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Epidemiological dynamics of dengue fever in mainland China, 2014–2018

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ABSTRACT

Objective: To explore the epidemiological dynamics of dengue fever.
Methods: Epidemiological dynamics of imported and indigenous dengue cases during 2014-2018, including demographic, time-series, spatial and spatio-temporal features, were analyzed.
Results: There were 5 458 imported dengue cases and 59 183 indigenous dengue cases during 2014-2018. Both imported and indigenous dengue cases show seasonal patterns from August to November. 12.9% (12.9/100) of dengue cases were from businessmen. 58.2% (58.2/100) of dengue cases were from individuals between 21-50 years old. Imported dengue cases, mainly from Southeastern Asia, had doubled, and were distributed in 734 counties, 29 provinces, with 50% (50/100) in Yunnan. Except in 2014, indigenous dengue cases were under 5 000 every year, but the number in counties increased dramatically from 51 to 127. The total cases were distributed in 314 districts, 13 provinces. They were clustered in Yunnan border and southern Guangdong. They emerged gradually from southwestern and southern provinces to southeastern coastal provinces, and then to central and northern provinces every year. They spread from the southern regions to the central and northern regions in 2014-2018.
Conclusions: The findings of epidemiological dynamics of dengue fever are helpful to formulate targeted, strategic plans and implement effective public health prevention and control measures.

Introduction

Dengue fever, one of the most prevalent mosquito-borne diseases in humans, is mainly transmitted by *Aedes aegypti* and *Aedes albopictus* (Bhatt et al.,2013). There are four serotypes for dengue fever: Flavivirus, i.e. Dengue-1, Dengue-2, Dengue-3, and Dengue-4 (Sang et al., 2015). Dengue fever is endemic in more than 100 countries in Southeast Asia, the Americas, Western Pacific, Africa, and Eastern Mediterranean regions (Guzman and Harris, 2015). Dengue fever has evolved from a sporadic disease to a major public health problem as geographical extension, numbers of cases, and disease severity increases (Guzman and Harris, 2015). It is estimated that 390 million people had dengue virus infections with 96 million cases annually worldwide (Bhatt et al.,2013). World Health Organization (WHO) estimates that more than 50 million dengue infections and 20 000 dengue-related deaths occur annually worldwide (World Health Organization, 2007, 2012).

A total of 655 324 cases and 610 deaths were reported in mainland China from 1978 to 2008. A total of 52 749 cases and six deaths were reported from 2009 to 2014 (Chen and Liu, 2015). A dengue fever outbreak occurred in China in 2014, with 47 127 dengue cases according to the China National Notifiable Disease Surveillance System (Yue et al., 2018). Dengue fever outbreaks have spread from Guangdong and Hainan in the southern coastal areas to the relatively northern and western areas including Fujian, Zhejiang, and Yunnan, with shorter outbreak intervals as compared to those before the 1990s (Wu et al., 2010).

A better understanding of dengue fever outbreaks can help in the planning of resource allocation for dengue fever prevention and control (Lai et al., 2015). Many studies have been conducted to explore the characteristics of dengue fever in mainland China. including the overall demographic features, geographical distribution, temporal distribution, spatio-temporal characteristics and seasonal distribution (Bhatt et al., 2013; Castro et al., 2018; Chen and Liu, 2015; Corner et al., 2013; Dewan et al., 2017; Fan et al., 2014; Hashizume et al., 2012; Lai, 2011; Lippi et al., 2018; Liu et al., 2014; Liu et al., 2018a; Liu et al., 2018b; Sun et al., 2017; Wang et al., 2013a, 2013b; Yue et al., 2018). However, most of the research is

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focused on indigenous dengue fever. The analysis of imported dengue fever is rare. Spatial emerging analysis of dengue fever over time every year in mainland China is also unclear. Moreover, the further spatial diffusion of dengue fever is unclear for recent years. Therefore, this study analyzed epidemiological dynamics of imported and indigenous dengue fever in 2014-2018 in mainland China, including demographic features, time-series features, spatial features, spatio-temporal features, spatial diffusion, and so on.

Materials and methods

Data collection and processing

Dengue cases were defined based on clinical diagnosis and laboratory confirmation according to diagnostic criteria and principles of management for dengue (WS 216-2001, before 2008) or diagnostic criteria for dengue (WS 216-2008, after 2008) (WS 216-2001; WS 216-2008).

Dengue fever is a vector-borne notifiable disease in China. The attending physicians are required by law to report to Chinese Center for Disease Control and Prevention (China CDC) through the Chinese National Notifiable Infectious Disease Reporting Information System (NNDS). Each dengue case is confirmed through clinical diagnosis or laboratory diagnosis. A dengue case report includes sex, age, occupation, national code of current address, date of illness onset, and remarks, etc. There are several kinds of occupations, such as Businessman, Student, Farmer, etc. Daily dengue case reports from January 1st 2014 to December 13th 2018 were obtained from NNDS. Demographic data at the county level in 2010 were obtained from the sixth population census of the National Bureau of Statistics of China.

