

Surveillance of Hand, Foot, and Mouth Disease in Mainland China (2008–2009)

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Abstract

Objective Since HFMD was designated as a class C communicable disease in May 2008, 18 months surveillance data have been accumulated to December 2009. This article was to describe the distribution of HFMD for age, sex, area, and time between 2008 and 2009, to reveal the characteristics of the epidemic.

Methods We analyzed weekly reported cases of HFMD from May 2008 to December 2009, and presented data on the distribution of age, sex, area and time. A discrete Poisson model was used to detect spatial–temporal clusters of HFMD.

Results More than 1 065 000 cases of HFMD were reported in Mainland China from May 2008 to December 2009 (total incidence: 12.47 per 10 000). Male incidence was higher than female for all ages and 91.9% of patients were <5 years old. The incidence was highest in Beijing, Shanghai, Zhejiang and Hainan. The highest peak of HFMD cases was in April and the number of cases remained high from April to August. The spatial–temporal distribution detected four clusters.

Conclusion Children <5 years old were susceptible to HFMD and we should be aware of their vulnerability. The incidence was higher in urban than rural areas, and an annual pandemic usually starts in April.

Key words: Hand, foot, and mouth disease; Mainland China; Surveillance; Epidemiologic features

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INTRODUCTION

Hand, foot, and mouth disease (HFMD) is a common febrile illness of early childhood, which is characterized by 3-4 days of fever and the development of a vesicular exanthem on the buccal mucosa, gums, and palate and a papulovesicular exanthem on the hands, feet and buttocks; some patients may suffer fatal complications such as myocarditis, pulmonary edema and aseptic meningitis. HFMD is caused by acute enterovirus infection, particularly viruses belonging to the human enterovirus A family^[1]. The most common causes are coxsackievirus A16 (COX A16)

and enterovirus 71 (EV71). Sometimes, HFMD may be caused by other enteroviruses, but most patients with fatal complications are infected by EV71.

In 1957, this disease was first reported in New Zealand along with the isolation of coxsackievirus as the pathogen^[2]. This emerging infectious disease was then named as HFMD according to its typical symptoms in 1959. Epidemics of HFMD have been reported in most parts of the world, but the recent epidemics have tended to be located in Asia. Several widespread epidemics have been recorded in Japan since 1970, in which EV71 and COX A16 were the main pathogens^[3]. An epidemic of 2 628 cases with an average age of 18 months was reported in

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Malaysia from April to August 1997^[4]. There were 29 deaths and 17 of these cases experienced rapid progression of pulmonary edema, and the major pathogen of this epidemic was EV71. During the epidemic of HFMD in Singapore from 2006 to 2007, the incidence rate reached 6% in children under 4 years old^[5].

In China, HFMD was first reported in Shanghai in 1981, and since then, many papers have reported the incidence of HFMD in Beijing, Hebei, Tianjin, Fujian, Jilin, Shandong, Hubei, Xining, and Guangdong provinces in 1980s^[6]. During the period of 1983 to 1997, three major epidemics broke out in Dandong, Wuhan and Hong Kong. The 1998 HFMD epidemic in Taiwan was the most serious one in China, with a total of 129 106 cases between July and October. There were 405 severe cases and 78 deaths, with most patients being children aged <5 years old. The most common complications were encephalitis, aseptic meningitis, pulmonary edema or pulmonary hemorrhage, acute flaccid paralysis, and myocarditis^[7].

Recently, nationwide HFMD epidemics have become a significant public health concern in China. In 2007, a total of 83 344 HFMD cases and 17 deaths were reported; nearly 40 000 cases were located in Shandong province and >10 000 cases were confirmed in large cities such as Beijing and Shanghai. During the period of March to April 2008, a large epidemic with a total number of 1 884 HFMD cases and 20 deaths broke out in Fuyang city, Anhui province^[8]. Children under 5 years of age comprised 94% of cases. After this serious HFMD pandemic, the Ministry of Health of the People's Republic of China upgraded HFMD to a Class C communicable disease on May 2, 2008. Since then, HFMD has been included into the Communicable Disease Surveillance Network.

The purpose of this study was to describe the distribution of HFMD for age, sex, area, and time between 2008 and 2009, to reveal the characteristics of the epidemic. In addition, the question about the association of population density with risk of HFMD was addressed.

