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Spatiotemporal risk mapping of hand, foot and mouth disease and its association with meteorological variables in children under 5 years

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SUMMARY

Hand, foot and mouth disease (HFMD) risk has become an increasing concern in the Beijing–Tianjin–Hebei region, which is the biggest urban agglomeration in north-eastern Asia. In the study, spatiotemporal epidemiological features of HFMD were analysed, and a Bayesian space–time hierarchy model was used to detect local spatial relative risk (RR) and to assess the effect of meteorological factors. From 2009 to 2013, there was an obvious seasonal pattern of HFMD risk. The highest risk period was in the summer, with an average monthly incidence of $4{\cdot}17/10^3$, whereas the index in wintertime was $0{\cdot}16/10^3$. Meteorological variables influenced temporal changes in HFMD. A 1 °C rise in air temperature was associated with an 11·5% increase in HFMD (corresponding RR 1·122). A 1% rise in relative humidity was related to a 9·51% increase in the number of HFMD cases (corresponding RR 1·100). A 1 hPa increment in air pressure was related to a 0·11% decrease in HFMD (corresponding RR 0·999). A 1 h increase in sunshine was associated with a 0·28% rise in HFMD cases (corresponding RR 1·003). A 1 m/s rise in wind speed was related to a 6·2% increase in HFMD (corresponding RR 1·064). High-risk areas were mainly large cities, such as Beijing, Tianjin, Shijiazhuang and their neighbouring areas. These findings can contribute to risk control and implementation of disease-prevention policies.

Key words: Foot and mouth disease, hand, meteorological factors, risk mapping.

INTRODUCTION

Hand, foot and mouth disease (HFMD) is an emerging contagious infectious disease, which primarily affects infants and children [1]. Pathogens belonging to the enterovirus family, such as Coxsackievirus A16 and Enterovirus 71, are primarily responsible for the disease [1]. The main clinical symptoms include mouth ulcers and a vesicular rash on the hands, feet and mouth [1, 2]. HFMD is transmitted through close personal contact via the oral–faecal route and by contact with contaminated fluids and respiratory droplets [3].

Worldwide, HFMD epidemics have been reported in many counties and regions, including Singapore, Malaysia, Hong Kong and Japan [4–7]. The majority of new cases have been reported in mainland China, with at least 6·5 million paediatric cases of HFMD recorded in 2008–2012, of which more than 2000 died [8]. At the national level, HFMD epidemics have become a significant public health problem [9].

The HFMD incidence shows apparent seasonality in many regions. In mainland China, the HFMD incidence peaks in April [9], and in Japan, the seasonal peak occurs

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during the summer months [10]; whereas in Hong Kong and Taiwan, a seasonal peak occurs in late spring/early summer between May and July [11, 12]. The seasonality of HFMD suggests that meteorological variables are important temporal risk factors influencing the disease transmission [13, 14].

Many studies have examined the association between HFMD and meteorological variables, including air temperature, which shows significant seasonal periodic variation [1, 13, 14]. Studies of the link between meteorological factors and HFMD in different countries reported that air temperature had a positive influence on HFMD, with higher temperatures associated with a greater risk of HFMD [13, 15–20]. Research also reported that relative humidity had a significant influence on HFMD transmission, showing that high relative humidity resulted in a greater risk of HFMD infection [13, 15–20]. In addition to air temperature and relative humidity, other meteorological factors, such as air pressure, wind speed and sunshine hours, also appeared to influence HFMD transmission [3, 17]. Although the previous studies detected a link between the risk of HFMD and meteorological factors, the association between these factors differed, depending on the region. For example, although most studies concluded that high temperatures and relative humidity were associated with a high risk of HFMD[15–17], some studies reported apparent differences in the exposure–response relationship in different locations and inverse influences of these factors [10, 13, 15, 20–23].

Other than seasonality in the incidence of HFMD, the disease also demonstrates a heterogeneous spatial distribution. The identification of high-risk areas is crucial for disease control. However, using traditional methods, the statistical probability of risk area cannot be obtained [24, 25]. The ability to produce a risk map based on statistical probability would benefit model making and disease control strategies.