According to the remarks of dengue case reports, dengue cases were divided into indigenous cases, imported cases and others as 5 458 cases, 59 183 cases and 983 cases, respectively. Other cases included what we were not sure how to classify, for example, some cases were from other provinces according to the remarks of dengue case reports, but we did not know which counties these cases were from. Finally, Indigenous dengue cases occurred from June to December. In order to perform spatio-temporal analysis, dengue cases were aggregated at the county level according to national codes of current addresses, and then were geocoded and matched to the county-level administrative boundaries using ArcGIS version 9.5 (ESRI, 2017). There are 31 provinces (or municipalities) comprised of 2 922 counties in mainland China, with populations ranging from 7,123 to 5,044,430, with geographic areas ranging from 5.4 to 197,346 square kilometers (Wu et al., 2016).

Spatial, temporal and spatio-temporal analyses of dengue fever

Time-series mapping analyses for imported and indigenous dengue cases were conducted using IBM SPSS Statistics version 24.0 (IBM Corp., NY, USA). Spatial distribution analyses and spatial diffusion analyses for indigenous and imported dengue cases were conducted using ArcGIS version 9.5.

Global Moran's I for global indication of spatial autocorrelation (GISA) reflects the similarity of attributes in spatial adjacent regions (Wang, 2006). Global Moran's I is calculated on the basis of Z-test ($P \leq 0.05$). Global Moran's I scores range from -1 to 1.The closer Global Moran's I approaches 1, the more aggregated the whole attributes are (High-value aggregation or Low-value aggregation). The closer Global Moran's I approaches -1, the more dispersed the whole attributes are. Global Moran's I is 0, which represents global random distribution. GISA was adopted to identify the global clustering characteristic of indigenous dengue cases. Local Moran's I for local indication of spatial autocorrelation (LISA) is a measure of the similarity or difference between the attribute of the observation unit and those of surrounding units.

The LISA accumulative map is drawn on the basis of Z-test ($P \leq 0.05$) (Wang, 2006). LISA was adopted to identify significant hotspots (High-High), coldspots (Low-Low), and outliers (High-Low and Low-High) of indigenous dengue cases by calculating local Moran's I index between the value in a given county and those in the surrounding counties. The significance level of clusters was determined by a Z score generated by comparison of the Local Moran's I statistic for the average incidence in each county. A high positive Z score indicated that the surroundings had spatial clusters (High-High: high-value spatial clusters or Low-Low: low-value spatial clusters) and a low negative Z score indicated the presence of spatial outliers (High-Low: high values surrounded with low values or Low-High: Low values surrounded with high values) (Anselin, 1995). GISA analyses and LISA analyses can be realized by GeoDa version 0.9.

Kulldorff's space-time scan statistic software SaTScan version 9.3 was used to explore the locations of high-risk space-time clusters. The spatio-temporal scan statistic was defined by a cylindrical window with a circular (or elliptic) geographic base and with height corresponding to time (Kulldorff, 2014). Purely spatial analysis scanning for clusters with high rates using the Discrete Poisson model was employed for average monthly indigenous dengue cases in the counties. Circular scan windows were selected. The maximum spatial cluster size was set as 500 km. Likelihood ratio tests were evaluated to determine the significance of identified clusters and P-values were obtained through Monte Carlo simulation after 999 replications. The null hypothesis of a spatiotemporally random distribution was rejected when the P-value was ≤ 0.05 (Ling et al., 2014). Retrospective space-time analysis scanning for clusters with high rates using the space-time Permutation model was employed for monthly indigenous dengue cases from 2014 to 2018. Circular scan windows were selected. The maximum spatial cluster size was set as 500 km. Monte Carlo simulations after 999 replications were used to evaluate the significance of spatiotemporal clusters ($p \leq 0.05$) (Ling et al., 2014).

Results

Imported dengue cases analyses

Time-series analyses of imported dengue cases

There existed seasonal characteristic for imported dengue cases, which was from August to November. There were 5458 imported dengue cases in 2014-2018. There were 399 imported dengue cases in 2014, which multiplied each year in 2015-2018. The imported dengue cases in 2017 reached as high as in 2112.

Spatial mapping of imported dengue cases

Imported dengue cases during 2014-2018 originated from 52 countries, with 18 from Southeastern Asia, 19 from Africa, 9 from the America and 6 from Oceania. The largest number of imported dengue cases was 2 852 and was from Myanmar, which is in Yunnan border, China. The countries with more than 100 imported dengue cases were from Southeast Asia.

These imported dengue cases during 2014-2018 were distributed in 734 counties, 29 provinces (or municipalities), in China. The most imported dengue cases, 1640, were from Ruili City, Dehong Dai Jingpo Autonomous Prefecture, Yunnan Province. The number of imported dengue cases in Yunnan province, 2858, reached more than half of the total imported dengue cases. The imported dengue cases in 101-256 were distributed in the counties of Yunnan border, China. The imported dengue cases in 11-100 were distributed in the counties of Yunnan border, southeastern coast of Guangdong Province, Fujian Province, Zhejiang Province, Shanghai Municipality, Beijing Municipality and Chongqing Municipality.

