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Original Article

Characterization of dengue epidemics in mainland China over the past decade

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Abstract
Introduction: Dengue is an important public health concern in developing countries. As it is increasingly serious in mainland China, its spatiotemporal variations in this region must be further understood.
Methodology: On the basis of the data on dengue cases in 2004–2013 collected from the China Information System for Disease Control and Prevention, examinations of spatiotemporal variations of local, imported, and total dengue cases were conducted to characterize this epidemic at the city scale in China.
Results: Local cases in September and October accounted for more than half of the total cases in each year. The cities with more than 50 accumulative local cases were mainly distributed along the southeast coastal areas and southwest border regions of China. In 2004–2013, local dengue transmission (indicated by the number of local cases and the locally infected cities) increased yearly and was closely associated with epidemics (represented by the amount of imported cases and the cities with imported cases). At the city level, local transmission tended to be spatially clustered in the Zhejiang-Fujian coastal area, the Pearl River Delta, and Yunnan-Burma border region, especially in 2005, 2010, 2012, and 2013.
Conclusions: The results showed that China's local dengue transmission is spatially and temporally featured, and that the prevalence of this epidemic is mostly related to imported cases from overseas epidemic areas. This study provides useful support for hygiene authorities of central and local governments to take effective measures to prevent and control this disease.

Key words: mainland China; spatiotemporal variations; local dengue fever epidemic; imported dengue fever epidemic.

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Introduction

Dengue is a mosquito-borne tropical disease caused by dengue virus. Over the past 50 years, the global geographic distribution of dengue has grown 30-fold [1], and the incidence rate has also increased nearly 30-fold during the past decade [2]. At present, there is no vaccine or antiviral treatment specifically for dengue. As a result, dengue is now a serious public health issue, especially in developing countries.

In China, dengue has been included in the list of notifiable communicable diseases since the 1990s [3]. However, this disease has shown an ever-increasing trend both in its extent and severity, particularly in Guangdong, Fujian, Zhejiang, and Yunnan Provinces in recent years [4, 5]. Many studies have focused on its epidemiologic features and some influential factors in the regions with high incidence [6-8]. Recent studies have revealed that all dengue epidemics in China are caused by imported dengue cases [9-11]. In addition to the direct role of imported cases, the epidemics are also attributed to natural factors that affect the breeding and survival of the *Aedes* mosquitoes, such as climatic (temperature, humidity), vegetative, and socio-economic factors that affect human-mosquito contact, such as population density, population mobility, economic development, and living conditions of a specific city [7,12-14]. These studies provide strong support for the necessity of appropriate prevention and control measures against dengue in China. However, in the above studies, imported cases were seldom removed from the data on total incidence, which renders it difficult to analyze the effects of such environmental and socio-economic factors on the local dengue epidemic in China. This can affect characterizations of spatiotemporal features of risk prevalence as well as the scientific establishment and effective implementation of measures for prevention and control.

Therefore, based on the dengue epidemic data from 2004 to 2013, this study was undertaken to characterize the spatiotemporal variations of local epidemics at the city level in China, and to explore the relationship of local epidemics to imported cases.

Methodology

Data collection

In this study, the city-scale data of confirmed dengue cases across mainland China from 2004 to 2013 were collected by the China Information System for Disease Control and Prevention, including patient identification information, hospital information, patient addresses, and recent trip records including overseas and domestic travel experience.

Using the month of onset, the city at where the patient was diagnosed, the number of imported cases (defined as cases in which the patient either resided in or worked at an overseas location with known epidemic status within 15 days prior to dengue onset [15,16]), and the number of local cases (defined as cases in which the patient neither worked at nor resided in an overseas location with known epidemic status within 15 days prior to dengue onset), the number of total cases were statistically analyzed by month on both a nationwide and regional basis. If the origin of one case was unknown, but its location theoretically supported only imported cases, the case was considered an imported case. If one case had no overseas travel experience but recently visited domestic cities with known local dengue transmission, the case was considered a local case belonging to the visiting cities. As the total number of cases was small, these cities were divided into two categories during mapping, based on whether the total number of local cases was less or more than 50 over the previous decade.