METHODS

Data Collection

Data of HFMD in Mainland China (excluding Hong Kong, Macao, and Taiwan) from May 2008 to December 2009 were obtained from the weekly report of HFMD compiled and published by the National Center for Public Health Surveillance and

Information Services, China CDC. The diagnosis of cases reported to the system was based on the clinical criteria set by the Hand, Foot and Mouth Disease Control and Prevention Guide published by the Chinese Ministry of Health in 2008^[9], in which, patients with the following symptoms were defined as having HFMD: acute onset with fever, maculopapules and herpes-like lesions on the palms or soles, with rashes also on the hips or knees; inflammatory flushing around the rashes and little fluid in the blisters; sparse herpes-like lesion on oral mucosa, which produces obvious pain. Some infants may have symptoms such as cough, crying, appetite loss, nausea, vomiting, and headache.

Demographic data were obtained from the China Statistical Yearbook 2009 to calculate the annual incidence rates of HFMD for each province.

Data Analysis

The date of onset was used to establish the occurrence of cases in this study. According to weekly national communicable disease information, months were divided into four weeks as follows: week 1, days 1-7; week 2, days 8-14; week 3, days 15-21; and week 4, day 22 to the last day of the month. The frequencies of HFMD were summarized weekly, monthly and annually by geographic area, sex and age. The present study did not analyze mortality, due to small number of fatal cases.

There are 31 geographic areas in Mainland China. Children <5 years old were most susceptible to this disease, therefore, cases were divided into five age groups: 0-, 1-, 2-, 3-, and 5-. The incidence rate was the number of new emerged cases of HFMD in the population during a defined period of time (for example, 1 year), and it was expressed as the number of cases per 10 000 population, and calculated for each geographic area or age group. After the annual incidence rate of each province was calculated, the correlation between the incidence rate and population density was assessed by Spearman correlation coefficient.

Retrospective space-time analysis based on a discrete Poisson model was used to find spatial-temporal clusters of HFMD^[10]. Two-dimensional space-temporal scanning windows were first created in the map; the scan window was cylindrical with a circular geographical base and with height corresponding to time. The base and the height of the windows underwent dynamic changes to detect possible spatial-temporal clusters; the center of the base changed according to geographical area, the radius

of the base changed according to the population range of the area (from zero to the pre-set percentage of the total population), and the height changed according to the defined time interval. The difference in the incidence inside and outside the window was then calculated by the log likelihood ratio (LLR)

$$LLR = \log(c/n)^c [(C-c)/(C-n)]^{(C-c)}$$

In the equation, C denotes the total number of cases; c denotes the number of actual cases in the window; and n denotes the number of expected cases in the window.

The scan window with the largest LLR value was defined as the most likely cluster; other scan windows for which the LLR value was statistically significant were defined as secondary clusters. The relative risk (RR) and the P value were calculated for each cluster. RR measured the risk of HFMD in this cluster was how many times as much as the scan window which had the same length of time period and the same radius of circular geographical base calculated by the total time dimension and spatial dimension.

SatScan 8.2 software was used to perform the retrospective space-time analysis, the spatial units were the 31 geographic areas of Mainland China, the time units were the 20 months from May 2008 to December 2009, the largest radius was 20% of the total population, the Monte Carlo simulation times were 999, and RR was considered statistically significant if the P value of LLR was <0.05 .

RESULTS

Between May 2008 and December 2009, $>1\ 065\ 000$ cases of HFMD were reported to the Communicable Disease Surveillance Network based at China CDC. The total incidence rate was 12.47 per 10 000; the male incidence rate (15.34 per 10 000) was higher than the female rate (9.45 per 10 000). The proportion of children <5 years old was 91.9% and the proportion of male patients was 63.1%.

The number of cases reported from May to December in 2008 was about 500 000, with an incidence rate of 3.74 per 10 000. In the same period in 2009, the number was around 876 000, with an incidence rate of 6.60 per 10 000. The total number of HFMD cases in 2009 was >1.1 million and the annual incidence rate was 8.73 per 10 000; the annual incidence rate of HFMD was 1.27% in children <5 years old in 2009.