Population analyses of imported dengue fever

The top five yearly occupation rates for imported dengue cases were Farmer, Businessman, Student, Housework or Unemployment, and Worker. The yearly rate of the occupation Farmer reached the highest at 34.7/100 (34.7%) in 2017. The yearly rate of Businessman was more than 20/100 (20%). The yearly sexual rate of Male was significantly higher than that of female, reaching about 60/100 (60%) every year. The top three yearly age rates were from the age groups of 21-30, 31-40 and 41-50, accounting for 29.3/100 (29.3%), 24.7/100 (24.7%) and 18.3/100 (18.3%) of the total cases in five years, respectively. There were 1833 foreigners among the total imported dengue cases, and the occupations of the top three cases were Farmer, Businessman, and Student, with 770, 330 and 303, respectively.

Indigenous dengue cases analyses

Time-series analyses of indigenous dengue cases

There were 59 183 indigenous dengue cases in 2014-2018, which were distributed in 314 counties, 13 provinces (or municipalities). There existed seasonal characteristics from August to November. Dengue fever outbreak occurred in mainland China in 2014, with 46 105 indigenous dengue cases distributed in 207 counties, and both cases and counties reached the largest numbers in 2014-2018. Over the past five years, the number of cases and counties had both declined and increased again. The changes in number of counties were larger than those in cases.

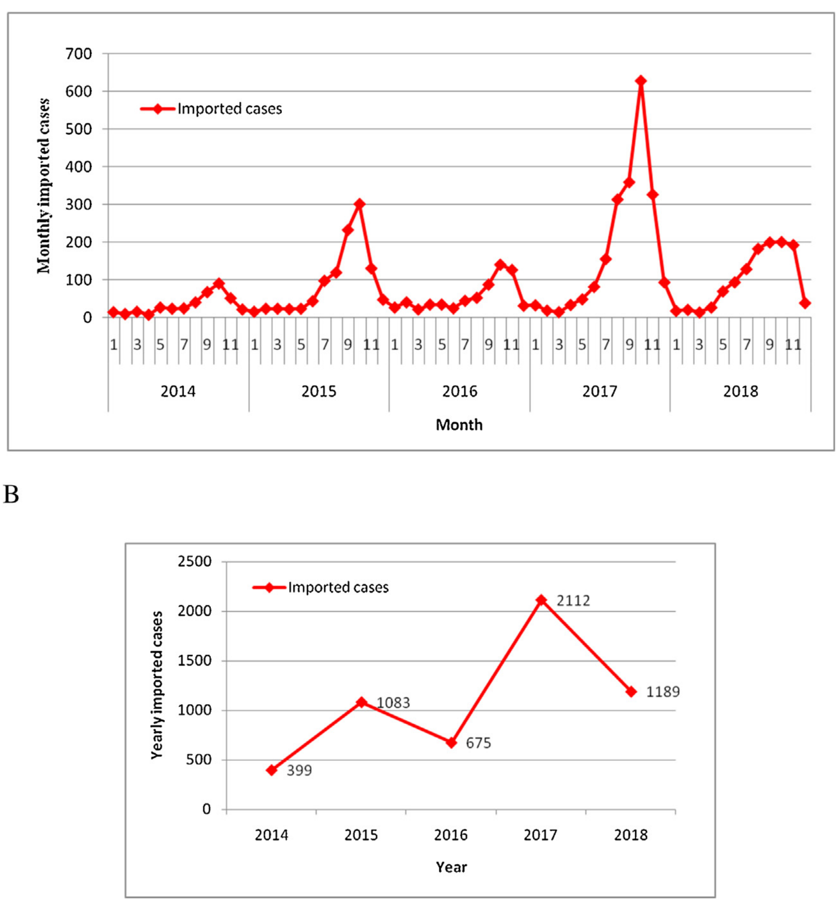
Spatial mapping of indigenous dengue fever

The largest yearly indigenous dengue cases at the county level from 2014 to 2018 were 11 834, 1 250, 500, 1 033 and 486, respectively, which were distributed in Baiyun County (located in Guangzhou City, Guangdong Province), Xiangqiao County (located in Chaozhou City, Guangdong Province), Minhou County (located in Fuzhou City, Fujian Province), Jinghong City (located in Xishuangbanna Dai Autonomous Prefecture, Yunnan Province), Jinghong City, respectively. There were 29, 3, 5, 11 and 15 counties with more than 100 yearly indigenous dengue cases in 2014-2018, which were distributed in Yunnan Province, Guangxi Province, Guangdong Province, Fujian Province and Zhejiang Province. There were 47 counties with more than 100 yearly indigenous dengue cases, which were distributed in Yunnan Province, Guangxi Province, Guangdong Province, Fujian Province and Zhejiang Province. The largest yearly indigenous dengue cases at the county level were 12 177, which were distributed in Baiyun County, Guangzhou City, Guangdong Province (Figures 1–5).