The municipal administrative divisions used for this study were generated in accordance to the basic geospatial database published by the Resource and Environmental Science Data Center (RESDC) of the Chinese Academy of Science and were based on the national standardized geographic coding of each city and its dengue epidemic data, as well as the corresponding spatial positions (administrative divisions). It should be noted that municipalities have not been further divided into individual counties.

Pearson's correlation

Pearson's correlation was used in the analysis of local dengue transmission (cases and infected cities) associated with the amount and distribution (infected cities) of imported cases. P values of less than 0.05 or 0.01 were considered to indicate statistical significance. All analysis were carried out using Statistical Package for Social Sciences (SPSS) version 14.0.

Spatial analysis

As a typically useful method, spatial autocorrelation analysis is widely utilized to explore the spatial patterns of incidence or mortality of diseases in terms of Moran's I [17-19], which was selected due to its greater statistical power. According to the following formula [20], Moran's I is produced by standardizing the spatial autocovariance by the variance of the data using a measure of the connectivity of the data.

$$I = \frac{N\sum_i\sum_j \omega_{ij}(x_i-\bar{x})(x_j-\bar{x})}{(\sum_i\sum_j \omega_{ij})\sum_i(x_i-\bar{x})^2} \quad (1)$$

where n is the total number of cities; ω_{ij} is the spatial weight between city i and j; x_i and x_j are the numbers of dengue cases (local or imported) in i-city and j-city, respectively; and $\bar{x}$ is the mean of the city-level dengue cases. Moran's I value ranges from -1 to 1. Generally, a higher positive Moran's I value represents a tendency toward clustering, which means that adjacent cities have similar levels of cases, whereas a lower negative value indicates a tendency toward dispersing, which means that the cities with a large number lie next to cities with a low one. A fuller description is provided by Anselin and Getis [20].

Compared to the capability of spatial autocorrelation to indicate the spatial patterns (global clustering or dispersing) of the cities, hotspot analysis could further capture the detailed spatial variations by means of locating the hot or cold clusters [21, 22]. In this study, Gettis-Ord G*i** [23] was chosen to identify the locations of statistically significant hotspots and cold spots by the following formulas:

$$G_i^* = \frac{\sum_{j=1}^{n}\omega_{i,j}x_j - \bar{X}\sum_{j=1}^{n}\omega_{i,j}}{S\sqrt{\frac{\left[n\sum_{j=1}^{n}\omega_{i,j}^2-\left(\sum_{j=1}^{n}\omega_{i,j}\right)^2\right]}{n-1}}} \quad (2)$$

$$\bar{X} = \frac{\sum_{j=1}^{n}x_j}{n} \quad (3)$$

$$S = \sqrt{\frac{\sum_{j=1}^{n}x_j^2}{n} - (\bar{X})^2} \quad (4)$$

The G*i** statistic is a *Z*-score, so no further calculations are required. A high Z-score and small p value for a city indicates a significant hotspot. A low negative Z-score and small p value indicates a significant cold spot. The higher (or lower) the Z-score is, the more intense the clustering. A Z-score near zero means no spatial clustering.

Both spatial autocorrelation and hotspot analysis were completed using Arcgis 10.0.

Results

Imported dengue cases

Generally, the pattern of imported dengue cases from 2004–2013 showed temporal and spatial variation. The amount of imported cases (Figure 1a) and the number of cities reporting imported cases (Figure 1b) tended to increase yearly. In particular, the number of imported cases in 2013 was three times of that in 2012.

During 2004–2013, all the cities with imported cases were mostly distributed in eastern, southern, northeastern, and central China (Figure 2a). Among them, Beijing, Dehong, Xishuangbanna, Kunming, Guangzhou, Shenzhen, and Fuzhou had more than 50 imported cases. In addition, cities with imported cases tended to be spread from southern to central and northern China, according to the distribution of cities with imported cases from 2004 to 2013 (Figure 2b-k).

Local dengue transmission

The ratios of monthly local cases to yearly cases showed that the local dengue epidemics occurred in an obviously seasonal pattern. Most of the local dengue cases were reported from August to October in 2004–2013, where local cases in September and October accounted for more than 50% of the yearly cases except in 2005 (Figure 3).

