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An epidemiological analysis of the Beijing 2008 Hand-Foot-Mouth epidemic

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This paper presents an empirical analysis of the epidemiological data concerning the 18445 HFMD-infected cases in Beijing in 2008. The main findings are as follows. (i) Seasonal variations in incidence were observed, with a peak observed during the summer season, especially in May. Male patients outnumber female patients by 1.57:1. (ii) Most cases occurred in children 4 years old or younger. Outperforming Weibull distribution and Gamma distribution as to model fitness when analyzing patient ages, log-normal distribution indicates that the estimated mean age is 3.4 years. (iii) The age distribution seems to indicate cyclic peaks with roughly one-year intervals. (iv) Correlation analyses (ρ = 0.9864) show that time of birth in different months has an impact on the chance of being infected by HFMD. Birth month seems to present a high risk factor on infants and young children. (v) The morbidity rate is 132.7/100000 during the HFMD epidemic in Beijing in 2008. The morbidity map shows that the risks of HFMD infection in areas close to the city center and suburbans are much lower than those in the urban-rural transition zones. Spatial risks inferred from the morbidity map demonstrate a clear circular pattern. (vi) The prevention and control measures taken by the public health departments seem to be effective during the summer season, resulting in the early ending of the epidemic (one month earlier than the natural season) and reduced outbreak size.

Hand-Foot-Mouth disease, epidemiological analysis, spread mechanism, risk factor, morbidity map, Beijing

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Hand-Foot-Mouth disease (HFMD) is a common infection caused by the intestinal virus, Entrovirus 71. The main transmission route for Enterovirus 71 is via respiratory droplets, contact with fluid in the blisters or with infected faeces [1,2]. Since the first HFMD case was reported in New Zealand in 1957, subsequent outbreaks have been reported worldwide. In mainland China, the first reported HFMD cases occurred in Shanghai in 1981. Since then, HFMD cases have been reported in Beijing, Hebei Province, Tianjin, Fujian Province, Jilin Province, Shandong Province, Hubei Province, Qinghai Province and Guangdong Province [3]. Nowadays, the HFMD epidemics have affected most provinces, cities, and regions in China, posing a threat to a large population [4].

Over the past few decades, many scientists around the world have conducted HFMD-related research from the point of view of molecular biology [5–9], clinical medicine [10] and epidemiology [1,6,11]. Chinese researchers have also contributed to the HFMD literature. Dong et al. [7] studied the evolution and genetic variability with worldwide Enterovirus 71 strains isolated from 1970 to 2004. Zhu et al. [12] conducted a molecular epidemiological analysis of Echovirus 19 isolated from an HFMD outbreak in Shandong Province. Chen et al. [2] analyzed epidemiologic features of the Taiwan HFMD epidemic.

Molecular biology and pathology are essential to a fundamental understanding of pathogenesis of HFMD for vaccination and treatment purposes. Although some progress has been made in these areas, much work remains before effective

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treatment or vaccine approaches can be developed. With an effective treatment plan or vaccine absent, public health response measures are now restricted to case management (e.g., isolating known cases and quarantining close contacts) and proactive monitoring of high-risk groups. As such, from a practical standpoint, it is critical to examine various epidemiological features of the HFMD epidemic, identify the spatio-temporal evolutionary patterns, and study the spread mechanism. Such epidemiological studies aim to provide the scientific basis for public health response to and control measures for the HFMD epidemic.

In recent years, there have been some epidemiological studies based on data from outbreaks in Pingyi County [13], Fuyang City [14], Guangdong Province [15], Xintai City [16], Beijing City [17], Jinan City [18], Yun County [19], Zhoucheng City [20], Pudong Region in Shanghai [21], and Shanxi Province [22] in China. From these studies, one can easily summarize common features of the HFMD epidemic: (i) The infection occurs mainly in children under 4 years old; (ii) the infection occurs mostly in the summer; and (iii) the number of male child patients significantly exceeds that of female child patients. Issues of significant practical relevance such as spatio-temporal evolutionary patterns of HFMD, the spread mechanism, and risk factors, are currently under-studied. This paper is aimed at bridging this important research gap.