Spatial diffusion analyses of indigenous dengue fever

Indigenous dengue fever occurred in the Yunnan border, Guangdong Province and Guangxi Province in June-July firstly, and then it gradually emerged in the southeastern coastal provinces and the central and northern provinces in August-

A



B

Figure 1. Time-series analyses of imported dengue cases in mainland China, 2014-2018. A. Time-series mapping of monthly imported dengue cases. B. Time-series mapping of yearly imported dengue cases.

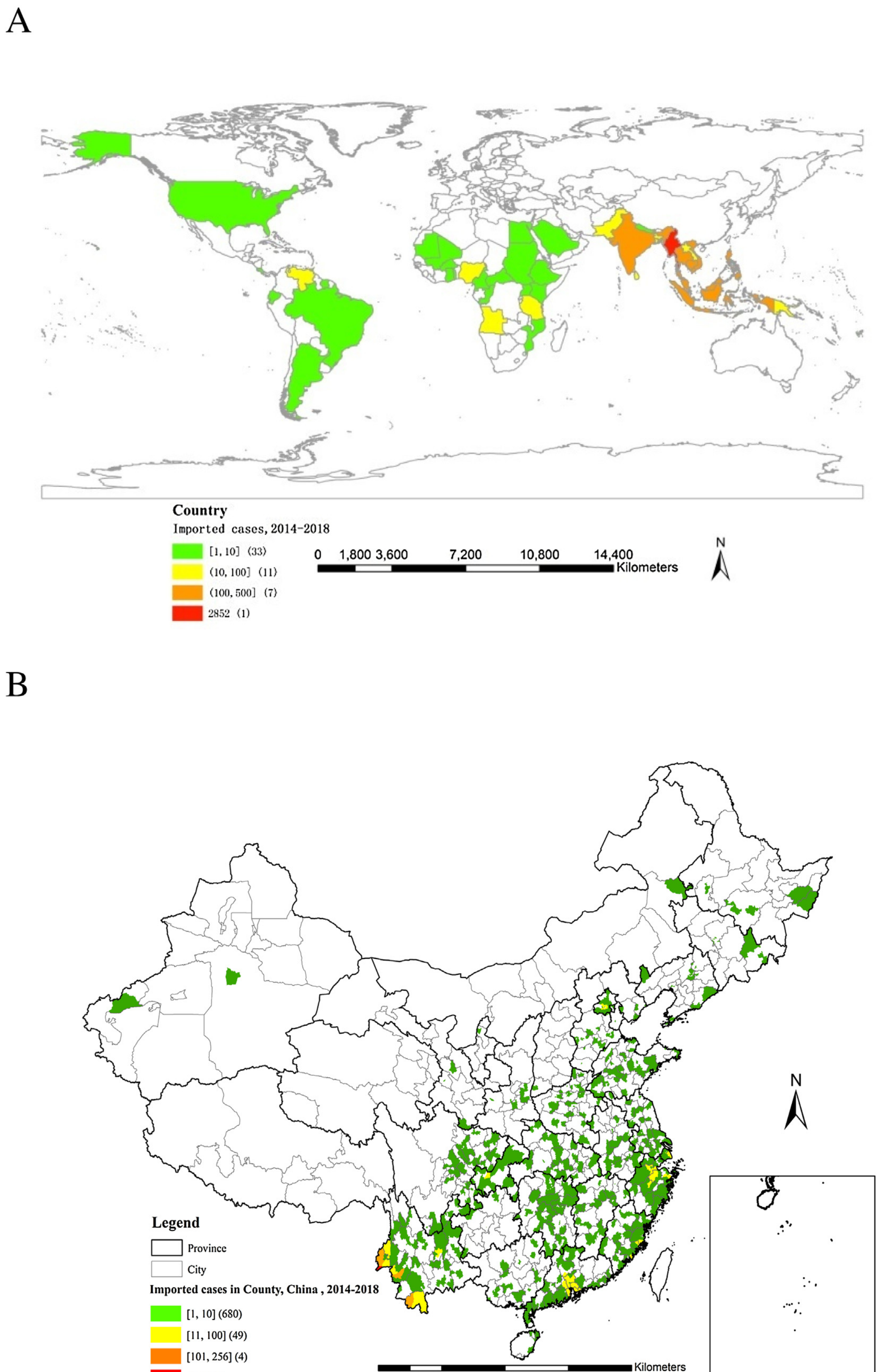


Figure 2. Distribution of imported dengue cases at home and abroad during 2014-2018. A. Overseas distribution. B. Domestic distribution.