Beijing–Tianjin–Hebei is located in a temperate monsoon climate zone, with distinct seasonal meteorological conditions: the region is cold and dry in the winter but hot and moist in the summer. Socio-economic status varies across the region, with underdeveloped areas outside the major city of Beijing, which is the capital of China and one of the world's largest metropolises.

The purpose of this study was to examine the spatiotemporal epidemiological features of HFMD, map the risk of HFMD and assess the impact of meteorological factors on this risk. A better understanding of seasonal and spatial variations in the risk of HFMD would benefit disease control in the region by aiding risk assessments and the implementation of effective strategies to reduce the burden of this disease.

METHODS

Study area

The Beijing–Tianjin–Hebei region is the largest urban agglomeration in northern China. It consists of three adjacent provincial levels of administrative regions. The Beijing–Tianjin–Hebei region encompasses an area of 210 000 km^2 and has a population of about 110 million (Fig. 1). Beijing has a population of about 21 million. As an international metropolis, it attracts large numbers of domestic and foreign workers, students, visitors, etc. Tianjin, to the southeast of Beijing near Bohai Sea, has a population of about 14 million. The cities of Beijing and Tianjin are surrounded by Hebei province, which has a population of about 73 million, the capital of which is Shijiazhuang. In the Beijing–Tianjin–Hebei region, Beijing is the most economically developed area, with tertiary industry making the largest contribution. The least developed areas are mainly located in Hebei province, in which primary and secondary industries account for a large proportion.

Study population and data collection

Monthly data on HFMD in children under the age of 5 years from January 2009 to December 2013 were obtained from the Chinese Centre for Disease Control and Prevention (CDC). There is a criteria for the clinical diagnosis of HFMD, ordinary cases usually have symptoms of fever accompanied by vesicular rash on the hand, foot, mouth. Severe cases present more severe symptoms, and usually have the clinical manifestation of circulatory, respiratory or neurologic complications [1]. The CDC surveillance data are collected from more than 90% of hospitals at the county level. The monthly HFMD case data were aggregated at the county level (Fig. 1).

Monthly meteorological data from January 2009 to December 2013 were obtained from the China Meteorological Data Sharing Service System. The data included average temperature, relative humidity, wind speed, air pressure and sunshine hours (http://data.cma.cn/) (Fig. 2).

Statistical modelling and analysis

A Bayesian space–time hierarchy model (BSTHM) was used to model the distribution of relative risk (RR) and detect the risk factors contributing to these

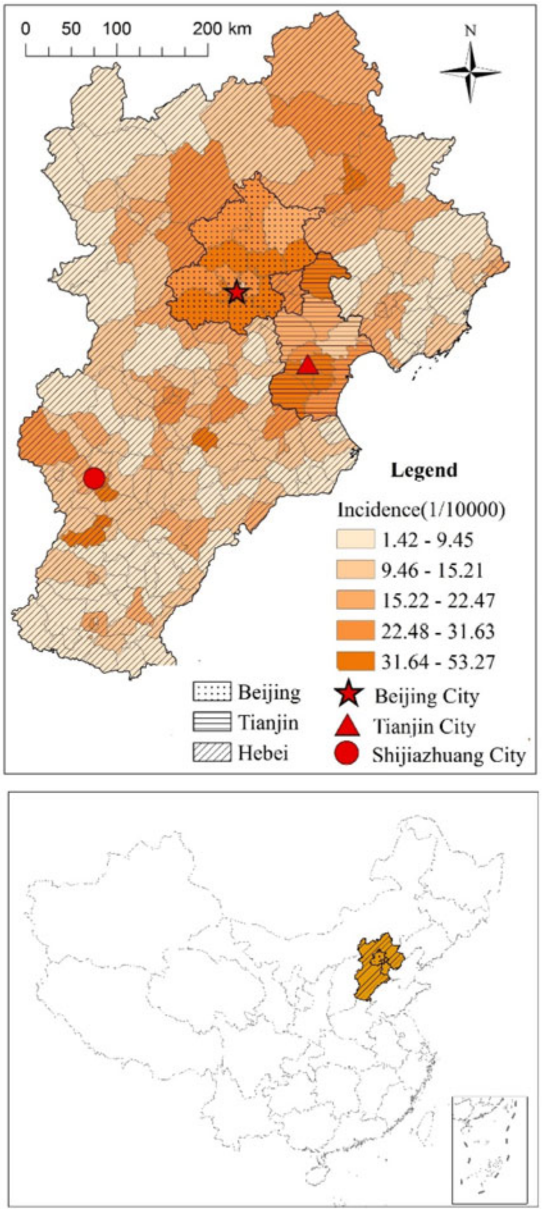

Fig. 1. Average monthly incidence of HFMD in Beijing–Tianjin–Hebei in 2009–2013 in different geographic regions in China.

