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Spatiotemporal decomposition and risk determinants of hand, foot and mouth disease in Henan, China

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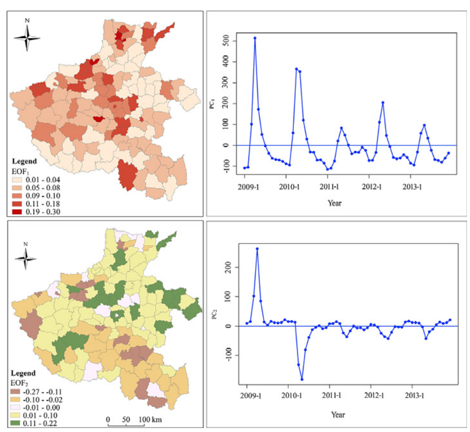
HIGHLIGHTS

- Spatial distribution of HFMD can be decomposed into distinctive spatial patterns.
- The dominant factors of HFMD were different for each spatial pattern.
- The GDP and relative humidity were the dominant driving factors of the first principal components.
- The ratio of the urban to rural population and precipitation the dominant driving factors of the second principal components.

GRAPHICAL ABSTRACT



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ABSTRACT

Hand, foot and mouth disease (HFMD) remains an increasing public health concern. The spatiotemporal variation of HFMD can be represented from multiple-perspectives, and it may be driven by different dominant factors. In this study, the HFMD cases in children under the age of five years in each county in Henan province, China, from 2009 to 2013 were assessed to explore the integrative spatiotemporal patterns of HFMD and investigate their driving factors. The empirical orthogonal function was applied to identify representative spatiotemporal patterns. Then, GeoDetector was used to quantify the determinant powers of driving factors to the disease. The results indicated that the most prominent spatiotemporal pattern explained 56.21% of the total variance, presented in big cities, e.g. capital city and municipal districts. The dominant factors of this pattern were per capita gross domestic product and relative humidity, with determinant powers of 62% and 42%, respectively. The secondary spatiotemporal pattern explained 10.52% of the total variance, presented in the counties around big cities. The dominant factors for this pattern were the ratio of urban to rural population and precipitation, with determinant powers of 26% and 41%, respectively. These findings unveiled the key spatiotemporal features and their determinants related to the disease; this will be helpful in establishing accurate spatiotemporal preventing of HFMD.

1. Introduction

Hand, foot and mouth disease (HFMD) is an infectious disease caused by various enteroviruses, and it primarily affects infants and

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children. Most patients show self-limiting illness typically including fever; rash on the hands, feet and buttocks; mouth ulcers; poor appetite; and vomiting and diarrhoea (Li et al., 2014a; Qiu, 2008), however, some patients rapidly develop fatal neurological and systemic complications (Sabanathan et al., 2014). It is transmitted mainly through close personal contact with an infected person, fluid from blisters or contaminated objects and surfaces, and its average incubation period is 3–7 days (Li et al., 2014a; Liao et al., 2016; Zhu et al., 2016). So far, there is no specific curative treatment or vaccine for HFMD (Zhu et al., 2013).

In recent years, HFMD has been a growing public health problem worldwide, and it has attracted a lot of concerns. Since it was first occurred in 1957 (Robinson et al., 1958), HFMD has been reported worldwide; it is especially frequent and widespread in Asian countries, such as China (Wang et al., 2017), Singapore (Chan et al., 2003), Malaysia (Chua and Kasri, 2011) and Japan (Hosoya et al., 2007), where many large outbreaks of HFMD involving severe complications and deaths, predominantly among children, have been documented. Especially, in 2008, HFMD was listed as a category C infectious disease and made statutorily notifiable according to the Law of the People's Republic of China on the Prevention and Treatment of Infectious Diseases in China (Ministry of Health of the People's Republic of China, 2008).

Previous studies have found that there is manifest temporal variation of HFMD. For example, it peaks in June in northern China, whereas there are semi-annual outbreaks in May and September–October in the south of the country (Xing et al., 2014). Furthermore, HFMD peaks have been observed in the summer in Taiwan (Chang et al., 2002) and Hong Kong (Ma et al., 2010), while they have been found in March or May in Singapore (Ang et al., 2009) and parts of mainland China (Li et al., 2014b). The seasonality of HFMD illustrates that meteorological factors, such as the average temperature, relative humidity, precipitation, wind speed and air pressure, may play an important role in HFMD variation (Ang et al., 2009; Chang et al., 2002; Li et al., 2014b; Ma et al., 2010).