The remainder of this paper is structured as follows. We begin with a brief introduction to the epidemiological survey data used in our study, which consists of 18445 HFMD-infected cases. We then report an empirical analysis of this dataset using descriptive epidemiological methods and spatial statistical methods. Furthermore, we discuss the inherent spread mechanisms of HFMD derived from our epidemiological analysis.

1 Epidemiological survey data

The data used in this paper were extracted from an epidemiological survey of 18445 HFMD-infected cases reported to the surveillance systems at the Beijing Centers for Diseases Control and Prevention. The onset dates range from December 24, 2007 to December 31, 2008. These patients lived in all 16 districts and 2 counties of Beijing (Figure 1). Most patients are local Beijing residents with a few visiting Beijing from other places for treatment.

2 A time-series analysis

Figure 2(a) shows a plot of weekly counts of new HFMD-infected cases and the patients' average ages during the Beijing 2008 HFMD epidemic. We observe a seasonal variation with incidence peaked during the summer season. More than 2000 new cases occurred every week in mid-May. The average age is about 3 years with little change during the entire year. Figure 2(a) also shows an abnormality in average patient age in the starting weeks, which is due to the small sample size as very few HFMD cased occurred in the winter.

From Figure 2(a), we note two peaks occurring during the summer season, the first peak appearing in mid-May, and the second around the end of June. In 2008, two major events, "Beijing 2008 Olympic Games" and "5.12 Wenchuan Earthquake", had a significant impact on public health and response in China. During these events, the government had taken extraordinary control measures, which may have contributed to the abnormal trend against normal seasonal features of the HFMD epidemic from mid-May to the end of June. The impact of these measures is worth further exploration.

This paper presents a dynamic model for the spread of HFMD in population. One popular epidemic model is the susceptible-exposed-infected-removed (SEIR) model. An SEIR model divides the population into 4 categories, the susceptible class S, the exposed class E, the infectious class I, and the removed class R, and uses ordinary differential

Figure 1 Beijing's districts and counties

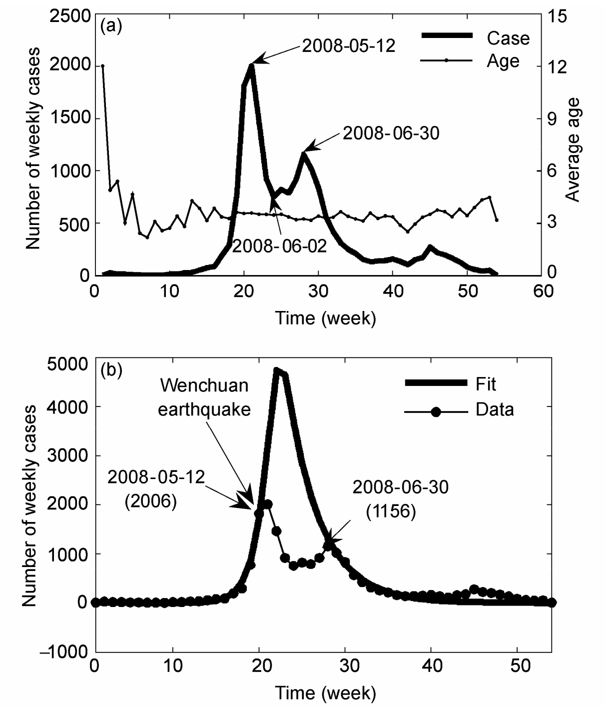

Figure 2 Time-series features of the Beijing 2008 HFMD epidemic. (a) Weekly reporting of new HFMD cases and the average patient age; (b) using a dynamic model to simulate the HFMD epidemic based on the observed data before 12 May and after 30 June.

equations to simulate the $S \rightarrow E \rightarrow I \rightarrow R$ dynamic process: When the outbreak of an infectious disease begins, an infected person is introduced in the susceptible individuals S. When there is an adequate contact of a susceptible with an infective so that disease transmission occurs, the susceptible enters the exposed class E of those in the latent period, who are infected but not yet infectious. After the latent period ends, the individual enters the class I of infectives, who are infectious in the sense that they are capable of transmitting the infection. When the infectious period ends, the individual enters the removed class R consisting of those with permanent infection-acquired immunity and death caused by disease.

