, 2016. Accepted: May 30 2017.
Published online: September 11, 2017.
DOI: 10.7883/yoken.JJID.2016.407

Advance Publication articles have been accepted by JJID but have not been copyedited or formatted for publication.
Spatial Clustering of Severe Hand-Foot-Mouth Disease Cases in Hainan Island, China

Shao-Ming Chen¹, ²*, Li Qiu¹, Zhong-Hua Du¹, Yu-Ming Jin¹, Jian-Wei Du¹, Yan Chen¹, Chiho Watanabe², Masahiro Umezaki²

¹Hainan Provincial Center for Disease Control and Prevention, Haikou 570203, Hainan, China
²Department of Human Ecology, School of International Health, Graduate School of Medicine, The University of Tokyo, Tokyo 113-0033, Japan

*Corresponding author: Mailing address: Hainan Provincial Center for Disease Control and Prevention, Haikou 570203, China. Tel: +86-898-65228905, Fax: +86-898-65351552, E-mail: csm456@hotmail.com

Key words: Hand-Foot-Mouth Disease; Spatial Clustering; Hainan Island, China

Running head: Spatial Clustering of Severe HFMD in Hainan Island
SUMMARY

The incidence of severe Hand-Foot-Mouth disease (HFMD) in Southeast/East Asia has recently increased. This study explored spatial clusters of the incidence and proportion of severe HFMD cases in Hainan Island, where the prevalence and mortality of HFMD were the highest in China in 2011. A spatial autocorrelation statistic (Anselin’s Local Moran I) was calculated for the Empirical Bayesian (EB) smoothed dataset of severe HFMD cases. Significantly spatial clusters were detected for both incidence and the proportion of severe HFMD cases. Population density was higher in spatial clusters with a high proportion of severe HFMD cases among total HFMD cases. We speculate that a higher proportion of severe HFMD cases were diagnosed in densely populated townships. This should be considered when analyzing the HFMD database of Hainan.
INTRODUCTION

Hand-foot-mouth disease (HFMD) is a common infectious disease among children. It is mostly mild and self-limited. However, some Asia-Pacific countries and regions have recently experienced pandemic of severe/fatal cases of HFMD (1-5). In China, the number of such cases has dramatically increased: 18,759 severe cases and 509 fatal cases were reported in 2011, equivalent to 136% and 144%, respectively, of the cases reported in 2009 (6).

Investigation of spatial clusters of severe HFMD is important because such areas likely have environmental factors associated with its incidence. However, no spatial clustering studies of the incidence of severe HFMD or the proportion of severe HFMD cases among total HFMD cases have been conducted. Several studies have reported spatial clustering of the incidence of general HFMD (7-11), although all previous studies of HFMD clusters used district-level incidence data, which might have masked the potential effect of local environment. Thus, we analyzed the incidence of severe HFMD and the proportion of severe HFMD among total HFMD cases at the township level, which facilitated evaluation of the link between severe HFMD and environment factors at a higher geographical resolution.

Hainan Island is one of the provinces in China most seriously affected by recent outbreaks of severe HFMD. In 2011, the HFMD-specific mortality rate and the proportion of severe HFMD cases among total HFMD cases on Hainan Island were ranked first and sixth, respectively, of all provinces in China (12). In the present study, we investigated the spatial clustering of severe HFMD on Hainan Island, China. Population density data were compared in terms of high- and low-incidence
and proportion clusters of severe HFMD. Population density is an important factor in the incidence of general HFMD (13); however, no study has investigated the associations between population density and severe HFMD.

MATERIALS AND METHODS

Study area: Hainan Island is located south of mainland China. The Island, which lies in Hainan province, has an area of 35,354 km² and a population of 8.6 million according to the 2010 Chinese census. It has a subtropical monsoon climate. Hainan Island comprises 22 counties and 281 townships; economically developed regions are located mainly along the coast and have high population densities, whereas the inland mountainous areas are comparatively underdeveloped and have relatively low population densities. Highway and railway networks extend along the coast but did not reach the inland regions in 2013.

