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 pandemics of severe or fatal HFMD cases (1–5). In China, the number of such cases has dramatically increased: 18,759 severe cases or fatal HFMD cases (1–5). In China, the number of such regions have recently experienced pandemics of severe self-limited. However, some Asia-Pacific countries and infectious disease among children. It is mostly mild and

SUMMARY: The incidence of severe hand-foot-mouth disease (HFMD) in Southeast and East Asia has increased in recent years. This study explored spatial clusters of the incidence and proportion of severe HFMD cases on Hainan Island, where the prevalence and mortality of HFMD were the highest in China during 2011. A spatial autocorrelation statistic (Anselin’s Local Moran I) was calculated for the Empirical Bayesian (EB)-smoothed dataset of severe HFMD cases. Significant spatial clusters were detected for both the incidence and 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 Island.

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 pandemics of severe or fatal HFMD cases (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 the 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. 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 studies have investigated the association between population density and severe HFMD.

MATERIALS AND METHODS

Study area: Hainan Island is located south of mainland China. The island, which lies within Hainan Province, has an area of 35,354 km² and a population of 8.6 million according to the 2010 Chinese census. The climate is subtropical monsoon. 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 serological testing. Children were diagnosed with severe HFMD if they developed at least one of the following: (i) neurological manifestations (e.g., listlessness, convulsions, hypersomnia, 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); (ii) respiratory manifestations...
(e.g., dyspnea, purple lips, expectoration of blood, moist rales, or gurgling with sputum); or (iii) 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, or dysarteriotony).

**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 online Chinese Information System for Disease Control and Prevention (CSDC). We analysed data from the CSDC database. The database included 185,775 HFMD cases (2,038 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 unavailable. Residential address was coded by township name. Township-level demographic data were obtained from the 2010 Hainan census.

**Base map preparation:** The layers of the county boundaries (there were 22 counties were in Hainan Province in 2014) were obtained from the website of the Environmental Systems Research Institute (ESRI, Redland, CA, USA; <http://www.esri.com>). The latitude and longitude of the location of township governments (n = 281) were identified on Google Maps. Based on the assumption that township government locations 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.

**Analysis of severe HFMD parameters:** In this study, we investigated 2 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 the scan statistic is that it can detect clusters over space and time. However, some geographic units are sometimes included in both high-risk and low-risk clusters, this made it difficult to compare population density between high- and low-risk townships in our study. Anselin’s Local Moran I was calculated for each geographic unit, therefore it is 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 clusters of severe HFMD cases in our study.

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 and can be calculated as follows (17):

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

where $n$ is the total number of locations (281 townships); $x_i$ indicates the value of the variable of interest, $x$ at location $i$; $x_i$ 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 low–low townships as high-risk clusters for incidence of severe HFMD and proportion of severe HFMD cases; low–low and low–high townships were defined 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. GeoDa 1.8.14 software (University of Chicago, IL, USA) 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 on Hainan Island according to the Environmental Systems Research Institute (ESRI, Redland, CA, USA; <http://www.esri.com>). The latitude and longitude of the location of township governments (n = 281) were identified on Google Maps. Based on the assumption that township government locations 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.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (yr)</th>
<th>Population</th>
<th>Total case</th>
<th>No. of severe case</th>
<th>Incidence of severe HFMD (100,000)</th>
<th>Severe HFMD proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0–4</td>
<td>395,116</td>
<td>113,158</td>
<td>1,349</td>
<td>341.4</td>
<td>11.9</td>
</tr>
<tr>
<td></td>
<td>5–9</td>
<td>242,333</td>
<td>3,072</td>
<td>7</td>
<td>2.9</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>10–14</td>
<td>357,578</td>
<td>1,188</td>
<td>4</td>
<td>1.1</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>15 ≤</td>
<td>3,560,422</td>
<td>405</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>subtotal</td>
<td>4,555,449</td>
<td>117,823</td>
<td>1,360</td>
<td>29.9</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td>0–4</td>
<td>364,663</td>
<td>64,314</td>
<td>649</td>
<td>178.0</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td>5–9</td>
<td>211,794</td>
<td>1,861</td>
<td>6</td>
<td>2.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Women</td>
<td>10–14</td>
<td>279,965</td>
<td>642</td>
<td>5</td>
<td>1.8</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>15 ≤</td>
<td>3,228,847</td>
<td>318</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>subtotal</td>
<td>4,085,269</td>
<td>67,135</td>
<td>660</td>
<td>16.2</td>
<td>9.8</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>4,085,269</td>
<td>70,087</td>
<td>2,020</td>
<td>23.4</td>
<td>10.9</td>
</tr>
</tbody>
</table>
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 men than in women. The highest proportion of severe HFMD cases was among children 0–4 years of age.

Fig. 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 Hainan Island. The proportion of severe HFMD cases showed a similar geographic pattern to that of the incidence of severe HFMD.

Fig. 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 were found in high-high and high-low townships identified by Local Moran I. Low-risk clusters were low-low and low-high townships identified by Local Moran I.

Fig. 3 shows the population density between high- and low-risk clusters for severe HFMD incidence in township level. Fig. 4 shows the population density between high- and low-risk clusters for severe HFMD population in township level.

Spatial autocorrelation statistic: Fig. 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: Fig. 3 and 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 with respect to incidence of severe HFMD ($U = 798, p = 0.067$); however, density was significantly higher in high-risk clusters for the populations of severe HFMD than in 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 an infectious diseases that is transmissible from human to human, and higher population density can result in a higher frequency of contact between individuals and subsequent infection. In previous studies, the authors have compared the biological and behavioral characteristics of children with severe and non-severe HFMD on Hainan Island (27). We showed that in addition to human enterovirus 71 infection and a peak body temperature $>39^\circ C$, individual characteristics associated with the development of severe HFMD that are generally shared by children from households with low socioeconomic status in rural communities (e.g., not being breastfed during the first 6 months of life, being cared for by grandparents, and having caregivers who were less educated). Therefore, we assumed that the proportion of severe HFMD would be higher in rural than in urban areas, and thus, higher in less-densely populated areas than in more-densely populated ones. However, the data in the present study 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 within a single township in China. Typically, hospitals, schools, markets, and residential areas are located near the township government offices, whereas farming villages are scattered throughout the entire township area. Therefore, townships have both rural and non-rural characteristics, irrespective of the population density (with the exception of the provincial capital, where farming villages have been transformed into urban residential areas).

To date, there has been no evidence that can be used to explain why more severe cases developed from general HFMD cases in densely populated townships of Hainan Island. We speculate that a higher proportion of severe HFMD was diagnosed in densely populated townships. In low-risk clusters (low population density) of Hainan Island, medical facilities are of lower quality than those in densely populated areas; therefore, severe HFMD cases are more likely to remain undiagnosed. This should be considered in future analyses of the CSDC database; stratification by township population density is recommended for studies of the risk factors for severe HFMD.

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

The present study has some limitations. HFMD cases were obtained from the CSDC database, which consists of case reports of HFMD complied from hospitals/clinics in China. It is likely that some individuals with mild HFMD did not visit a hospital or clinic, which would result in underestimation of the number of mild HFMD cases in the dataset. In addition, since the age-specific population by township was unavailable in the Chinese census, we could not adjust for age in the spatial statistics model.

In conclusion, spatial clustering analysis of HFMD cases in the CSDC database between January 2009 and December 2013 on Hainan Island, China, revealed high-risk clusters for the incidence and proportion of severe HFMD cases. We speculate 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 Island.

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**