We use logistic functions to represent seasonality of the HFMD epidemic. As the exposed individuals of HFMD are infectious, we have constructed an adoptive epidemic model for the HFMD epidemic as follows, $dS(t)/dt = -\beta(t)\,S(t)\,(I(t) + E(t))/N$, $dE(t)/dt = \beta(t)\,S(t)\,(I(t) + E(t))/N - \sigma E(t)$, $dI(t)/dt = \sigma E(t) - \gamma I(t)$, $dR(t)/dt = \gamma I(t)$, $\beta(t) = p_1 - p_2 + p_2/(1 + exp(p_3 \times (p_4 - t))) + p_2/(1 + \exp(p_5 \times (p_6 - t)))$, where $S(t)$ is the number of susceptibles at time t, $E(t)$ is the number of exposed persons at time t, $I(t)$ is the number of infectives at time t, $R(t)$ is the number of removed persons at time t, $\beta(t)$ is the infection rate at time t, σ is the conversion rate, γ is the transition rate, and p_1, p_2, p_3, p_4, p_5 and p_6 are the control parameters of the two logistic functions.

From Figure 2(a), we observe that the HFMD epidemic demonstrates patterns not consistent with expected seasonal patterns for the period from 12 May to 30 June. Based on this observation, we simulated the natural trends without intervention based on observed data before 12 May and after 30 June using the above epidemic model. The results are shown in Figure 2(b). Comparing the predictions from the model with the real cases, we note that (a) the actual epidemic ended one month earlier than what the model predicts, and (b) the size of the epidemic during the summer season was significantly reduced. We strongly suspect that these positive results are due to intensive public health control measures during the summer season of 2008.

3 Patient population

3.1 Gender and occupation of patients

Among all 18445 infected cases, 11262 of them involve male patients, and 7193 female. The male/female ratio of HFMD patients is 1.57:1, which is statistically significant ($P<0.05$).

Most patients are diasporas or stay in kindergartens or nursery schools. The number of diaspora children is 10078 and the number of patients in kindergartens or nursery schools is 7006, representing 54.64% and 37.98% of all the patients. The remaining 6.57% of the patients were students in elementary schools.

3.2 Age distribution

Figure 3 shows three age-related distributions of the HFMD-infected patients in Beijing in 2008. We can conclude that the patient age lies mainly in the range from 1 to 4. There are no significant differences in the age distribution between the male and female patients.

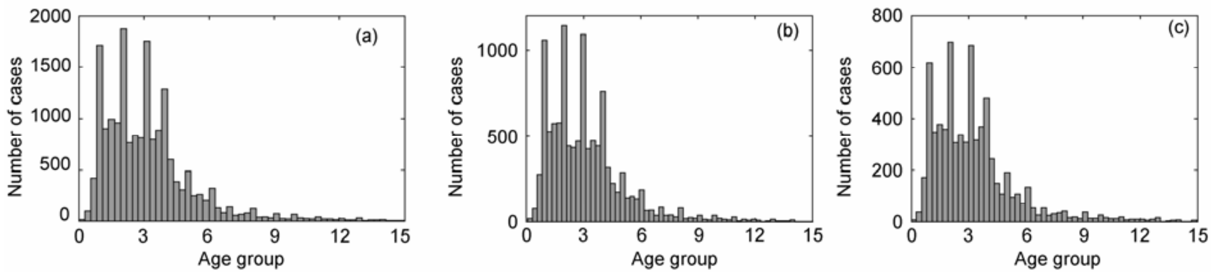

Figure 3 Age distribution of the HFMD-infected patients in Beijing in 2008. (a) All patients; (b) male patients; (c) female patients.

From Figure 3, to our surprise, we found that some abnormal high-frequency components occurred with some periodic patterns. To better illustrate this phenomenon, we further analyzed the characteristics of these high-frequency components among the patients under 15 years of age using following approach: (i) Divide the HFMD-infected patients into different groups based on age, where the step size is 1/10 year. We use a_i (i = 1, 2, 3, …, 60) to represent the group i with age range $[(i-1)/10, i/10]$; (ii) calculate the number n_i of the HFMD-infected patients whose ages belongs to group i; (iii) calculation a smoothened version of a_i as $fn_\mathrm{i} = (n_{i-2} + n_{i-1} + n_\mathrm{i} + n_{i+1} + n_{i+2})/5$ using a moving window centered on each group i; (iv) calculate the ratio fn_i/n_i (i = 3, 4, 5, …, 58); (v) plot fn_i (y-axis) against with a_i (x-axis), using a threshold value of 1.5 to determine whether a group is abnormal (Figure 4).