spatiotemporal patterns and variations [26]. A Poisson regression (log-link) function was used in the model. Assuming that y_{it} and n_{it} were the number of cases and the risk population in county i at time t (in the study, $i = 1, 2, \ldots, 208$, and $t = 2009\text{-}1, 2009\text{-}2, \ldots, 2013\text{-}12$), r_{it} was the RR of HFMD.

$$y_{it} \sim \text{Possion}(n_{it} r_{it}),$$

r_{it} was expressed as:

$$\log(r_{it}) = \alpha + s_i + \sum_{m=1}^{M} \beta_m x_{mit} + \varepsilon_{it},$$

where α was the overall log-transformed HFMD risk in the spatiotemporal dimension. The spatial RR of HFMD in county i compared with that in the whole region was quantified by the posterior estimated $\exp(s_i)$, which was the stable spatial pattern and not variant in the time series. Meanwhile the variable also was the confounder to be adjusted, which had both effect on dependent variable and the other explanatory variables. β was the coefficient of the model, and x_{mit} was the m-th risk factor in location i and time t. ε_{it} was the overdispersion parameter, which contained the variation not yet explained by the spatial pattern and risk factors in the model, and a normal distribution was assumed in the term.

The Besag, York and Mollie spatial model was used to model the common spatial component s_i [27], which consisted of two components: spatially structured random effects and spatially unstructured random effects. Spatially structured random effects were calculated by a convolution algorithm, and spatially unstructured random effects were assumed to follow a Gaussian distribution. The spatial structured effect was used to explain the phenomena that neighbouring regions tend to have similar overall disease risks, and spatial unstructured effect was used to explain the phenomena having no spatial autocorrelation. In the spatial structure estimation, a conditional autoregressive prior was used, in which a spatial adjacency matrix, w_{ij}, was created. The value was 1 if county i and j had a common administrative boundary. Otherwise, the value was 0.

If a county had a persistent and stable higher or lower risk compared with the overall level in the region, it was classified as a hot spot or cold spot, respectively [28]. In the estimation, hot and cold spots were calculated by the following process: if the posterior probability $p(\exp(s_i) > 1|\text{data})$ was $>0{\cdot}95$, then the county i was classified as a hot spot. Similarly, if the posterior probability $p(\exp(s_i) > 1|\text{data})$ was $<0{\cdot}05$, then the county i was classified as a cold spot. Counties with $p(\exp(s_i) > 1|\text{data})$ between $0{\cdot}05$ and $0{\cdot}95$ were classified as neither hot spots nor cold spots.

The BSTHM method was implemented in WinBUGS [29], in which the Markov chain Monte Carlo simulations method was used to estimate the posterior distribution of the parameters.

RESULTS

Spatiotemporal patterns

In total, there were 598 835 cases of HFMD cases from 2009 to 2013 among children under the age of 5 years. The largest number of cases occurred in