In addition to the seasonality, HFMD also exhibits obvious spatial variation, which can be observed from various spatial patterns. Some studies have found that a high risk of HFMD is closely correlated to high population density (Hu et al., 2012; Wang et al., 2011). Cheng et al. found that the number of urban HFMD cases was much greater than that of rural ones, with the incidence of HFMD 3.6 times higher in urban areas (Cheng et al., 2014). Moreover, Hu et al. demonstrated that the child population density could explain 56% of the variance in the cumulative monthly HFMD incidence in 2912 counties in China (Hu et al., 2012). In addition, the rural-to-urban migrant-worker parents were found to be the major risk factor associated with HFMD in children (Zeng et al., 2013). These findings showed that economic, demographic and infrastructural conditions among the different regions may also play an important role.

Previous studies have mainly focussed on the HFMD variation and assessed the influence of potential factors in time or space (Hu et al., 2012; Li et al., 2014b). However, space and time are inseparable in the real world, and the spatiotemporal variation of HFMD can be represented in multi-perspective, which is driven by different dominant factors. This study has the following aims: 1) to explore the spatiotemporal variation characteristics of HFMD incidence in children under the age of five years from a multi-perspective using the empirical orthogonal function (EOF), and 2) to estimate the determinant power of driving factors for each spatiotemporal pattern of HFMD variation using GeoDetector.

2. Methods and materials

2.1. Study area

Henan province is one of the greatest exporters of people in China. It has a population of approximately 95.32 million and a total land area of 167,000 km^2. Henan falls in the warm temperate monsoon climate zone, and it is characterised by a dry and windy spring, hot and humid summer, autumn in sunshine, cold and rainless in winter. The annual average temperature and precipitation in the province are 15 °C and 672 mm, respectively (Fig. 1).

2.2. Materials

From January 1, 2009 to December 31, 2013, all HFMD cases (aged under 5) in 126 administrative units of Henan Province from the Chinese Centre for Disease Control and Prevention were employed in the study (Fig. 2). The criteria for HFMD clinical diagnosis is that: symptoms of fever accompanied by vesicular rash on the hand, foot, mouth is recognized as ordinary cases. Cases have severe symptoms, such as the clinical manifestation of circulatory, respiratory or neurologic complications is recognized as severe cases (Wang et al., 2012). Monthly meteorological data from January 2009 to December 2013 were obtained from the China Meteorological Data Sharing Service System (http://data.cma.gov.cn/), including average temperature, relative humidity, air pressure, precipitation and wind speed (Fig. 2). The monthly county level climate variables were calculated using general spatial Inverse Distance Weighted methods based on surveillance stations within Henan and surrounding provinces. Demographic and socioeconomic data from 2009 to 2013 in each county (Fig. 3) were collected from the government's economic statistical yearbooks of Henan province. The Pearson correlation coefficient was considered here to remove the factors that presented strong correlation, and the selected factors are shown in Tables 1 and 2.

2.3. Empirical orthogonal function (EOF) method

The EOF method (Storch and Zwiers, 2001) is a multivariate statistical technique for revealing both the spatial and temporal variations exhibited by the field being analysed, and it has been widely used in atmospheric science, coastal process, et al. (Aubrey, 1979; Fiore et al., 2003; Pu et al., 2016; Shen et al., 2015; Winant et al., 1975). This method is characterised by decomposing raw data into representative spatiotemporal patterns, without influencing most of the explained variance. More importantly, it can estimate the "significance" of each spatial-temporal pattern. Spatial patterns (EOF_i), also called principal components in some fields, and time variation (PC_s) are also regarded as EOF time series in other disciplines.

The EOF method is essentially a linear algebra methodology based on matrix transformation, where the calculation process follows three steps. The first step is the conversion of the spatiotemporal data into a matrix. Namely, we construct a matrix (X), where each column is the incidence of all counties in a month, and each row is the time variation of each county. The second step is computing the anomalous values of the analysed data, representing the extent of deviations from the average incidence level. The next step in applying the EOF method involves calculating the covariance matrix (A) according to Eq. (1):

$$A = X^T \times X \tag{1}$$

where $X^T$is the transpose of X. Then, the eigenvalue is calculated by Eq. (2):

$$X \times B = B \times \Lambda \tag{2}$$

where $\Lambda$is a diagonal matrix composed of the eigenvalues of X. Each column b_i of B is composed of eigenvectors corresponding to the eigenvalues of X. Each of these eigenvectors can be considered a map of EOF_i (or principal spatial patterns). In general, the eigenvectors are assumed to be arranged in ascending order of their corresponding eigenvalues (i.e. $\lambda_1 > \lambda_2 > \ldots > \lambda_n$). Thus, EOF_1 is the eigenvector corresponding to the largest eigenvalue. The contribution of the total variance in X explained by EOF_i is found by dividing the λ_i by the sum of all the eigenvalues. Finally, the time series (PC_s) are calculated