From Figure 4, we observe that these abnormalities follow a periodic pattern with the time gaps between them equal to one year. The age range of group i corresponding to these abnormalities are almost all round integers, e.g., 1, 2, 3, with deviations mostly less than 0.1.

3.3 Impact of birth time

Figure 5(a) shows that the HFMD cases in May, June and July are much more than other months from the point of

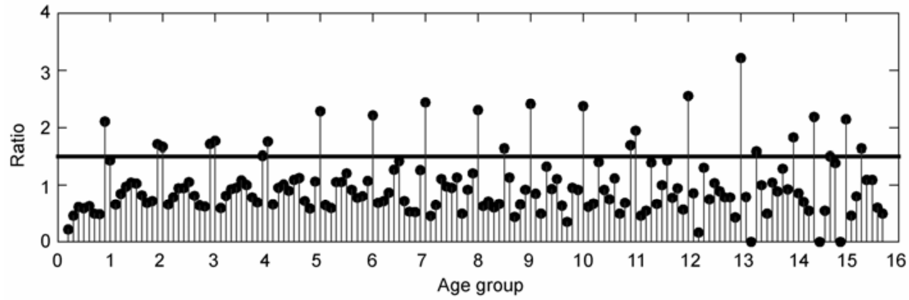

Figure 4 Periodic patterns of abnormal high-frequency components in age distribution of HFMD-infected patients

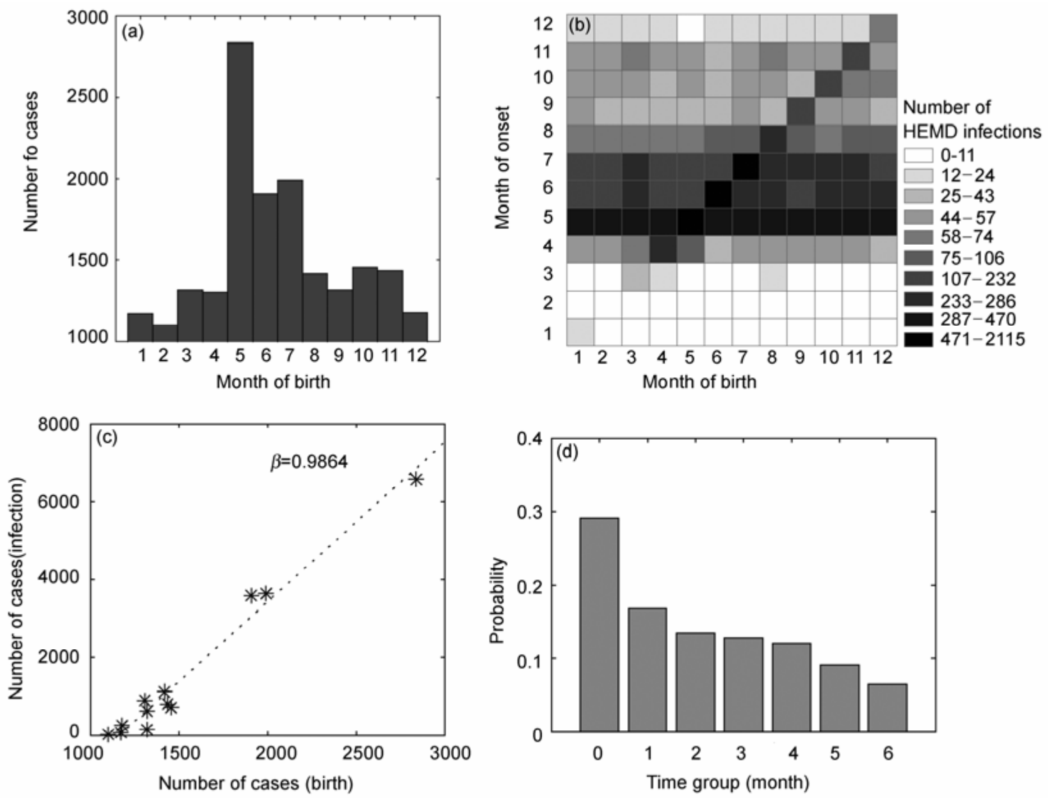

Figure 5 The impact of birth time on HFMD cases. (a) Number of HFMD cases in different months of birth; (b) HFMD cases in a 2-dimensional table: month of birth vs. month of onset; (c) correlation analysis of the HFMD cases in different months between birth and infection; (d) probabilities of being infected vs. the gap between month of birth and month of infection.