Definition of HFMD: The HFMD diagnostic criteria were based on the Chinese Guidelines for HFMD diagnosis and treatment (2010 Edition) issued by the Ministry of Health (14). Children were diagnosed with HFMD if they had at least one of the following features: a maculopapular or vesicular rash on the palms, soles or buttocks, and vesicles or ulcers in the mouth. The diagnosis is expected to be given with etiology or serology examination. Children were diagnosed with severe HFMD if they developed at least one of the followings: (1) neurological manifestations (e.g. listlessness, convulsions, hypsomnia, hyperarousal, delirium, headache, vomiting, limb shaking, myoclonus, nystagmus, ataxia, eye movement disorders, weakness or
acute flaccid paralysis, meningeal irritation, pathologic reflexes, or reduced or absent tendon reflexes); (2) respiratory manifestations (e.g. dyspnoea, purple lips, expectoration of blood, moist rales, or gurgling with sputum); or (3) circulatory manifestations (e.g. a grey complexion, mottled skin, cool extremities, peripheral cyanosis, cold sweat, prolonged capillary refill time, increased or decreased heart rate, arrhythmia, asphygmia, ordysarteriotony).

**Data collection:** Since May 2, 2008, HFMD has been classified as a category C notifiable infectious disease in China, and all medical institutions must report cases of HFMD to the Chinese Information System for Disease Control and Prevention (CSDC) online. Data from the CSDC database were analyzed. The database included 185,775 HFMD cases (2,038 were severe cases) registered between January 1, 2009 and December 31, 2013. The following individual characteristics were available for the analysis: sex, date of birth, residential address, day of onset, and severity of the case (mild/severe). The final analysis included 184,958 HFMD cases (2,020 severe cases). A small number of HFMD cases (817, including 18 severe cases) were excluded from the analysis because the residential address was not available. The residential address was coded by township name. Township-level demographic data was obtained from the 2010 Hainan census.

**Base map preparation:** The layers of the county boundaries (number of counties were 22 in Hainan Province in 2014) were obtained from the website of the Environmental Systems Research Institute (ESRI, http://www.esri.com). The latitude
and longitude of the locations of township governments (n=281) were identified on Google map. Based on the assumption that the locations of township government represent those of the township, township boundaries were generated by Voronoi tessellation using geographic information system software (ArcGIS 10.2.1). The area within each township boundary was calculated using the same software.

**Severe HFMD parameters analyzed:** In this study, we investigated two parameters: the incidence of severe HFMD among the total population of each township (incidence of severe HFMD) and the proportion of severe HFMD cases among the total HFMD cases in each township (proportion of severe HFMD).

**Spatial autocorrelation statistics:** A spatial autocorrelation statistic (Anselin’s Local Moran I) was calculated for an empirical Bayesian (EB)-smoothed dataset of severe HFMD cases. EB smoothing was used because some townships had few or no cases of severe HFMD (15-17).

Spatial scan statistics and Anselin’s Moran I are widely used to detect spatial cluster for infectious disease (18-19). The strength of Scan statistic is that it can detect cluster over space and time. But some geographic units sometimes were included both in high-risk and low-risk clusters, which make it difficult to compare population density between high- and low-risk townships in our study. Otherwise, Anselin’s Local Moran I is calculated in each geographic unit, thus not sensitive to the shape of geographic features and the detected clusters do not geographically overlap (19-21). Hence, we chose Anselin’s Local Moran I to identify cluster for severe HFMD in our
Spatial autocorrelation measures the similarity of a set of spatially distributed points and their associated values (22-23). Anselin’s Local Moran I is a Local test statistic for spatial autocorrelation. It can be calculated as follows (17):

\[ I_i = \frac{(x_i - \bar{x}) \sum_{j=1}^{n} W_{ij} (x_j - \bar{x})}{\frac{1}{n} \sum_{i=1}^{n} (x_i - \bar{x})^2} \]

Where \( n \) is the total number of locations (281 townships); \( x_i \) indicates the value of the variable of interest, \( X \) at location I; \( x_j \) denotes the observation at neighboring locations J, and \( \bar{x} \) is the mean of \( X \). \( W_{ij} \) is the spatial weight matrix between I and J, which reflects the intensity of the geographic relationship across the study regions. In this study, spatial weight matrix was created with the first order queen’s contiguity, which defines spatial neighbors as those townships with shared borders and vertices.