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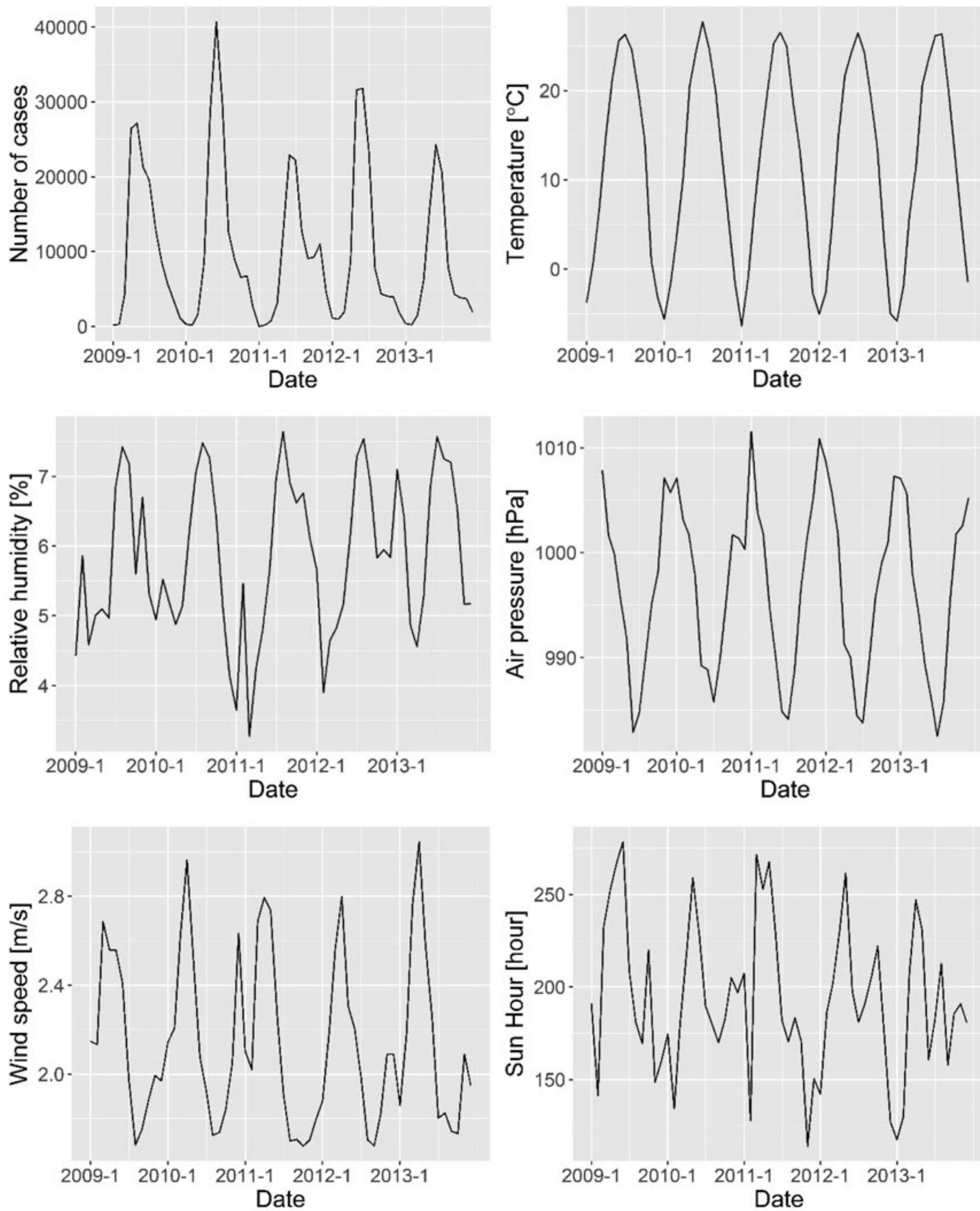

Fig. 2. Temporal variations in the monthly incidence of HFMD and its association with five meteorological factors.

2010, with an average monthly incidence of $2{\cdot}06/10^3$. The least number of cases was recorded in 2013, when the average monthly incidence was 1·27/103. The monthly incidence of boys ($1{\cdot}94/10^3$) was higher than that of girls ($1{\cdot}40/10^3$). There were apparent differences for the incidence among the age groups, 1-year-old children had the highest monthly average incidence ($2{\cdot}42/10^3$), while the 4-year-old children had the lowest monthly incidence ($1{\cdot}00/10^3$). Among all of the cases, 78% of which were scattered children, and 22% of which were kindergarten/daycare children.

The number of HFMD cases displayed an obvious pattern of seasonality. In the 5 years between 2009 and 2013, the highest risk period occurred during the summer season (May, June and July), with an average monthly incidence of $4{\cdot}17/10^3$. During the winter season (December, January and February), the average monthly incidence was $0{\cdot}16/10^3$ (Fig. 2).