From 2004 to 2012, the number of annual local cases was less than 500, except in 2006, where the number rose beyond 1,000 cases (Figure 1a). In 2013, it rapidly increased to over 4,000 cases (approximately 1.55 times the total from 2004 to 2012). As far as the relationship between local and imported cases was concerned, the number of local cases was significantly correlated with that of imported cases during the past decade ($r = 0.88$, $p < 0.01$).

As the number of both local and imported cases increased (the cross bar in Figure 1b) during 2004–2013, the number of cities with local (only) cases did not show an increasing trend simultaneously (the dense bar in Figure 1b). However, the number of total cities, including the cities with only local, only imported cases, and those with both local and imported cases, was remarkably associated with that of

Figure 1. Numbers of local and imported dengue cases (a) and cities with imported (only), local (only), and both local and imported cases (b) in mainland China, 2004–2013

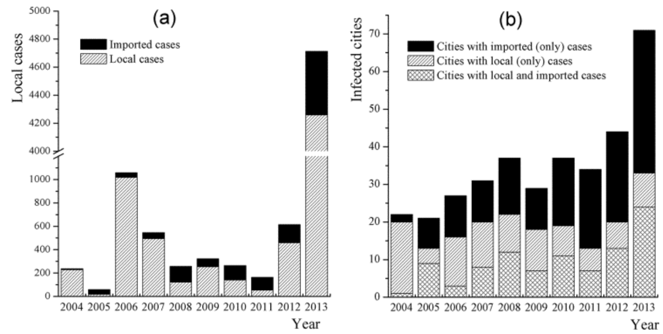


Figure 2. Spatial distribution of cities with accumulative (a) and annual (b-k) imported cases during 2004–2013

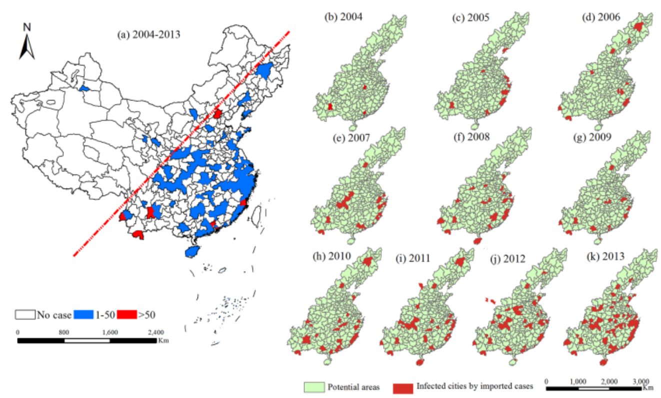
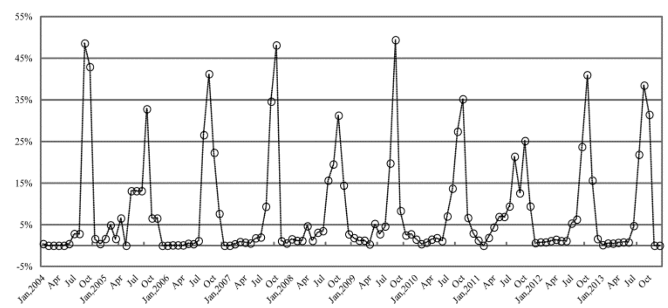


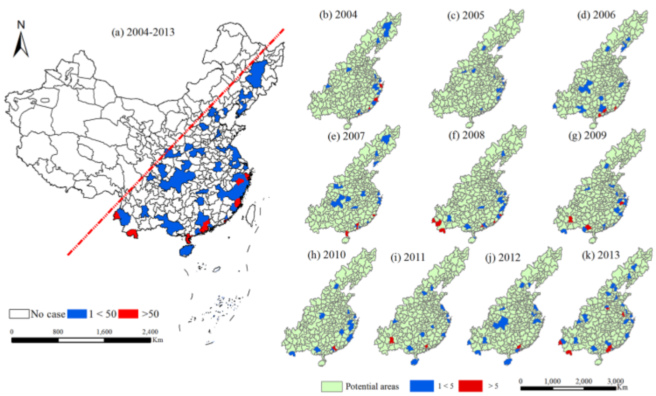
Figure 3. Ratios of monthly local cases to the annually summed local cases in 2004–2013



cities with imported cases and both local and imported cases ($r = 0.97$, $p < 0.01$).