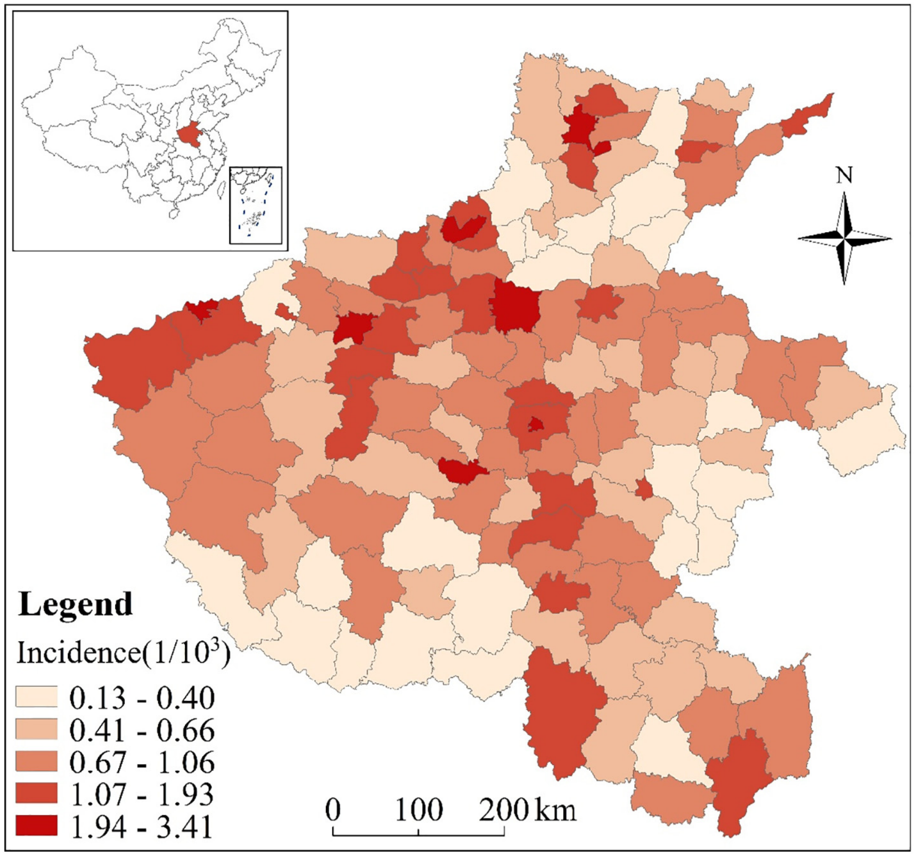

Fig. 1. Location of Henan province and cumulative monthly incidence of hand, foot and mouth disease (HFMD) from 2009 to 2013.

according to Eq. (3):

$$\alpha_i = X \times EOF_i \tag{3}$$

In this study, the PC_s are time series of HFMD incidence from January 2009 to December 2013, corresponding to the EOF_i (spatial patterns). The EOF method is expected to provide three important results, as follows: the spatial patterns (EOF_i); their time evolution (PC_s), whose components are called loadings; and the percentage of spatial variance explained by each EOF, which is calculated by dividing each λ by the trace of Λ.

2.4. GeoDetector

The GeoDetector method is used to quantify the relationships between each of the spatial patterns (EOF_i) and temporal variation (PC_s)