view of birth time. The highest number of HFMD patients per month is 2839, occurred in May, and the lowest is 1100, occurred in February. The ratio of cases between the highest and the lowest month is 2.58:1. The risk of been infected for children born in summer is higher than those born in other seasons. We have divided 18445 HFMD-infected persons into two categories in terms of time of birth and onset (both with month as the unit) and then constructed a two-dimensional space Z^2. Figure 5(b) shows the frequency of HFMD-infected incidents in this space Z^2 (Z = 1, 2, 3, …, 11, 12). We note that the risk of being infected from May to July is always high. In addition, the cells along the diagonal line are associated with larger numbers of cases than other cells in the same column. These observations seem to be indicative of some non-random patterns. Furthermore, the monthly new cases of HFMD-infected persons were compared to the monthly cases in terms of time of birth (Figure 5(c)). The correlation of the number of cases per month between birth and onset is 0.9864 (P<0.01), demonstrating a strong trend of co-variation. Figure 5(d) provides further evidence showing higher risks of infection when the gap between month of birth to month of infection is smaller.

We conclude that month of birth has an impact on the chance of being infected by HFMD in different months. HFMD poses a high risk for patients in birth month and the risk of infection decreases as the deviation from birth month increases. These observations help explain why periodic patterns of abnormal high-frequency components occur in age distribution (Figure 4) and why HFMD patients' birth times aggregate on the summer season (Figure 5(a)). From Figure 4, we observe that the periodic pattern identified does not change in the entire age distribution of 1–15.

3.4 Age optimal estimation

The sample or arithmetic mean is typically used to estimate an unknown expected value. However, it is not a robust statistic because it is greatly influenced by outliers. From Figure 3, we note that the age distribution of HFMD patients is skewed. The corresponding arithmetic mean is not a good descriptive measure to represent HFMD's average tendency. As such, we attempt to use the maximum likelihood method to estimate the expected average age of HFMD-infected persons in Beijing in 2008.

Three probability density functions, log-normal, weibull, and gamma distribution, were selected to fit the age distribution of 18445 HFMD-infected persons. Table 1 lists the optimal estimation results of the expected average age. Figure 6 plots both estimation and original data. The three probability density functions used are described in Appendix A.

Table 1 Estimated expected average age[a)]

Distribution	Sample	Maximum likelihood	a	b	Expected average	Variance
Log-normal	Total	−19150.40	0.9903	0.6834	3.4001	6.8817
	Male	−11433.01	0.9733	0.6678	3.3080	6.1505
	Female	−7694.60	1.0169	0.7064	3.5478	8.1432
Weibull	Total	−39909.27	3.8011	1.3307	3.4947	7.0342
	Male	−23748.44	3.6996	1.3921	3.3749	6.0297
	Female	−16067.15	3.9601	1.2641	3.6791	8.5871
Gamma	Total	−38742.55	2.1595	1.5991	3.4533	5.5222
	Male	−23042.16	2.3057	1.4480	3.3387	4.8345
	Female	−15636.90	1.9807	1.8342	3.6330	6.6638

a) Parameters a and b are discussed in Appendix A.