All the cities with local cases were mainly located in eastern, southern, northeastern, and central China (Figure 4a). However, the distribution of cities with local cases (Figure 4b-k) was not similar to that of cities with imported cases, which exhibited a spreading trend (Figure 2b-k). As an exception, in 2013, when the nation-level local cases came to more than 4,200, two inland cities, including Nanjing and

Figure 4. Spatial distribution of cities with accumulative (a) and annual (b-k) local cases during 2004–2013



Xuchang cities, had 7 and 29 local cases, respectively (Figure 4k).

Among the southeastern and southwestern cities of China, Dehong, Xishuangbanna, Zhanjiang, Guangzhou, Foshan, Jiangmen, Zhongshan, Zhuhai, Shantou, Fuzhou, Putian, Ningbo, and Jinhua each had more than 50 local cases during 2004–2013. Meanwhile, yearly accumulative local cases in these areas accounted for 79% of the national-level local cases during 2004–2013 (Table 1).

Spatial clustering of dengue epidemics

Using spatial analysis methods, spatial distribution of local cases was analyzed at the city level. As illustrated in Figure 5, there was no obvious spatial clustering of local cases in 2004, 2006–2009, and 2011 due to the lower Moran's index (Moran's I < 0.01, p >

Figure 5. Spatial autocorrelation coefficients of city-level local cases from 2004 to 2013

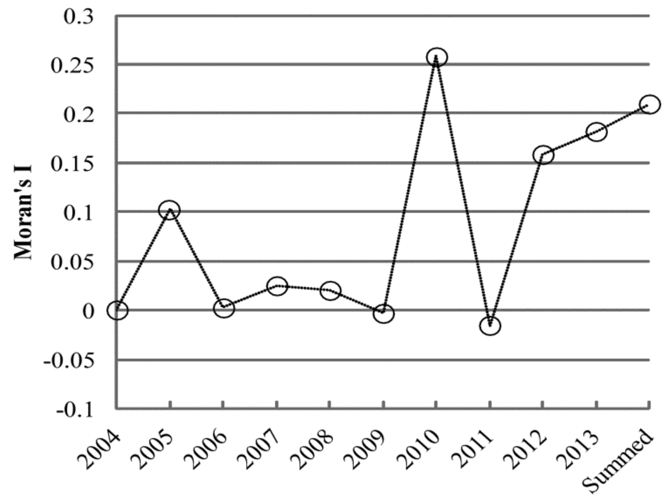


Figure 6. Hotspot areas of city-level local cases in the potential areas in 2005 (a), 2010 (b), 2013 (c), and the period from 2004–2013 (d)

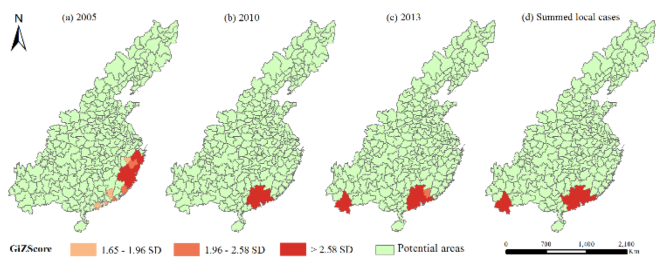


Table 1. Summary of the amount of local dengue cases of cities in the three main hotspot areas in mainland China, 2004—2013

Provinces	Municipal areas	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
Guangdong	Guangzhou	1	1	771	22	4	4	65	34	151	1,290	2,343
	Zhongshan	35	0	0	20	0	2	4	0	3	804	868
	Foshan	1	0	29	1	34	0	1	0	280	432	778
	Zhanjiang	0	0	0	205	0	0	0	0	0	0	205
	Zhuhai	0	0	0	129	0	0	0	0	8	27	164
	Jiangmen	0	0	0	0	3	0	0	0	1	242	246
Zhejiang	Ningbo	73	1	0	1	0	1	0	2	0	1	79
	Jinhua	1	0	0	0	1	196	1	0	0	0	199
Yunnan	Xishuangbanna	0	0	0	0	9	1	3	0	1	1,303	1,317
	Dehong	0	0	1	0	9	0	0	0	1	150	161
	Kunming	0	0	0	0	3	13	0	7	1	2	26
Fujian	Fuzhou	94	3	0	0	0	2	1	1	0	3	104
	Putian	1	3	0	104	9	0	3	0	0	2	122
Total local cases of above regions		206	8	801	482	72	219	78	44	446	4,256	6,412
The whole nation		229	19	1,018	494	122	254	140	54	459	4,259	7,048
Percentage of above local cases		90%	42%	79%	98%	59%	86%	56%	81%	97%	100%	91%