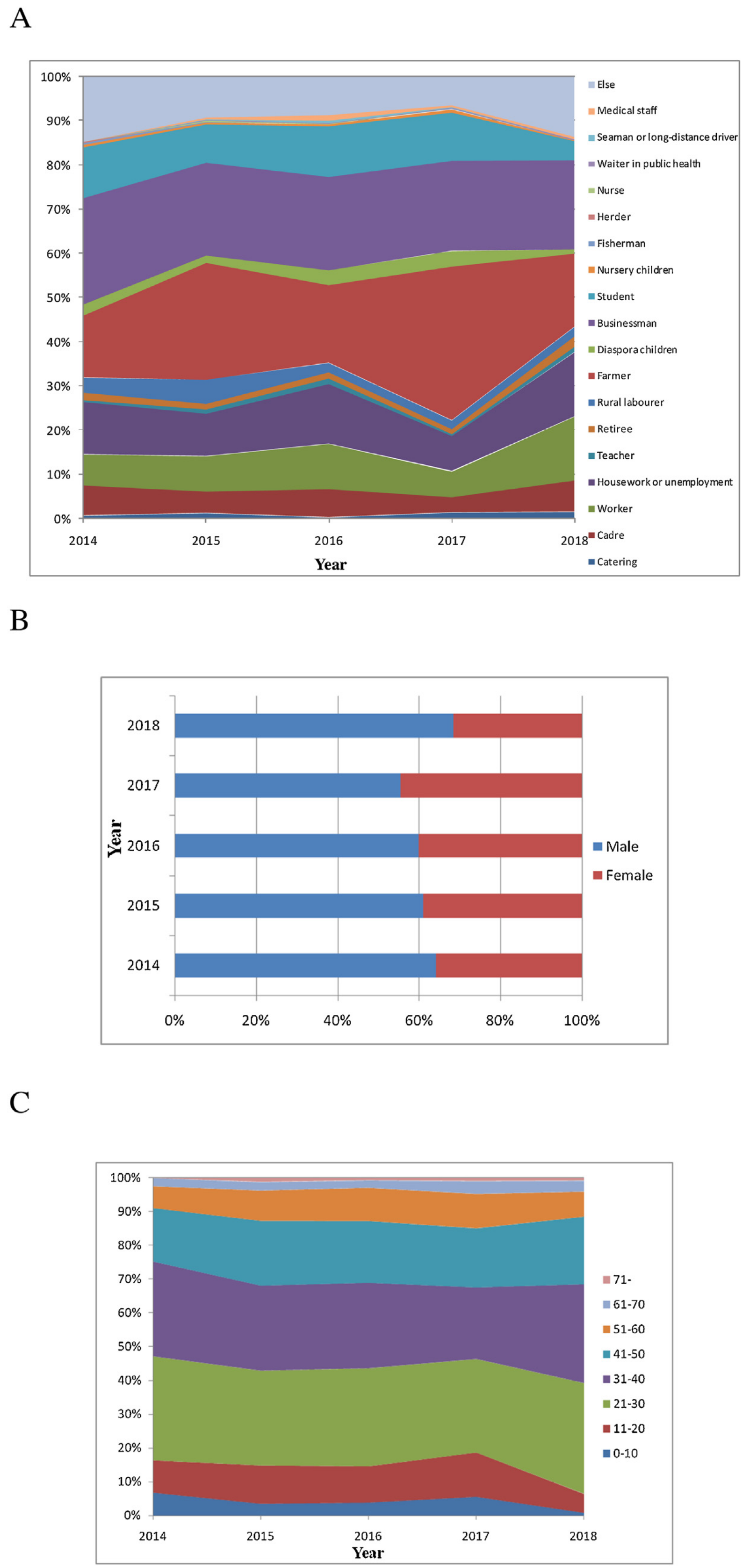
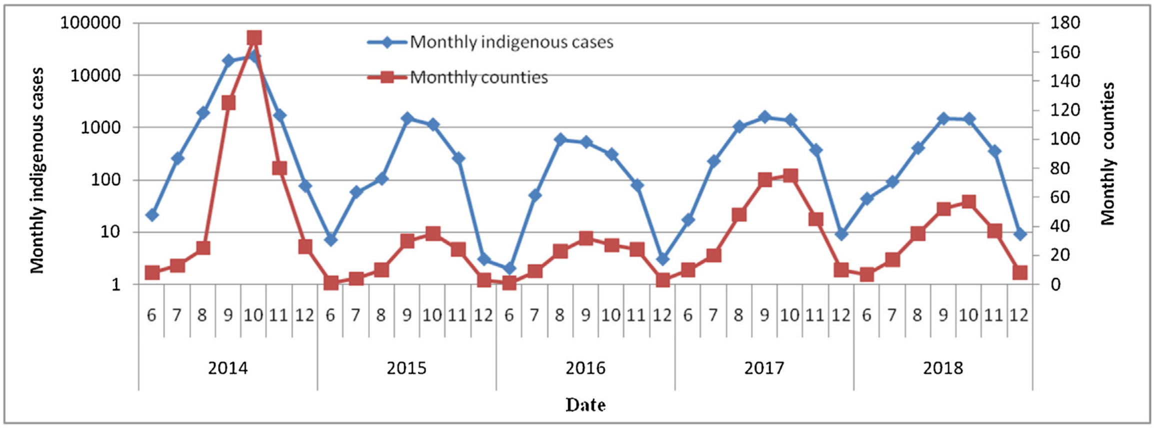


Figure 3. Population analyses of imported dengue cases. A. Yearly career rates. B. Yearly sex rates. C. Yearly age rates.