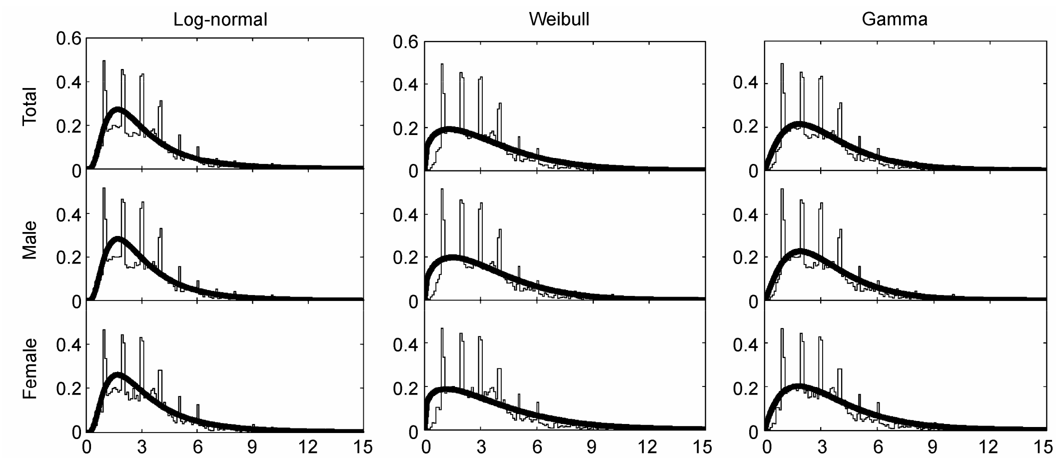

Figure 6 Comparison of original data and the estimation using 3 probability density functions.

From Table 1 and Figure 6, we conclude that log-normal distribution fits the age distribution better than the other two distributions. Using log-normal distribution, we estimate the expected average age of HFMD patients to be 3.4 years during the Beijing 2008 HFMD epidemic.

4 Spatial patterns of the HFMD epidemic

4.1 Spatial distribution of HFMD-infected cases

The epidemiological survey data used in our study contain information about patient gender, age, home address, work address, and onset of symptoms among others. This dataset enables us to analyze the spatial patterns and understand the complexity of spatial transmission risks. In this study, we have adopted home addresses as spatial locations of cases. Using name matching, we obtained the spatial data of 18445 HFMD-infected cases with spatial data analysis unit set to the street and township level (Figure 7(a)).

Using the Monte Carlo sampling method, we obtained the spatial distribution of the 18445 HFMD-infected cases, shown in Figure 7(b). The implementation of this sampling-based simulation is as follows. Given an administrative district as a polygon *P*, we first calculated the maximum horizontal extension length *W* and the maximum vertical extension height *H*. We then obtained a rectangle C. In the next step, we generated two random numbers n_x and n_y from uniform distributions $U[0, W]$ and $U[0, H]$, respectively, to obtain a point (n_x, n_y). Final, we identified whether point (n_x, n_y) lies in polygon *P*. If so, we took point (n_x, n_y) as effective (such as n_1 in Figure 8). Otherwise, point (n_x, n_y) was discarded (such as n_2 in Figure 8). We continue to repeat these steps until the number of all effective points reaches the number of HFMD-infected cases in the given administrative district.

Figure 7 shows a clear cluster of HFMD cases in the urban-rural transition zones. In fact, few patients lived in areas close to the city center or suburbans. One possible explanation is as follows. Although population density is rather high around the city center, these areas are in good conditions as to public health. In contrast to the city center, many suburban areas have poor public health conditions. But with low population density and good air quality and ventilation, HFMD transmissions are unlikely. However, in the urban-rural transition zones, there are many high risk factors of HFMD infection, including a large number of migrating population, high population density, and poor public health conditions. As such, the children in these areas are exposed to higher risk of HFMD infection.

4.2 Spatial analysis of morbidity

(i) Morbidity map. The morbidity rate refers to the frequency of new infected cases during a given time interval, which equals the number of new cases occurring during a given time interval divided by the population in the same period. The morbidity rate represents the prevalence of a disease. The average morbidity rate of the Beijing 2008 HFMD epidemic is about 132.7/100000. This rate is slightly higher than that of Fuyang City (89.35/100000) [14], Weihai City (92.28/100000) [23], Yantai City (98.95/100000) [24], Jinan City (101.74/100000) [18] and Yun County (9.38/100000) [19]. This elevated rate may be due to higher population density and higher population interaction frequencies.