Figure 3 shows the common spatial pattern structure of HFMD risk in the study region in 2009–2013. The estimates of the common RR suggested that the spatial distribution of HFMD risk exhibited explicit spatial heterogeneity. As shown in Figure 3, the common RR value of counties in the mid-north region of the study was higher (more than 1·0) than that of counties in the other regions. This finding implied that the counties in the mid-north region had a relatively higher HFMD risk. The highest level of stable spatial RR (more than 2·0) was found in cities and surrounding areas, for example, in the cities of Beijing, Tianjin, Shijiazhuang and their neighbouring regions. The counties located in the south and west regions had a lower level of HFMD risk, with a spatial RR smaller than 1·0, as compared with the whole region.

The posterior probability of RR was used to identify hot and cold spots (Fig. 4). From the spatial distribution of the posterior probability of RR, we can see that 64 counties, accounting for 31% of all counties, were classed as hot spots, and they were mainly distributed in urban and western areas of the study region. The cold spot regions were predominantly distributed in underdeveloped rural areas in the west and south of the study region ($n = 63$ counties), accounting for 30% of all counties. Counties classified as neither hot nor cold spots were mainly located in the northeast, mid-west, mid-south and some eastern areas (total number of counties: $n = 81$), accounting for 39% of all counties.

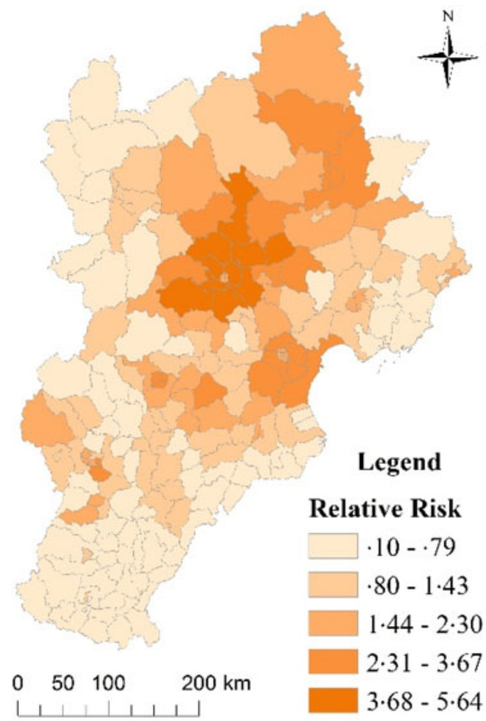

Fig. 3. RR of HFMD in Beijing–Tianjin–Hebei.

Risk factors

There was a positive highly significant association between HFMD and temperature. A 1 °C rise in the average temperature was associated with a 11·5% (95% confidence interval (CI) 11·0–11·9%) increase in the number of cases of HFMD, and the corresponding RR was 1·122 (95% CI 1·116–1·126) (Table 1).

A positive association was also found between HFMD and relative humidity, with a 1% increment in relative humidity associated with a 9·51% (95% CI 4·92–14·1%) increase in the number of cases of HFMD, and the corresponding RR was 1·100 (95% CI 1·050–1·151) (Table 1).

Air pressure had a negative association with HFMD. A 1 hPa rise was related to a 0·11% (95% CI 0·042–0·19%) decrease in the number of cases of HFMD. The corresponding RR was 0·999 (95% CI 0·998–1·000) (Table 1).

Sunshine hours and wind speed showed a weakly positive relationship with HFMD. A 1 h rise in sunshine hours was related to a 0·28% (95% CI 0·1–0·39%) increase in the number of cases of HFMD, and the corresponding RR was 1·003 (95% CI 1·002–1·004). A 1 m/s rise in wind speed was related to a 6·2% (95% CI −0·89 to 13·3%) increase in the number of cases of HFMD, and the corresponding RR was 1·064 (95% CI 0·991–1·142) (Table 1).

DISCUSSION

In recent years, the risk of HFMD has increased notably in the Beijing–Tianjin–Hebei region, and HFMD has become an important public health concern [2]. The present study analysed the spatial-temporal epidemiological characteristics of the disease and mapped the risk of HFMD and its associations with meteorological factors. The results demonstrated that the highest risk distribution of HFMD was in major cities and surrounding regions with high levels of economic development. Meteorological factors were significantly associated with temporal variations in HFMD.