Anselin’s Local Moran I shows the extent of spatial autocorrelation (20, 24-26): significantly positive values indicate that the township and neighboring townships were similarly high or similarly low (high–high or low–low), whereas significantly negative values indicate that a township and the neighboring townships were dissimilar (high–low or low–high). In this study, we defined high-high and high-low townships as high-risk clusters of the incidence of severe HFMD and proportion of severe HFMD cases, and low-low and low-high townships as low-risk clusters. The statistical significance of Anselin’s Local Moran I was tested by comparison with a reference distribution obtained by 999 random permutations. The GeoDa 1.8.14
software was used for the analysis. The significance level was set at $\alpha = 0.05$.

**Cluster population density:** The population densities of clusters with a high and low incidence of severe HFMD and high and low proportion of severe HFMD cases were compared using the Mann–Whitney U-test. PASW Statistics 18.0.0 (SPSS, Chicago, IL, USA) was used for the statistical analysis. The significance level was set at $\alpha = 0.05$.

**RESULTS**

**Epidemiology:** The characteristics of severe HFMD cases from 2009 to 2013 in Hainan Island according to sex and age are shown in Table 1. The incidence and proportion of severe HFMD cases were 23.4/100,000 and 10.9‰, respectively. The proportion of severe HFMD cases was higher in males than in females. The highest proportion of severe HFMD cases was among 0-5 year old age children.

Figure 1 shows the incidence and proportion of severe HFMD cases in 281 townships. The map was drawn using a quantile classification scheme. The incidence of severe HFMD was higher in townships in the north, northeast, and west of the Island. The proportion of severe HFMD cases showed a similar geographic pattern to that of the incidence of severe HFMD.

**Spatial autocorrelation statistic:** Figure 2 shows high- and low-risk clusters in terms of the incidence and proportion of severe HFMD cases identified by Anselin’s Local Moran I for the entire study period. High-risk clusters for the incidence of severe HFMD were found in the north and northeast parts of Hainan Island. Low-risk
clusters were detected in the inland and southern regions. Regarding the proportion of severe HFMD cases, high-risk clusters were detected in the north, west, and northeast of the island. Low-risk clusters were detected in the inland and southern regions of Hainan Island.

**Cluster population density**: Figure 3 and Figure 4 show the population density of clusters at high and low risk for incidence of severe HFMD and proportion of severe HFMD cases. Population density did not differ between high-risk and low-risk clusters regarding the incidence of severe HFMD (U = 798, p = 0.067), but density was significantly higher in high-risk clusters for the severe HFMD proportion than in the low-risk clusters (U = 577, p = 0.017).

**DISCUSSION**

In this study, the incidence and proportion of severe HFMD cases were clustered. Population density was higher in townships belonging to high-risk clusters for a high proportion, but not for a high incidence, of severe HFMD.

Population density is an important factor in the incidence of general HFMD (7, 11); the child population density was found to explain >50% of the variation of HFMD incidence in China (13). HFMD is a human-to-human infectious disease, and higher population density can result in a higher frequency of individual’s contact and the subsequent infection.

Previous studies by the authors compared the biological and behavioral characteristics of severe and non-severe HFMD children in Hainan Island (27). It
showed that, in addition to HEV71 infection and a peak body temperature >39°C, individual characteristics that are generally shared by children in low socioeconomic status households in rural communities (e.g., children who were not breastfed during their first 6 months, who were cared by grandparents, and those whose caregivers were less educated) were associated with the development of severe HFMD. Therefore, we assumed that the proportion of severe HFMD would be higher in rural areas than in urban areas, thus higher in less-densely populated areas than in more-densely populated areas. However, in the present study the data showed the opposite tendency, i.e., the proportion of severe HFMD cases was higher in densely populated areas.

This discrepancy can be explained by the co-existence of rural and urban communities in a single township in China. Typically, hospitals, schools, markets and residential areas are located near the township government office, while farming villages scattered in the whole township areas. Therefore, townships have both rural and non-rural characteristics irrespective of the population density (an exception is the provincial capital, where farming villages have been transformed into urban residential areas).