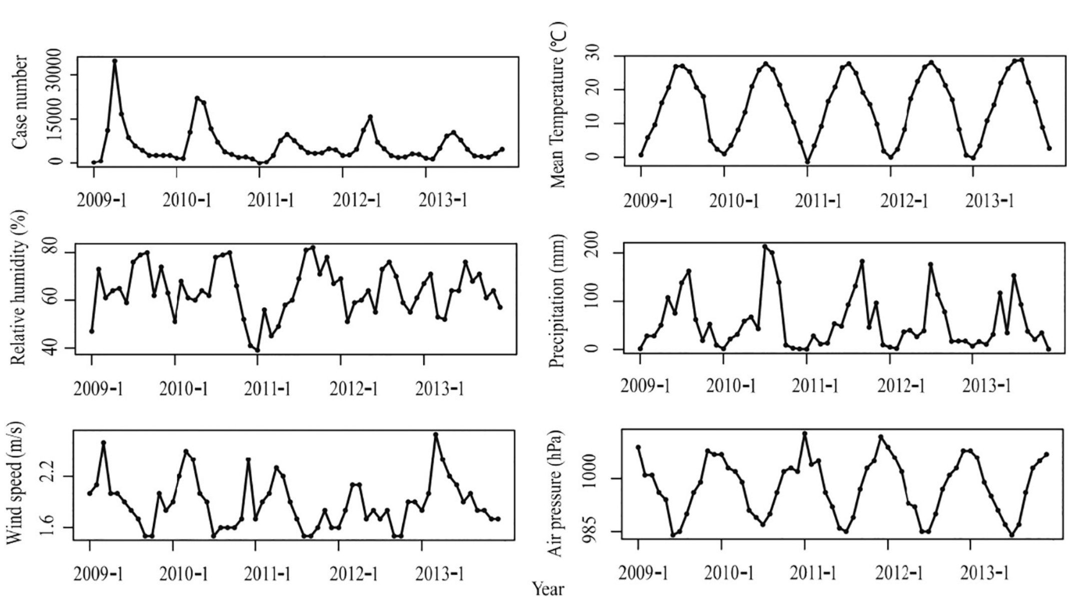

Fig. 2. Temporal variation of meteorological factors of Henan province from 2009 to 2013.

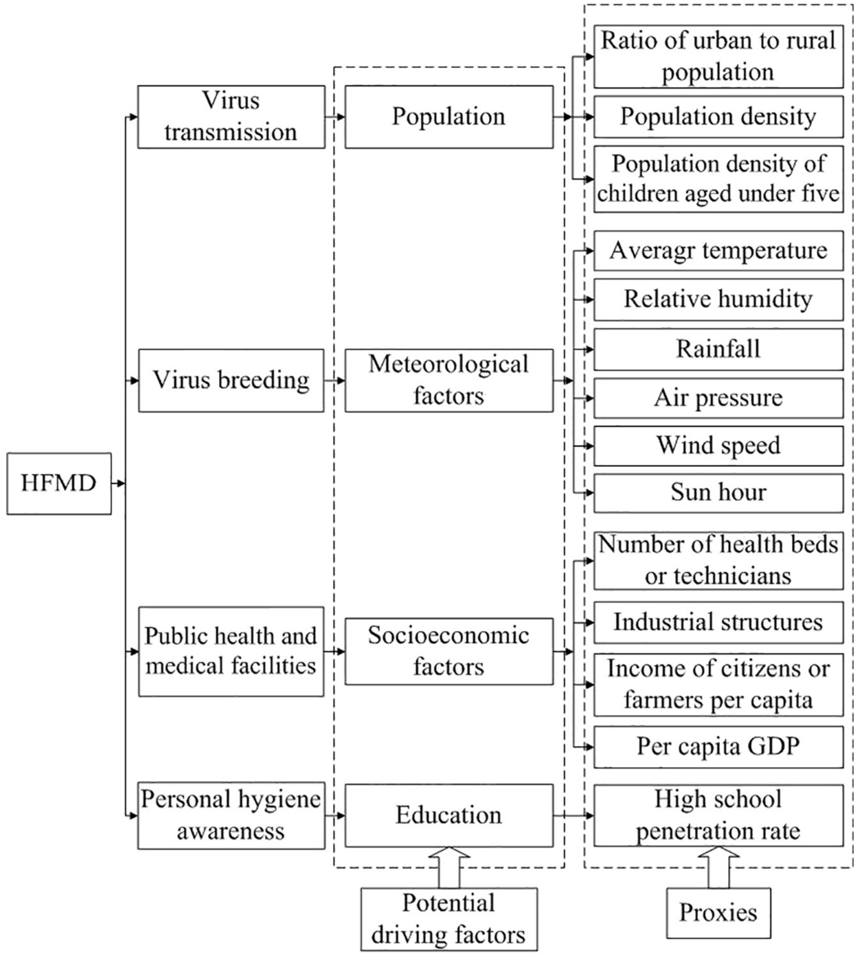

Fig. 3. Potential driving factors and proxies of hand, foot and mouth disease (HFMD).

of HFMD and risk factors. The assumption of this method is that if a potential factor leads to a disease, the disease would exhibit a spatial distribution similar to that of the factor (Wang et al., 2010). This method can be used to measure the determinant power of potential risk factors (Hu et al., 2011).