Distribution of HFMD in different Populations

The incidence rates from May to December in 2008 are shown in Figure 1. The annual incidence rates in 2009 are described in Figure 2. Both incidence rates are stratified by age and sex.

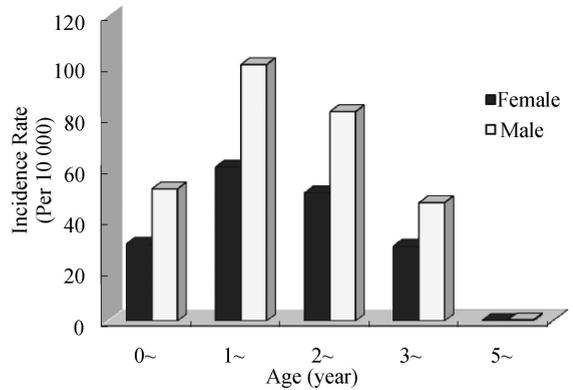


Figure 1. Incidence rates of HFMD during May to December in 2008, by age and sex.

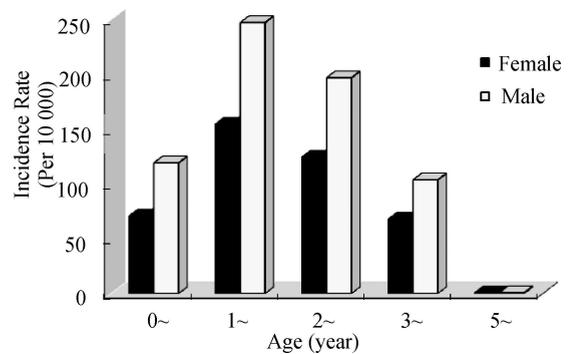


Figure 2. Annual incidence rates of HFMD in 2009, by age and sex.

The age distribution of HFMD in 2009 was similar to that in 2008. The incidence in male subjects was higher than in female subjects in all age groups, and children <5 years old were most susceptible to HFMD. The annual incidence rate in the population >5 years old was <1 per 10 000.

Distribution of HFMD by Area

There are 31 geographic areas in Mainland China according to administrative divisions. The incidence rates in each area in 2008 and 2009 are presented in Figures 3 and 4, respectively. During May to December 2008, Beijing, Shanghai and Hainan had the highest incidence rates (>8 per 10 000), followed by Tianjin and Zhejiang (>6 per 10,000). In 2009, Beijing, Shanghai, Hainan, and Zhejiang were again among the six areas with the

highest annual incidence rates (>13 per 10 000); the other two areas were Heibei and Shandong. In the West of China, the incidence rates maintained a relatively low level between 2008 and 2009. We found that the geographical distribution of HFMD was similar to the population density distribution in the same period. The Spearman correlation coefficient between the 2009 annual incidence rate and population density in 2008 in 31 provinces was calculated and moderate correlation was found ($r_s = 0.568, P = 0.001$).

Children <5 years old are more susceptible to HFMD than other age groups. Figure 5 shows the annual HFMD incidence rates of this population in different areas in 2009. The distribution of annual HFMD incidence rates of children <5 years old was similar to that of the total population (Figure 4). The incidence rates of HFMD in Beijing, Shandong, Shanghai, and Zhejiang were higher than those in other areas (>200 per 10 000), and the incidence rates in the east were higher than in the west.

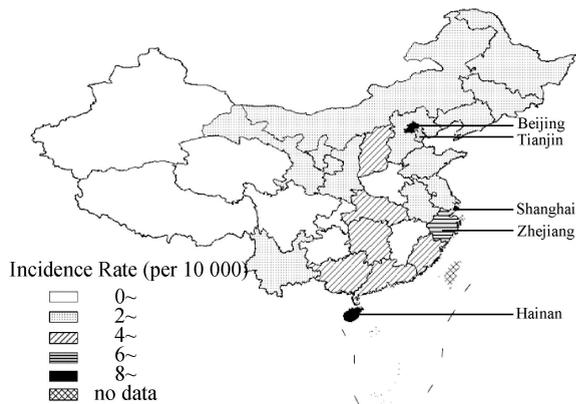


Figure 3. Incidence rates of HFMD from May to December in 2008 by area.