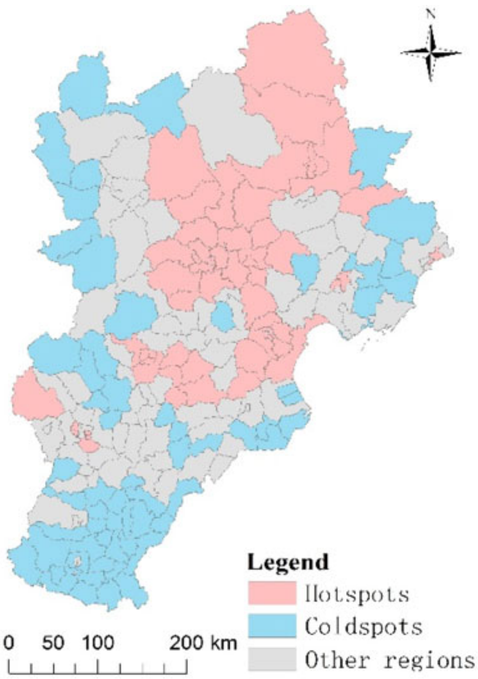

Fig. 4. Hot spots (high-risk areas) and cold spots (low-risk areas) of HFMD in 2009–2013.

In the present study, temperature and relative humidity were positively associated with the incidence of HFMD, with an increased incidence of the disease linked to higher levels of temperature and relative humidity indexes. This finding was consistent with that of previous studies in Jinan in northern China [30], Guangzhou in southern China [13, 15], South Korea [31], Tokyo and Fukuoka in Japan [10, 16], Hong Kong [17] and Taiwan [18]. Both temperature and relative humidity are two important meteorological indexes, with previous studies demonstrating that they affected the reproductive capacity of enteroviruses, influenced the survival of viruses and altered patterns of human behaviour [32, 33]. For example, an earlier study found that in hot and humid summers, outdoor activity was reduced, and people tended to spend more time indoors in air-conditioned houses, thereby providing more opportunities for contact with each other [13].

Although most studies confirmed the association of high temperature and relative humidity with a high HFMD risk, some studies reported apparent differences in the elastic coefficients of these variables in difference locations [10, 13, 15, 20–23]. A study in the city of Guangzhou in south China city reported that a rise of 1 °C in air temperature corresponded to an almost 10% increase (about 9·5%) in the risk of HFMD [15]. Another study in Guangzhou showed that an increment of 1 °C in temperature was associated with an increased HFMD risk of about 1·9% [13]. A study conducted in Guangdong province showed that a rise of 1 °C in air temperature led to an increase of about 9% in the risk of HFMD [19]. In four cities in Shanxi province in Northern China, the same increase in temperature corresponded to an increase of about 0·8–2% in the risk of HFMD [14]. In Fukuoka, Japan, a 1 °C increment in air temperature corresponded to an increased HFMD risk of about 11% [10].

Similar risks were reported with a rise in relative humidity. In one study, for every 1% rise in relative humidity, there was an increase of about 1·5% and 3% in the risk of HFMD in two models having different variables combination in Guangzhou [15]. Another study in Guangzhou showed that an increase of 1% in relative humidity enhanced the risk of HFMD by about 1·4% [13]. In Guangdong province, a rise of 1% in relative humidity was associated with a 4% increase in the risk of HFMD [19]. In Fukuoka, a similar rise in relative humidity corresponded to an increase of about 4·7% in the risk of HFMD [10].

Various factors may explain the discrepancies in HFMD risk reported by the aforementioned studies. The study site is one possible reason, with both the climate and socio-economic level varying in different regions. Both factors influence HFMD transmission. Other possible reasons are the models that were used in the studies and differences in their spatial-temporal scales. The aforementioned can induce differences in the elastic coefficients of these variables in different locations.