Figure 9(a) shows the morbidity map with the spatial data analysis unit set to the street and township level. The numbers of HFMD cases within each unit were obtained by matching patients' addresses against the spatial units. The population data for each unit was estimated based on 9‰ population sample survey conducted in 2005 and reported population data from the Beijing Municipal Bureau of

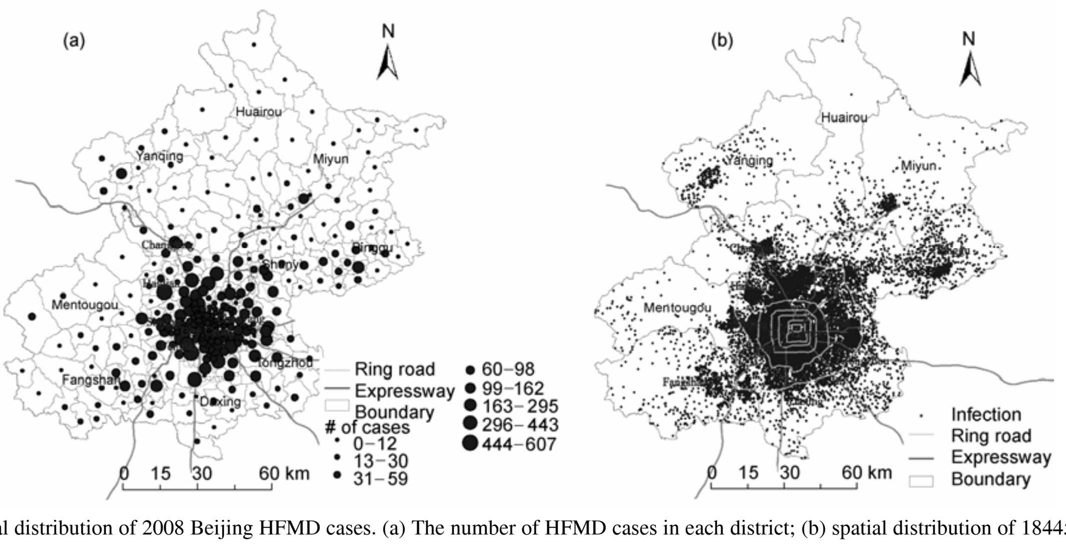

Figure 7 Spatial distribution of 2008 Beijing HFMD cases. (a) The number of HFMD cases in each district; (b) spatial distribution of 18445 HFMD infections.

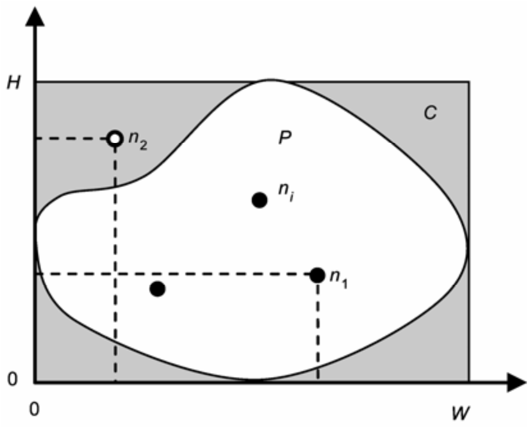

Figure 8 Monte Carlo sampling method.

Statistics in 2008 (Appendix B).

The morbidity map shows that the risks of HFMD infection in areas close to the city center and suburbans are lower than those in the urban-rural transition zones. The risk in the north-south direction of urban-rural transition zones is higher than those in other directions.

(ii) Bayesian adjustments. Raw morbidity rates may not effectively reflect true risks. The morbidity rates in spatial units with high concentration of population are more reliable indicators due to less randomness. As for the way these spatial units are partitioned administratively by the government, a unit with higher population density tends to be a smaller area, and *vice versa*. As a result, the map based on raw morbidity rates can lead to false conclusions.

To address this problem, we consider the raw, observed morbidity rates as realizations of a non-observable random process and propose to re-estimate morbidity rates using Bayesian adjustments in an effort to uncover true risks with an exposed population [25]. Figure 9(b) shows the morbidity map after Bayesian adjustments. An obvious change is that the morbidity rates in suburbans have been increased. There is little adjustment of the morbidity rates in center areas with high population density. The Bayesian adjustment approaches as applied to HFMD morbidity rates are discussed in Appendix C.

(iii) Spatial smoothing. Bayesian adjustments can help alleviate part of the data-related problems. However, additional challenges remain. As shown in Figure 9(a), noises in the raw data make the task of identifying the overall disease transmission trends hard. Spatial smoothing is a statistical method to solve this problem [26]. The purpose of spatial smoothing is to cope with functional variability that cannot be compensated by spatial normalization and to improve the signal to noise ratio. In other words, the smoothing aims to increase statistical power. At the same time, smoothing can lead to reduced sensitivity and loss of spatial details.