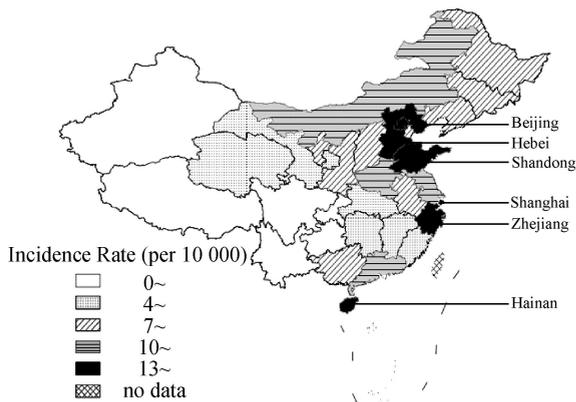


Figure 4. Annual incidence rates of HFMD in the year 2009 by area.

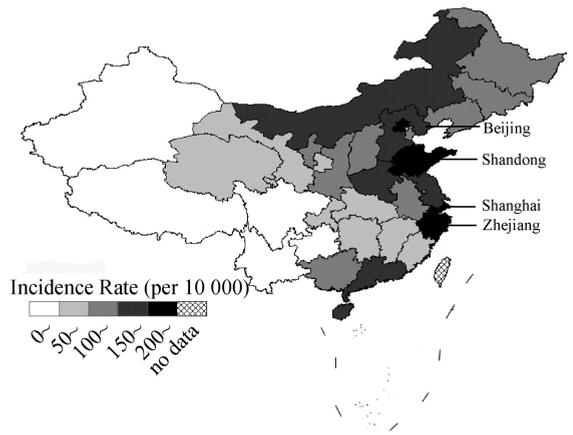


Figure 5. Annual HFMD incidence rates of children <5 years old in 2009 by area.

Distribution of HFMD by Time

Monthly reported cases are summarized in Figure 6. The highest peak of HFMD cases appeared in April and the number of cases remained high until August. From August to the following February, the incidence of HFMD was at a low level, but starting from March, the number of cases increased significantly.

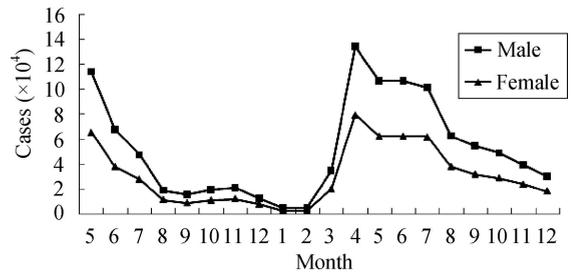


Figure 6. Longitudinal time trend of HFMD from May 2008 to December 2009.

A slight difference is shown in Figure 6 between 2008 and 2009. In 2008, the number of HFMD cases quickly dropped to a low level (<20 000 in each month) after July, while in 2009, the number of HFMD cases reduced slowly from August to December, with a higher incidence as compared to the same period in 2008.

To explore the data in more detail, the figure was drawn by weekly reported cases (Figure 7). The number of weekly reported cases fluctuated and an obvious peak was noted in almost every final week of each month (e.g. weeks 16, 20, and 24 in 2009).

Spatial-temporal Cluster Analysis of HFMD

Four spatial-temporal clusters could be found in Mainland China from May 2008 to December 2009. The most likely cluster was located in North China, which included seven geographic areas (Neimenggu, Shanxi, Hebei, Beijing, Tianjin, Ningxia, and Shandong) and the time period was April to August 2009. The latitude and longitude coordinates of the cluster center were 40.82N, 111.65E; the radius of the cluster was 655.33 km; the average annual incidence rate was 26.2 per 10 000; and RR was 3.97. Secondary cluster 1 included Shanxi and Henan; the time period was April to May 2009; the latitude and longitude coordinates of the cluster center were 34.27N, 108.95E; the radius of the cluster was 433.86 km; the average annual incidence rate was 32.4 per 10 000; and the RR was 4.42. Secondary cluster 2 included Jiangsu, Anhui, Zhejiang, and Shanghai; the time period was April to November 2009; the latitude and longitude coordinates of the cluster center were 32.05N, 118.78E; the radius of the cluster was 367.03 km; the average annual incidence rate was 14.4 per 10 000; and the RR was 2.03. Secondary cluster 3 included Guangdong, Hainan, Guangxi and Hunan; the time period was May 2008; the latitude and longitude coordinates of the cluster center were 23.17N, 113.23E; the radius of the cluster was 561.65 km; the average annual incidence rate was 28.3 per 10 000; and the RR was 3.82. More details are listed in Figure 8 and Table 1.