A



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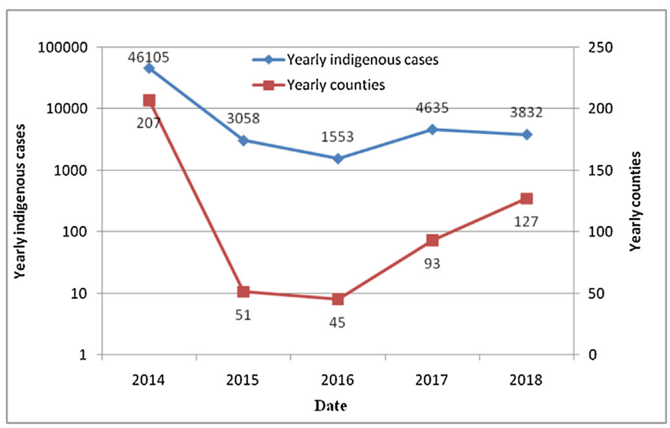


Figure 4. Time-series analyses of indigenous dengue cases in mainland China, 2014-2018. A. Time-series mapping of monthly imported dengue cases. B. Time-series mapping of yearly imported dengue cases.

December (Figure 6(A-E)). The counties where indigenous dengue cases occurred reached the largest at 207 in 2014. The number of new counties where indigenous dengue cases occurred were 17, 10, 38 and 42 from 2015 to 2018, respectively (Figure 4(B)). There were a total of 314 counties related to indigenous dengue fever from 2014 to 2018. The occurrence areas of indigenous dengue fever had spread to the central and northern regions step by step from 2014 to 2018. The areas of indigenous dengue fever in the southwestern border, the southern provinces and southeastern coastal provinces had expanded from 2014 to 2018 (Figure 6(F)).

Population analyses of indigenous dengue fever

The yearly top three occupation rates for indigenous dengue cases were from Housework or unemployment, Retiree, and Businessman, accounting for 22.3/100 (22.3%), 12.6/100 (12.6%) and 12.2/100 (12.2%) of the total indigenous dengue cases in five years, respectively. There were slightly more female than male cases; there was little difference between them. Females accounted for 50.5/100 (50.5%) in the five years. The yearly top three age rates were from the age groups of 21-30, 31-40 and 41-50, accounting for 21.1/100 (21.1%), 18.2/100 (18.2%) and 17.6/100 (17.6%) of the total cases in five years, respectively (Figure 7).

Spatial autocorrelation analyses of indigenous dengue fever

The counties with indigenous dengue morbidity more than 100 (Unit: $1/10^5$) were located in Yunnan Province border and southern areas in Guangdong Province, especially in Guangzhou City. The counties with indigenous dengue morbidity between 10 and 100 (Unit: $1/10^5$) were located in Yunnan border, southeastern coastal areas, southern areas, and southwestern areas in Hunan Province (Figure 8(A)).

The value of Global Moran's I on the basis of statistical significance was 0.475, which indicated that indigenous dengue morbidity had strong spatial clustering characteristics of high or low values (Figure 8(B)).

The LISA accumulative map of indigenous dengue morbidity was drawn on the basis of Z-test ($P \leq 0.05$). 15 counties were located in the High-High regions, and most of them were in Yunnan border and the southern areas of Guangdong Province. 65 counties were located in the Low-Low regions, mainly in Hunan Province, Hubei Province, Henan Province, Jiangsu Province and Guangxi Province (Figure 8(C)). The map of indigenous dengue morbidity (Figure 8(A)) was similar to the LISA accumulative map (Figure 8(C)).

Space-time scan statistic analyses of indigenous dengue fever

According to the results of purely spatial analysis scanning for indigenous dengue fever, there are six spatial clusters with LLR greater than 2000. Two clusters were located in the southwestern border in Ruili City, Dehong Dai Jingpo Autonomous Prefecture, Yunnan Province and Jinghong City, Xishuangbanna Dai Autonomous Prefecture, Yunnan Province. Three clusters were located in