The calculation of GeoDetector involves three main steps. First, the spatiotemporal data are collected; the spatial data refer to socioeconomic factors that are stable within a year but vary among counties, while the temporal data refer to meteorological factors that have great temporal variation, such as seasonality. In the study, the input spatiotemporal data are EOF_i and PC_s, calculated by EOF method. In the second stage, the q statistic value of the GeoDetector is calculated. Finally, the statistical significant index p-values are calculated through a noncentral F-distribution (Wang et al., 2016).

Table 1
The q values (q_1, q_2) calculated between the most two prominent spatial patterns (EOF_1, EOF_2) and socioeconomic factors, respectively.

Socioeconomic factors	q_1	q_2
Per capita gross domestic product (GDP) (10^4CNY)	**0.62**	0.10
Ratio of urban to rural population	0.56	**0.26**
Number of health technicians (per 10^3)	0.46	0.15
Population density of children under five (10^4person/km^2)	0.35	0.23
Income of farmers per capita (10^3CNY)	0.32	0.23
Proportion of the tertiary industry (100%)	0.23	0.21
Proportion of the secondary industry (100%)	0.24	0.18
High school penetration rate (100%)	0.38	0.18

In GeoDetector, the determinant power of potential driving factors (such as factor C) for EOF_i and PC_s is calculated using the following formula:

$$q_{C,B} = 1 - \frac{1}{N\sigma^2}\sum_{h=1}^{L} N_h \sigma_h^2 \tag{4}$$

where C is the influencing factor, B is the deviation extent of HFMD average incidence and $q_{C,\,B}$ is the determinant power of C to B. In addition, N is the number of counties and σ^2 denotes the variance over all the statistical units in the study area. The study area is stratified into L stratums, denoted by $h = 1, 2, \ldots, L$; σ_h^2 is the variance within stratum h. The value of q ranges from 0 to 1, denoting the determinant power or relative importance of a risk factor. If factor C has complete control of the B, the q value equals 1. If factor C is completely unrelated to the B, the q value equals 0. In this study, the software used to implement GeoDetector method was downloaded from www.geodetector.cn.

Table 2
The q values (q_1, q_2) calculated between the most two prominent temporal variances (PC_1, PC_2) and meteorological factors, respectively.

Meteorological factors	q_1	q_2
Relative humidity (%)	**0.42**	0.35
Precipitation (mm)	0.41	**0.41**
Air pressure (hPa)	0.39	0.35
Wind speed (m/s)	0.37	0.37
Average temperature (°C)	0.31	0.33

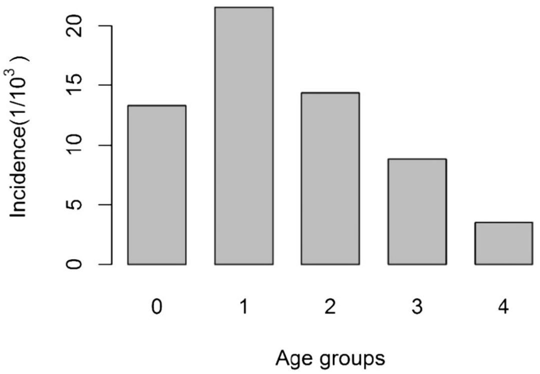

Fig. 4. Yearly average HFMD incidence in different age groups.

3. Results

3.1. Descriptive statistics

From January 2009 to December 2013, a total of 369,696 cases of HFMD were reported in children under the age of five years in all counties of Henan province. There presented distinct gender and age difference for HFMD risk. There were more cases in boys (236,777) than in girls (132,919), and the corresponding yearly average incidences were $12.58/10^3$ and $8.89/10^3$, respectively. Among the different age groups, the incidence showed apparent difference, in which the lowest risk was in four-year-olds, with a yearly average incidence of $3.53/10^3$, while the highest risk was in the one-year-old children with a yearly average incidence of $21.53/10^3$ (Fig. 4).

Meanwhile, the study found that there was an obvious seasonal variation of the HFMD incidence. The highest-risk season appeared during the spring (March, April and May) with an average monthly incidence of $1.97/10^3$, followed by the seasons of summer (June, July and August) and autumn (September, October and November), with the average monthly incidence of $0.92/10^3$ and $0.43/10^3$, respectively. The lowest-risk season appeared during the winter (December, January and February) with an average monthly incidence of $0.32/10^3$.