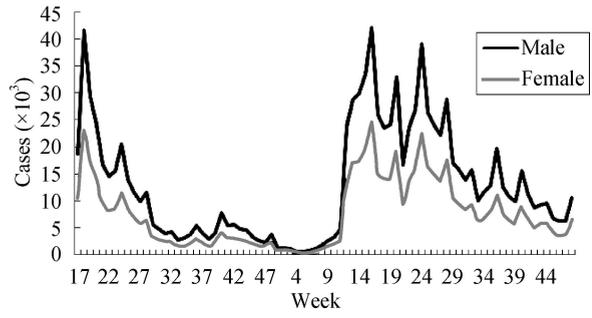


Figure 7. Longitudinal time trend of HFMD from week 17 in 2008 to week 48 in 2009.

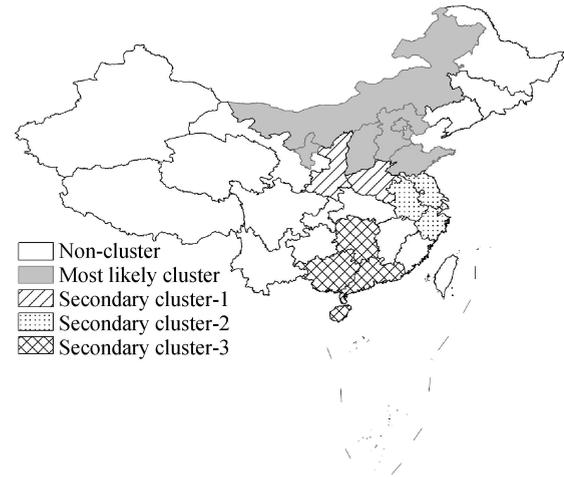


Figure 8. Spatial-temporal clusters distribution of HFMD in Mainland China, May 2008 to December 2009.

Table 1. Spatial-temporal Cluster Analysis Results of HFMD (Provincial Level, May 2008 to December 2009)

Clusters	TimePeriod	Provinces	Predicted cases	Actual cases	LLR	RR	P
Most likely cluster	2009/4/1 - 2009/8/31	Neimenggu, Shanxi, Hebei, Beijing, Tianjin, Ningxia, Shandong	81 595	282 530	163 374	3.97	0.001
Secondary cluster-1	2009/4/1 - 2009/5/31	Shanxi, Henan	16 693	71 370	49 938	4.42	0.001
Secondary cluster-2	2009/4/1 - 2009/11/30	Jiangsu, Anhui, Zhejiang, Shanghai	105 392	200 583	36 876	2.03	0.001
Secondary cluster-3	2008/5/1 - 2008/5/31	Guangdong, Hainan, Guangxi, Hunan	13 890	51 897	30 840	3.82	0.001

In the above analysis, 31 provinces were used as the spatial unit to detect spatial-temporal clusters of HFMD from a macro view. To explore in more detail, 2 951 districts of Mainland China were used as the spatial unit in the following analysis.

Four spatial-temporal clusters were found using the spatial unit of 2 951 districts in Mainland China from May 2008 to December 2009. The most likely cluster included 495 districts (located in Beijing,

Tianjin, Hebei, Shanxi, Shandong, Neimeng, Jiangsu, Henan, and Anhui) and the time period was March to August 2009; the latitude and longitude coordinates of the cluster center were 37.66N, 116.19E; the radius of the cluster was 413.48 km; the average annual incidence rate was 26.9 per 10 000; and the RR was 3.49. Secondary cluster 1 included 200 districts (located in Shanghai, Jiangsu, Zhejiang, Anhui, and Jiangxi) and the time period

was March 27 to December 24, 2009; the latitude and longitude coordinates of the cluster center were 30.01N, 120.61E; the radius of the cluster was 288.54 km; the average annual incidence rate was 17.2 per 10 000; and the RR was 2.35. Secondary cluster 2 included 466 districts (located in Fujian, Jiangxi, Hunan, Guangdong, Guangxi, Hainan, Chongqing, Guizhou, and Yunnan) and the time period was May 1 to June 5, 2008; the latitude and longitude coordinates of the cluster center were