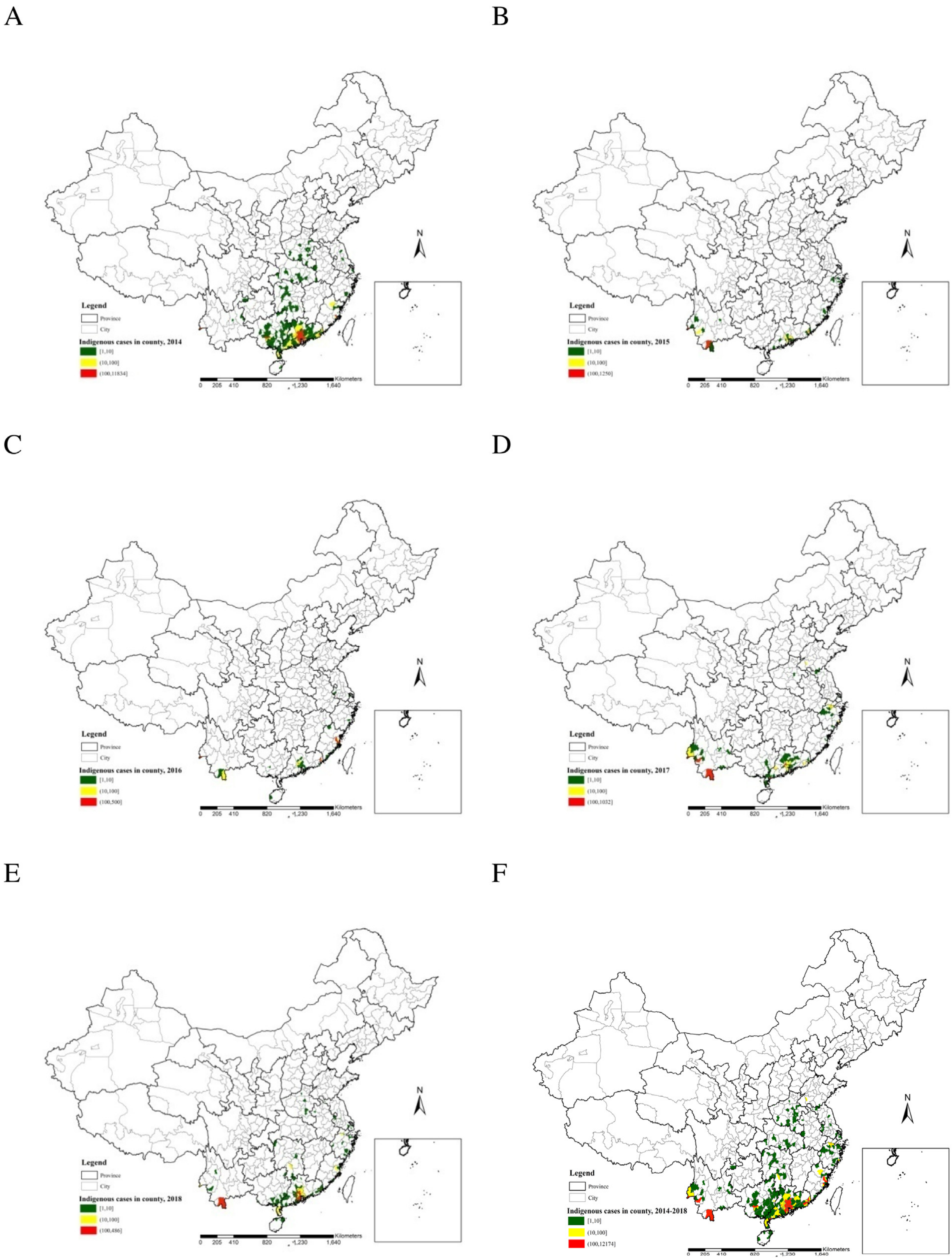


Figure 5. Distribution of indigenous dengue cases in mainland China, 2014-2018. A. in 2014; B. in 2015; C. in 2016; D. in 2017; E. in 2018; F. in five years.

Guangzhou City, Guangdong Province. One cluster was located in Xiangqiao County, Chaozhou City, Guangdong Province.

According to the results of retrospective space-time analysis scanning for indigenous dengue fever, there were seven spatio-temporal clusters. Three clusters were located in Guangdong Province, one in the urban area of Guangzhou City from June to October 2014, one in southern Guangzhou City, Dongguan City, Shenzhen City and Zhongshan City from October to December