3.2. EOF patterns and determinant factors

The first two dominant EOF patterns of HFMD incidence for 2009–2013 are shown in Fig. 5. Each pattern (EOF_i) reflects the spatial variation of the field to be analysed, which is its typical characteristic. These two patterns together accounted for 66.73% of the sum variance in HFMD incidence, and the remaining EOF maps were not presented because none of them explained >10% of the total variance. Similarly, the time series (PC_s) corresponding to the first two EOF patterns also accounted for 66.73%.

3.2.1. The predominant pattern

Spatially, the predominant pattern EOF_1 (first pattern showing the highest variance), corresponding to the time series of PC_1, described 56.21% of the total variance (Fig. 5). The regions with an absolute value of EOF_1 >10%, presenting a high level of variation intensity for the average incidence, corresponded almost exactly to the big cities,

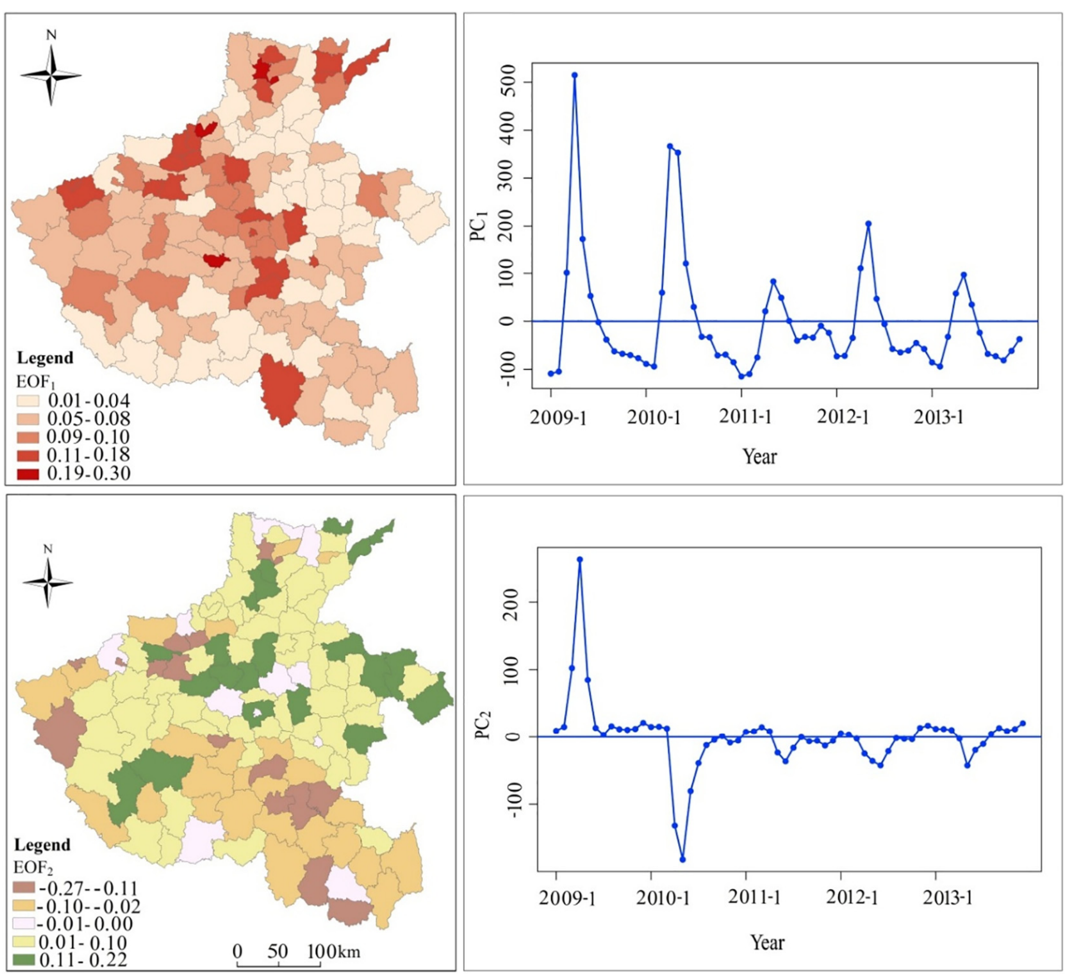

Fig. 5. Spatial distribution and temporal variances of the first two patterns of hand, foot and mouth disease (HFMD) incidence in Henan province.

e.g. capital city and municipal districts, with the higher incidence (Figs. 1 and 5).