0.05). However, there were positive results for the data of 2005, 2010, and 2012–2013 (Moran's I > 0.1, p < 0.01). The total local cases were also spatially clustered at the city level (Moran's I > 0.2, p < 0.01).

The Z-scores of the spatial analysis are given in Figure 6. In 2005, the cities with the largest number of local cases were spatially clustered along the coastal areas of Zhejiang and Fujian, and in 2010, the cities were clustered around the Pearl River Delta. In addition to the Pearl River Delta, Xishuangbanna and Simao in Yunnan near the Myanmar border were also hotspots of local cases clustering in 2013 and total local cases in 2004–2013.

Discussion

After analyzing the types of dengue virus isolated from local cases and imported cases, Luo [9] concluded that the current dengue epidemics in China are still imported infections. A quantitative relationship between local and imported dengue cases was obtained in our study, which supplied evidential support for this consideration. Therefore, finding and diagnosing imported dengue cases as early as possible is the first step in preventing the importation of dengue and any subsequent epidemic outbreak.

Whether the dengue epidemics in mainland China occurred from July to September [4, 24] or from June to October [25] is still debated. In this study, we found that more than half of the total local cases each year were reported from September to October, and we believe that this period is critical for the dengue epidemic outbreak. These differences may be due to data collection (*i.e.*, total number of cases/incidence rates, number of local cases), time scale, and indicators for analysis. However, because there is almost one month of lag time between imported cases and the local epidemic outbreak, which included extrinsic and intrinsic incubation period of dengue, the prevention and control measures should be initiated one month early, in the middle of July.

With the spatial analysis methods, Fan*et al.,* [26] and Liu*et al.,* [27] pointed out that county-level hotspot areas with higher risk of dengue are located in the Pearl River Delta and the Hanjiang River Delta in Guangdong Province. In this research, cities in the Pearl River Delta, the coastal areas of Fujian and Zhejiang, and the Sino-Myanmar border areas were all considered hotspot areas of dengue. These three regions cover four provincial areas, including Guangdong, Yunnan, Zhejiang, and Fujian, that accounted for 63%, 21%, 4%, and 3% of the national-level local cases in 2004–2013, respectively. Apart from the influence of imported cases, weather conditions of these four provinces are also regarded as important factors in dengue outbreaks. Suitable temperature and relative humidity in the early autumn in these areas are fit for the development of vector mosquitoes, and the high density of mosquitoes is an essential condition for the outbreak of dengue [27-31]. Accordingly, hygiene authorities of these provinces should make efforts to control vector mosquitoes before and in the dengue epidemic season.

Because of the importance of imported cases for dengue epidemics of China, the diagnosis and management of imported cases should be improved to decrease the risk of dengue outbreak. Now most hospitals and local CDCs of China diagnose dengue cases with serological methods to detect antibodies against dengue virus. Thus, almost one week is necessary for a dengue patient to be confirmed, and then all measures used in patient management will be useless for disease control and prevention. Now that the method of antigen detection is established and related kits are available, the diagnostic method should be improved to confirm and manage patients in time.

During the data analysis, many local cases were found to be reported from northern China, where the weather conditions are not suitable for dengue transmission. We suggest that the local CDC should confirm these cases, do comprehensive epidemiological investigation about these cases, and give enough information about the infection history of these patients. Only with this information can the public health authorities make an accurate assessment about the risk of dengue outbreaks in the area.

Conclusions

The local dengue epidemic in mainland China was caused by imported cases and was spatially and temporally clustered. We suggest that the public health authorities in southern China should strengthen the surveillance, diagnosis, and management of imported dengue cases, and continuously make efforts to decrease the density of mosquitoes in the summer and autumn. The methods for diagnosing dengue cases could be improved to make dengue case confirmation and management more effective.

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