In order to represent neighborhood relationships, a spatial weight matrix $n \times n$ was used to construct the moving scan window. For any two adjacent spatial units, if they share one or more borders, the weight is 1; otherwise, the weight is 0.

Figure 9(c) shows a spatially smoothed morbidity map corresponding to the Beijing 2008 HFMD epidemic. We can see a clear spatial trend from this map.

5 Concluding remarks

HFMD remains an important public health challenge in China. Since May 2, 2008, HFMD has been established as a class "C" notifiable disease. An implication of this classification is that all clinical and laboratory diagnosed cases are required to be reported through the Web-based national disease surveillance. From December 24, 2007 to December 31, 2008, 18445 confirmed HFMD cases were surveyed in Beijing. This paper studies the epidemiological features and spread mechanism of the Beijing 2008 HFMD epidemic using this survey data. Our analyses result in the following findings: (i) The peak HFMD season was from May to July with the largest number of cases occurring in May; (ii) male patients significantly outnumbered female patients; (iii) the majority of cases involved children 4 years old and younger;

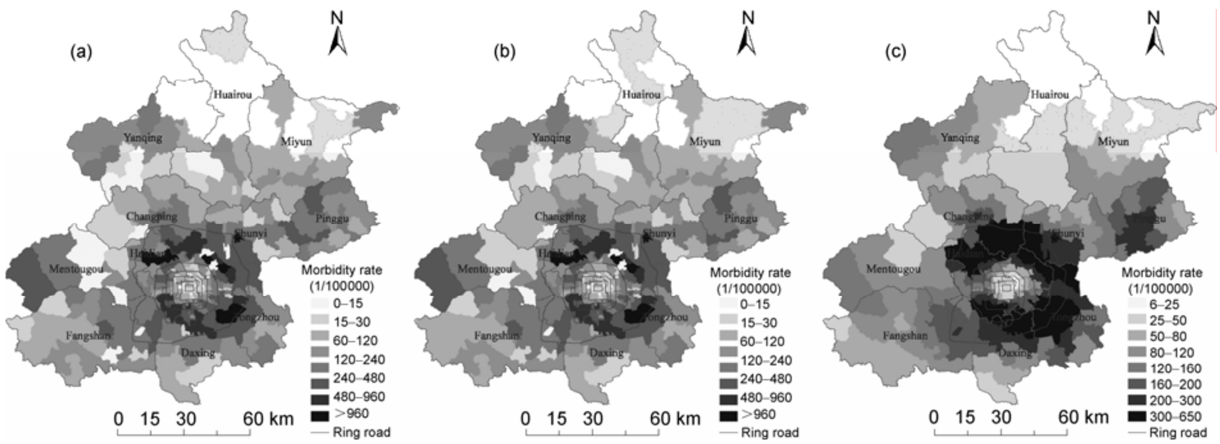

Figure 9 Morbidity map of the Beijing 2008 HFMD epidemic. (a) Raw morbidity rates; (b) after Bayesian adjustments; (c) after spatial smoothing.

(iv) log-normal distribution provides a good fit on patient age distribution and the estimated mean age is 3.4 years; (v) the morbidity rate, 132.7/100000, is higher than that in most other cities in China; (vi) the HFMD transmission risk in areas close to the city center and suburbans is much lower than that in the urban-rural transition zones.

In addition, we report two new findings of potential practical value: (i) a strong periodic pattern of high infection risk with length about one year was found in age distribution of HFMD cases; (ii) the correlation of the number of cases between month of birth and month of onset is 0.9864 ($P<0.01$). Month of birth has an impact on the chance of a patient being infected by HFMD in different months. In addition to the summer season, HFMD poses a high risk in birth month for a child and the risk of infection decreases as the gap from the birth month increases.

Our findings raise some interesting questions: does the HFMD virus have the ability to discriminate based on time of birth or pregnancy? Are there some gene fragments that "remember" the birth time and thus affect the immune system against the HFMD virus? We will work with public health researchers including epidemiologists and biologists trying to answer some of these questions. As the first step of our future research, we will design an experiment through monitoring 12 selected populations of children, with the same sex and age distribution, born in different months.

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