Temporally, the time series of PC_1 showed obvious temporal variation; from April to June, the value of PC_1 was positive and high. Considering the spatial pattern displayed in EOF_1, this implied that, during this period, there was an apparent HMFD epidemic in the large cities. These findings denoted that there may be strong associations between meteorological factors, socioeconomic factors and HFMD epidemics in the large cities from April to June.

Per capita gross domestic product (GDP), as a proxy for industrialisation and urbanisation, showed the strongest association with HFMD, with a q value of 0.62 ($p < 0.01$), it was the dominant factor explaining the spatial variation of the HFMD incidence, and the Pearson correlation coefficient was positive (Table S1). This indicates that, where the per capita GDP was high, there was a high incidence of HFMD.

A high urban-to-rural population ratio and large number of health technicians also had significant associations with a higher extent of deviations, with q values of 0.56 and 0.46, respectively ($p < 0.01$). In addition, the Pearson correlations coefficient between EOF_1 and these two factors were positive, implying that there was a closely positive relationship between the urbanisation level and EOF_1 (Tables 1 and S1). Furthermore, relative humidity played a leading role in the temporal variation of the extent of deviations, with a q value of 0.42 ($p < 0.01$), presenting a negative relationship with EOF_1 (Tables 2 and S2).

3.2.2. The secondary pattern

The secondary spatial pattern EOF_2 (corresponding to its time series of PC_2) described 10.52% of the total variance (Fig. 5). We found that the regions with the higher incidence corresponded almost exactly to the areas with the absolute value of EOF_2 >10% (Figs. 1 and 5), which showed that the high-risk areas were mainly distributed in the counties around the big cities. From April to July, the absolute value of PC_2 was high; considering the spatial pattern presented in EOF_2, it can be identified that there was a significant epidemic in the counties around the big cities in this period (Fig. 5).

The ratio of the urban to rural population was the dominant power in the spatial variation of HFMD in the EOF_2 pattern, with a q value of 0.26 ($p < 0.01$), and the Pearson correlation coefficient between them was negative, reflecting that the area with the lower ratio of urban to rural population would have a higher HFMD variation. Furthermore, precipitation also was the main driving factor affecting the variation, with a q value of 0.41 ($p < 0.01$); the Pearson correlation coefficient between them was negative, which indicated that a negative relationship was presented (Tables 2 and S2).

4. Discussion

HFMD remains a major public health concern in the world, and it has attracted increasing attention (Ang et al., 2009; Gopalkrishna et al., 2012; Yang et al., 2011). Henan, as one of the most populous provinces in China, and having millions of migrants, has experienced a notably high incidence of HFMD in recent years (Huang et al., 2015; Wang et al., 2015). In the present study, the EOF method was used to explore the epidemiological characteristics of the disease, detect its main spatial patterns (EOF_i) and analyse the temporal changes of high-risk areas in Henan for the period of 2009 to 2013. The determinant power of the potential driving factors was calculated using GeoDetector. The results indicated that the highest variation areas were mainly concentrated in big cities or their adjacent areas, especially during the late spring and early summer (April to June). Furthermore, meteorological and socioeconomic factors play important roles in the spatiotemporal variation of HFMD.

The time series PC_1 and PC_2 in the selected years for the study area presented manifest temporal variations. The peak of the absolute value for the deviations in the time series of PC_1 and PC_2 was from April to June, which was consistent with previous studies. For example, the HFMD peaks were observed from May to July in Hong Kong (Ma et al., 2010). Similarly, a previous study indicated that the highest risk appeared in May in parts of mainland China (Li et al., 2014b). An additional study reported that the epidemic peak of HFMD occurred in March or May in Singapore (Ang et al., 2009). These differences may be related to the seasonal variations of meteorological factors, as some studies suggested, the key environmental factors affecting the spread and survival of the HFMD virus (Ang et al., 2009; Aubrey, 1979; Li et al., 2014b; Ma et al., 2010; Wang et al., 2011).