In the present study, other than temperature and relative humidity, additional meteorological factors, such as air pressure, sunshine hours and wind speed, had important influences on HFMD transmission. This finding is generally consistent with that of other studies [13, 15, 17, 19]. For example, a rise of 1 hPa in air pressure was associated with a decline of about 8% in the risk of HFMD in Guangzhou city [15], and a rise of 1 h in sunshine hours was related to a decreased HFMD risk of about 16% in Guangdong province [19]. In Guangzhou city, an increment of one unit of wind speed was associated with an increased HFMD risk of about 2·2% and 4·6% in two models having different variables combination [15]. A study conducted in Hong Kong also found that wind speed was positively associated with the risk of HFMD [17]. However, a study conducted in Guangzhou found no statistically significant association between wind speed and HFMD risk [13]. In

Table 1. *Posterior means and RR coefficients according to the BSTHM*

Risk factors	Mean (95% CI)	RR (95% CI)
Average temperature (°C)	11·5% (11·0–11·9)	1·122 (1·116–1·126)
Relative humidity (%)	9·51% (4·92–14·1)	1·100 (1·050–1·151)
Air pressure (h Pa)	−0·11% (−0·19 to −0·042)	0·999 (0·998–1·000)
Sunshine hours (h)	0·28% (0·18–0·39)	1·003 (1·002–1·004)
Wind speed (m/s)	6·2% (−0·89 to 13·3%)	1·064 (0·991–1·142)

BSTHM, Bayesian space–time hierarchy model; RR, relative risk; CI, confidence interval.

common with temperature and relative humidity, air pressure, sunshine hours and wind speed influence the survival and reproduction of viruses, as well as human activities. For example, according to one study, the negative relationship between air pressure and HFMD risk was due to the adverse impact of air pressure on the immune system [34].

In addition to seasonality in meteorological variables, long-term stable factors, such as terrain, culture, customs and social conditions, influence the heterogeneous spatial distribution of HFMD risk in different regions. In the present study, the BSTHM was used to detect risk areas, while controlling for meteorological variables. In the method, the overall risks of the disease in the study region was quantified by common spatial component of BSTHM. If a disease has strong spatial autocorrelation, the spatially structured effects will have more contribution explaining the spatial variant of the disease risk; otherwise the component of spatially unstructured effects will have more explanatory power. The index was used to explore the geographic distribution of HFMD risk. The results revealed that high-risk area were mainly in large cities, such as Beijing, Tianjin, Shijiazhuang and their neighbouring areas. This finding was consistent with that reported in previous studies [3, 19, 35]. Deng *et al*. found that cluster centres of HFMD were almost the same in the capital of Guangdong province in China as in neighbouring areas [19]. Liu found that a cluster centre in Shandong province in China varied in different years [35]. Xu found that high-risk areas were mainly located in regions with a high level of economic development and population density [3].

Most previous studies of HFMD risk used SatScan [24] and LISA (Local Indicators of Spatial Association) [25]. In the SatScan method, the risk area is selected from a geographic region, usually defined as a circular shape, considering the number of cases and risk population [24]. The method is simple and easy to use, and it has been widely used in the public health area. However, the results are affected by the parameter of risk population. In addition, the risk area is restricted to a regular shape, it is not suitable for a disease risk distributed in irregular shapes of geographic regions. Using the LISA method, the high-risk area can be obtained under the condition that the area has a high disease risk while its neighbouring area also has a high risk. However, the local area having high risk resulted from the method may have no global meanings.

The present study has some limitations. We calculated spatiotemporal variations in HFMD at the scale of counties and months. However, micro-factors also influence HFMD transmission. These include personal hygiene and social customs, educational background, occupations and incomes of children's parents and living conditions. In addition, HFMD cases may be linked to large global and domestic events that are regularly held in large cities in the region. These events result in an influx of large numbers of people, which may potentially contribute to HFMD transmission. Future studies will consider the potential impacts of these factors.

In summary, In the Beijing–Tianjin–Hebei region, the risk of HFMD in 2009–2013 showed stable spatial heterogeneity, with high-risk areas mainly confined to large cities and neighbouring areas. Meteorological variables had an important influence on seasonal variations in HFMD transmission, with the highest risk found in periods of hot, humid weather. These findings will be helpful for risk control, forecasting and policies aimed at the prevention of HFMD transmission.

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DECLARATION OF INTEREST

None.

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