24.51N, 111.20E; the radius of the cluster was 570.79 km; the average annual incidence rate was 27.6 per 10 000; and the RR was 3.69. Secondary cluster 3 only included one district (Yuzhong district of Chongqing) and the time period was March 20 –to July 16, 2009; the latitude and longitude coordinates of the cluster center were 29.55N, 106.53E; the average annual incidence rate was 124.2 per 10 000; and the RR was 16.14. More results are presented in Table 2.

Table 2. Spatial-temporal Cluster Analysis Results of HFMD (District Level, May 2008 to December 2009)

Clusters	Time Period	Provinces (Number of Districts)	Predicted Cases	Actual Cases	LLR	RR
Most likely cluster	2009/3/20 - 2009/8/20	Beijing (18), Tianjin (18), Hebei (168), Shanxi (76), Shandong (129), Henan (71), Jiangsu (10), Anhui (4), Neimenggu (1)	82 226	286 949	167 920	0.001
Secondary cluster-1	2009/3/27 - 2009/12/24	Shanghai (19), Jiangsu (61), Zhejiang (90), Anhui (28), Jiangxi (2)	65 587	146 200	38 670	0.001
Secondary cluster-2	2008/5/1 - 2008/6/5	Fujian (3), Jiangxi (43), Hunan (120), Guangdong (118), Guangxi (108), Hainan (8), Chongqing (2), Guizhou (62), Yunnan (1)	18 689	67 003	37 959	0.001
Secondary cluster-3	2009/3/20 - 2009/7/16	Chongqing (1) "Yuzhong district of Chongqing"	160	2 580	4 754	0.001

DISCUSSION

In Mainland China, there was no systematic surveillance of HFMD before 2008, and most reports of the HFMD epidemics were from regions and for a short-term^[11-12]. Since the Chinese Ministry of Health designated HFMD as a class C communicable disease in May 2008, 18 months surveillance data had been accumulated to December 2009. These data were collected by national network reporting systems for communicable diseases. A recent data quality inspection report has demonstrated that data collected by this system are of good quality, apart from the following problems^[13]. First, the onset date of HFMD may be inaccurate because this information was retrospectively collected when patients were asked by doctors. Second, some mildly affected patients may not go to any medical institution, so they were not reported to the system. Lastly, HFMD-related policies may enhance the importance of reporting HFMD in medical institutions and lead to a minor increase in the number of reported cases. However, overall, the

data collected in this system were of good quality and the epidemic distributions of HFMD can be described objectively and comprehensively.

Consistent with previous reports in other countries^[5,14-16], most HFMD patients in Mainland China were young children (<5 years old), with the peak incidence occurring at <1 year of age. The incidence rate in male subjects was higher than in female subjects; a possible reason is that boys might be more restless and thus have more opportunities to contract the disease.

Previous reports have pointed out that the number of HFMD cases in rural areas is greater than in urban areas^[17-18]; this was different from our findings that showed that economically developed areas, such as Beijing, Tianjin, Shanghai, and Zhejiang, had higher incidence rates than underdeveloped areas. Our results also found that higher population density resulted in higher HFMD incidence. One possible reason is that most children in urban areas in Mainland China are sent to kindergartens, while children in rural areas usually stay at their own home and have few opportunities to gather with other children. Another possible

reason is that the diagnostic capacity of HFMD may vary from urban to rural areas, and the accuracy, completeness and timeliness of the reporting are different between urban and rural areas. This makes the disease surveillance system in urban areas more effective than that in rural areas. These factors could mean that it is not possible to compare the results between urban and rural areas.

The longitudinal time trend of HFMD in Mainland China during May 2008 to December 2009 was similar to that in the epidemic in Taiwan in 1998^[17,19]. The major pandemic wave of HFMD in Taiwan 1998 started at the beginning of April and lasted to the end of July, with a peak of 15 758 cases during the week beginning June 7, while in Mainland China, the major pandemic started in April and finished in August.