There have been so far no evidences with which we can interpret why more severe cases developed from general HFMD cases in densely populated townships in Hainan Island. We speculate that a higher proportion of severe HFMD were diagnosed in densely-populated townships. In low-risk clusters (low population density) in Hainan Island, medical facilities are not as good as those in densely populated areas; therefore, severe HFMD cases were more likely to remain undiagnosed. This should
be considered in future analyses of the CSDC database; stratification by population
township density is recommended for studies of the risk factors for severe HFMD.

In this study, Anselin’s Local Moran I was used to detect the clusters for severe
HFMD incidence and proportion. After comparing population density in high-risk and
low-risk clusters, we speculated that a higher proportion of severe HFMD cases were
diagnosed in densely populated townships. Anselin’s Local Moran I was
demonstrated to be an effective method to explore the spatial pattern of HFMD. This
method enables us to detect HFMD clusters and allow for better design and
implementation of HFMD preventive and control.

The present study has some limitations. The HFMD cases were obtained from
CSDC database which compiled case reports of HFMD hospitals/clinics in China. It is
probable that some mild cases HFMD patients did not visit the hospitals/clinics,
which result in underestimation of the number of mild HFMD cases in the dataset.
Also, since age-specific population by township was not available in Chinese census,
we could not adjust age in the spatial statistics model.

In conclusion, spatial clustering analysis of HFMD cases in the CSDC database
between January 2009 and December 2013 in Hainan Island, China, revealed high-
risk clusters for the incidence and proportion of severe HFMD cases. We speculated
that a higher proportion of severe HFMD cases were diagnosed in these high-risk
clusters. This should be considered in future analyses of the CSDC database of
Hainan.

Acknowledgments
This work was financially supported by Natural Science Foundation of Hainan Province, China (No. 813254). The study was conducted when Shao-Ming Chen studied as a master student in the graduate school of international health, the University of Tokyo under the support of Asia Development Bank scholarship. The authors thank the team members of Hainan CDC who have contributed to establish the CSDC database.

Conflict of interest

None to declare.

REFERENCES


<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (year)</th>
<th>Population</th>
<th>Total case</th>
<th>Number of severe case</th>
<th>Incidence of severe HFMD (100,000)</th>
<th>Severe HFMD proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0-</td>
<td>395116</td>
<td>113158</td>
<td>1349</td>
<td>341.4</td>
<td>11.9</td>
</tr>
<tr>
<td></td>
<td>5-</td>
<td>242333</td>
<td>3072</td>
<td>7</td>
<td>2.9</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>10-</td>
<td>357578</td>
<td>1188</td>
<td>4</td>
<td>1.1</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>15-</td>
<td>3560422</td>
<td>405</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>4555449</td>
<td>117823</td>
<td>1360</td>
<td>29.9</td>
<td>11.5</td>
</tr>
<tr>
<td>Female</td>
<td>0-</td>
<td>364663</td>
<td>64314</td>
<td>649</td>
<td>178.0</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td>5-</td>
<td>211794</td>
<td>1861</td>
<td>6</td>
<td>2.8</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>10-</td>
<td>279965</td>
<td>642</td>
<td>5</td>
<td>1.8</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>15-</td>
<td>3228847</td>
<td>318</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>4085269</td>
<td>67135</td>
<td>660</td>
<td>16.2</td>
<td>9.8</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>8640718</td>
<td>184958</td>
<td>2020</td>
<td>23.4</td>
<td>10.9</td>
</tr>
</tbody>
</table>
Figure 1. Incidence of severe HFMD and severe HFMD proportion by townships (n=281), Hainan Island, China, 2009-2013.
Figure 2. High- and low-risk clusters for incidence of severe HFMD and severe HFMD proportion identified by Anselin’s Local Moran I with Empirical Bayesian smoothing, Hainan Island, China, 2009-2013.
Figure 3. Population density between High- and Low-risk clusters for severe HFMD incidence in township level.
Figure 4. Population density between High- and Low-risk clusters for severe HFMD proportion in township level.