In this study, we found a greater association of relative humidity with EOF_1 and EOF_2, a dominant factor, especially with EOF_1, having a determinant power of 0.42, which was consistent with some previous studies (Hu et al., 2012; Onozuka and Hashizume, 2011; Yang et al., 2016). For example, a previous study indicated that the weekly number of HFMD cases increased by 4.7% for every 1% increase in relative humidity (Onozuka and Hashizume, 2011). Similarly, another study showed that a 1% rise of relative humidity was associated with a 13% increase in the risk of HFMD (Guo et al., 2016). In Hong Kong, researchers also demonstrated that relative humidity was the most influential factor (Ma et al., 2010). The potential reason for the effects of relative humidity may have been its profound influence on immunity-oriented problems (Guo et al., 2016).

Precipitation was another significant factor associated with EOF_1 and EOF_2, especially with EOF_2, and its determinant power was 0.41 in this study, which was comparable to the results reported in some previous studies (Cheng et al., 2014; Wang et al., 2011). For example, previous research found that precipitation played a crucial role in Jiangsu province, China (Liu et al., 2015). Moreover, one previous study showed that HFMD decreased 3.1% with a 1-mm increase in monthly cumulative precipitation in Vietnam (Dung et al., 2018). The potential mechanism may be that precipitation affects water and food sanitation, and thus, the transmission of HFMD.

Temperature was also an important influential factor in the study, with determinant powers of 0.31 and 0.33 in EOF_1 and EOF_2, respectively, which was widely considered factor in other previous studies (Onozuka and Hashizume, 2011; Wei et al., 2015; Xu, 2017). For example, one study showed that a 1 °C rise in the average temperature could lead to increases of 0.8%, 1.4%, 1.1% and 2.1% in the number of HFMD cases in Datong, Taiyuan, Changzhi and Yuncheng, respectively (Wei et al., 2015). One study revealed that the HFMD cases increased by 11.2% for every 1 °C increase in average temperature, and thus, the effect of temperature could not be neglected (Onozuka and Hashizume, 2011). These studies suggested that the temperature would influenced the transmission of HFMD viruses, which may be because the environmental temperature relates to behavioural patterns, and moderate weather may lead to increased contact among young children, thereby facilitating the spread of HFMD infection.

In addition to temporal variations, the EOF and GeoDetector results also showed obviously spatial variations, reflected in that the most spatial clusters were mainly located in urban areas or their neighbouring counties, which was consistent with previous studies. For example, it has been reported that large cities, such as Beijing, Tianjin, Shanghai and Zhejiang, have a higher disease incidence (Xu and Xiao, 2017; Zhu et al., 2011). Similarly, Huang et al. (2014) found that tertiary industry and population density had the highest determinant power for their selected factors, explaining 42% of the HFMD transmission. Furthermore, Shi et al. (2014) found that the areas with high HMFD incidence are mainly concentrated in the counties around the large cities. The potential mechanisms for this may be that there was relatively high population density and population movements in large cities or their adjacent counties due to the rapid economic development and urbanisation in recent years, which would accelerate the spread of HFMD; meanwhile, migrant workers mainly live in counties around large cities. They usually have less education, low economic status, lack of understanding of disease prevention, and less appropriate health care for the diagnosis and treatment of disease, also would result in its rapid spread.

In this study, EOF was used to analyse the spatiotemporal variation. The advantage of the EOF method lies in its greater emphasis on revealing the most essential characteristics of the spatiotemporal distribution of disease, and the research results are based on the variation, reflecting the real time–space fluctuation of the HFMD incidence for each area. A limitation should be mentioned in that the first few PC_s and EOF_i results may not contain enough raw data information, which could result in the loss of a small amount of information. This would introduce uncertainty into the study. Meanwhile, the data available in the study were from 2009 to 2013, therefore the findings and conclusions were applicable to this time period. HFMD data for longer time period and more regions will be collected for in the future studies.

5. Conclusions

We used the EOF and GeoDetector methods to analyse HFMD transmission from multi-perspective, which can offer distinctive and important information for epidemiological studies and disease control practices. We found that the spatiotemporal patterns and dominant factors were different for each EOF. In EOF_1, areas in big cities presented high risk, the per capita GDP and relative humidity were the dominant driving factors. While in EOF_2, counties neighbouring big cities showed high risk, the ratio of the urban to rural population and precipitation were the dominant driving factors. These findings can contribute to risk control and implementation of disease-prevention policies for HFMD. Currently, it is necessary to allocate more medical resources in big cities before April. In the coming years, more attention should be paid to the neighbouring areas of big cities, because the size of cities have been growing rapidly with the acceleration of urbanisation in China in the last decade and those areas will become urban area in the process, which will undoubtedly exerts inevitable public health problems (Gong et al., 2012; Li et al., 2016).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2018.12.039.

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