Urashima et al.^[18] used seasonal models to simulate the annual fluctuation of HFMD in Tokyo, Japan, and pointed out that warmer climate conditions could lead to an increased number of HFMD cases. This was consistent with our findings, because March is the beginning of spring in Mainland China and the weather starts to get warmer in April; June, July, and August are the hottest months of the entire year. The annual pandemic of HFMD also started in early April and ended in August. Besides, Hainan province is the southernmost area of China and has the highest average temperature, which may explain its high incidence of HFMD.

When cases were summarized by week, an obvious peak could be detected in almost every final week of each month (e.g. weeks 16, 20, and 24 in 2009). This phenomenon may be due to two reasons: first, these weeks were not natural weeks and the last week of each month contained >7 days, running from day 22 to the end of the month; second, at the end of each month, many primary health care institutions confirm the quality of their infectious disease reporting; check if they failed to report any cases over the whole month, and enter them into the system in the final week of the month.

Spatial-temporal cluster analysis is a method that considers both spatial and temporal distribution at the same time, detects possible clusters, and calculates RR. The result was consistent with previous analyses, which indicated that April is the most important time period in the prevention of HFMD, and North, East and South China should be more aware of the epidemic.

In the analysis of spatial-temporal clusters of HFMD in Mainland China, the results at district level

were similar to those at provincial level. Long-term epidemic trends of HFMD were detected in North China (March to August 2009) and in middle and lower regions of the Yangtze River (April to December 2009). Middle and South China experienced a short outbreak of HFMD in May 2008 (secondary cluster 3 at the provincial level and secondary cluster 2 at the district level). A large number of HFMD cases were reported in Yuzhong district of Chongqing during March 20 to July 16, 2009.

Secondary cluster 2 in the analysis at the provincial level and secondary cluster 1 in the analysis at district level had a long time period of 9 months. This seemed inconsistent with the longitudinal time trend of HFMD shown in Figure 6, which indicated that the number of HFMD cases decreased dramatically from August. Figure 9 presents the longitudinal time trend of HFMD for only the four areas (Jiangsu, Anhui, Zhejiang, and Shanghai) included in secondary cluster 2. Another small epidemic peak was detected from September to December in the four provinces, so the time period of secondary cluster 2 was reasonable.

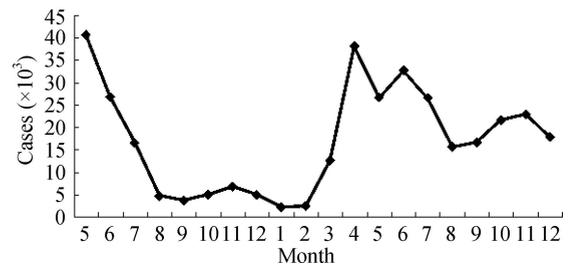


Figure 9. Longitudinal time trend of HFMD from May 2008 to December 2009 in Jiangsu, Anhui, Zhejiang, and Shanghai.

In April 2010, the number of reported HFMD cases increased dramatically in many parts of Mainland China compared to the same period in 2009, and the peak incidence seemed to be in concordance with that in previous years. The Chinese Ministry of Health issued the 2010 version of their HFMD diagnosis and treatment guidelines to guide the health sectors and residents to prevent and deal with this disease. With the experience of the 2007-2009 pandemic in China, many effective measures have been put in place in time to ease the epidemic wave.

In conclusion, the epidemic of HFMD in Mainland China tended to be more severe in 2009 than in 2008, in terms of incidence rates. There should be greater awareness about HFMD in

children <5 years old. The distribution of HFMD was not random and spatial-temporal clusters were detected. The incidence rate in urban areas was greater than that in rural areas. The annual pandemic usually started in April, thus the medical institutions and residents should be fully prepared to ease the pandemic.

This article mainly focused on the description of the prevalence of HFMD, found some phenomena and put forward possible causes of these phenomena, more researches should be carried out in the future to verify these assumptions.

Epidemiological knowledge of HFMD should allow public health personnel to predict outbreaks of the disease and implement effective interventions to reduce the burden of disease.

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