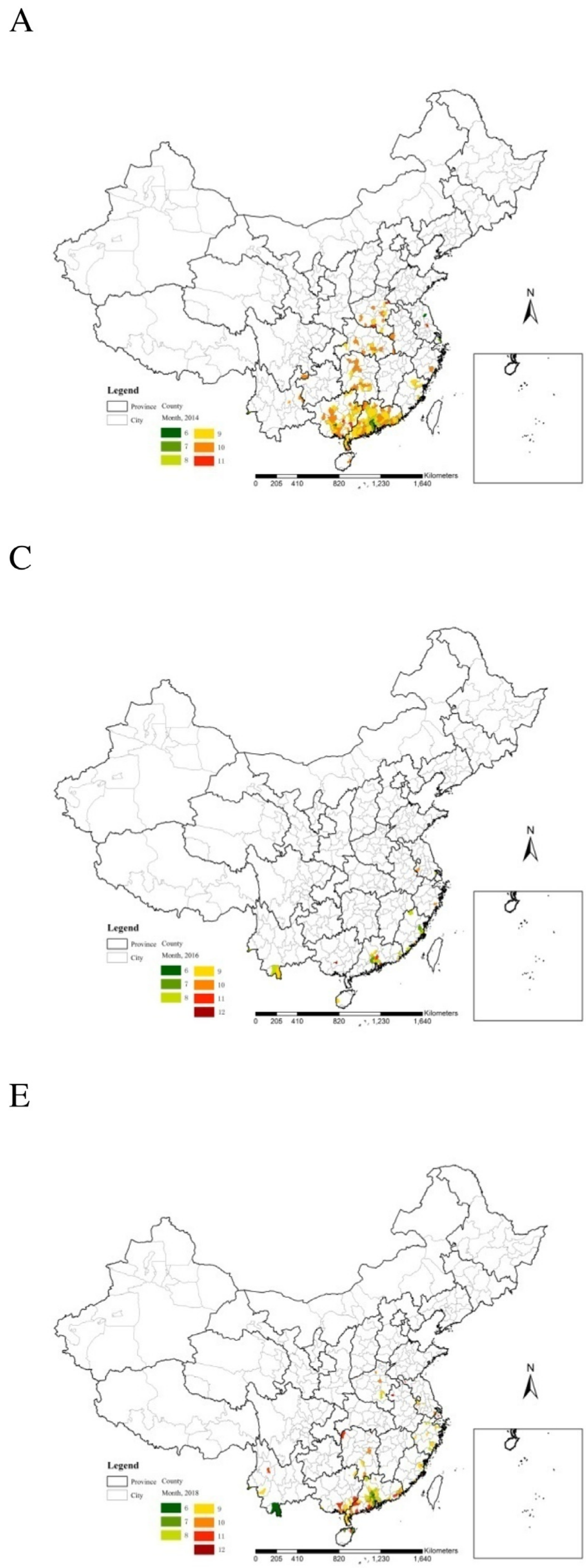
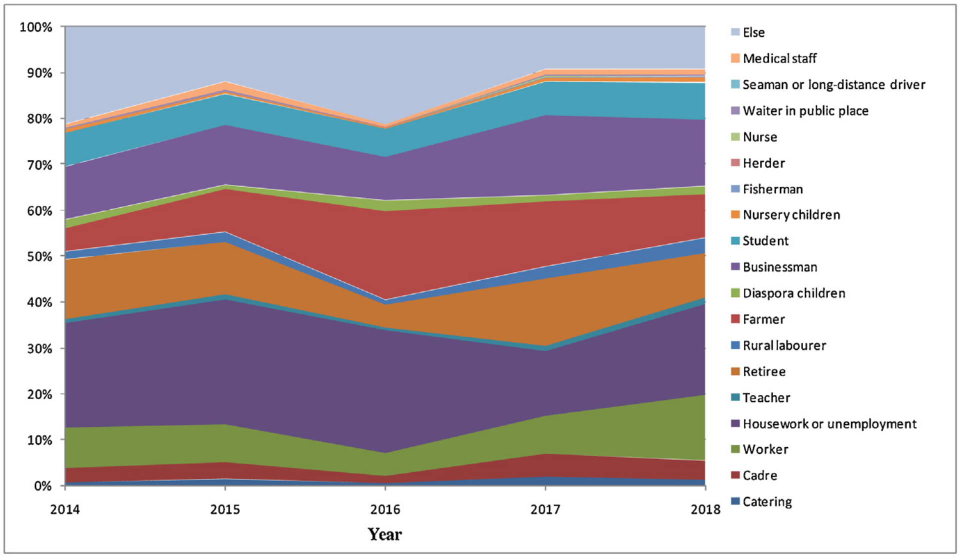


Figure 6. Spatial occurrence analyses every year and spatial diffusion analysis during 2014-2018 for indigenous dengue fever. A. in 2014; B. in 2015; C. in 2016; D. in 2017; E. in 2018; F. During. 2014-2018.

2018, and one in Zhanjiang City in September 2018. One cluster was located in the western Hunan Province in September 2018. One cluster was located in the southwestern border of Yunnan Province from July 2017 to June 2018. One cluster was located in the coastal areas of Fujian Province from September 2015 to August 2016. One was located in some areas of Jiangsu Province and Shanghai Municipality from August to September 2017 (Figure 9).

A



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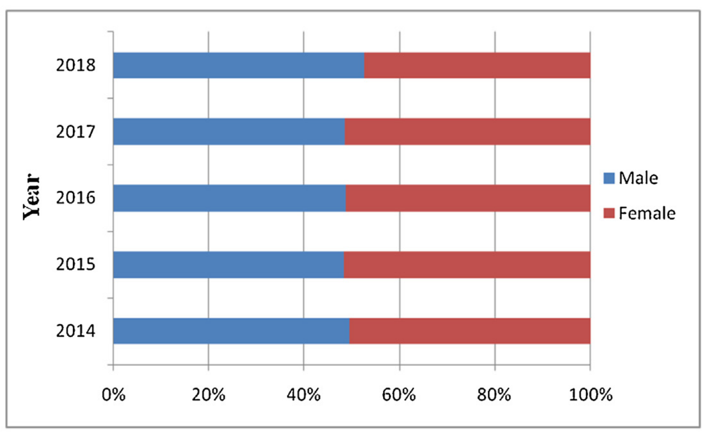

C

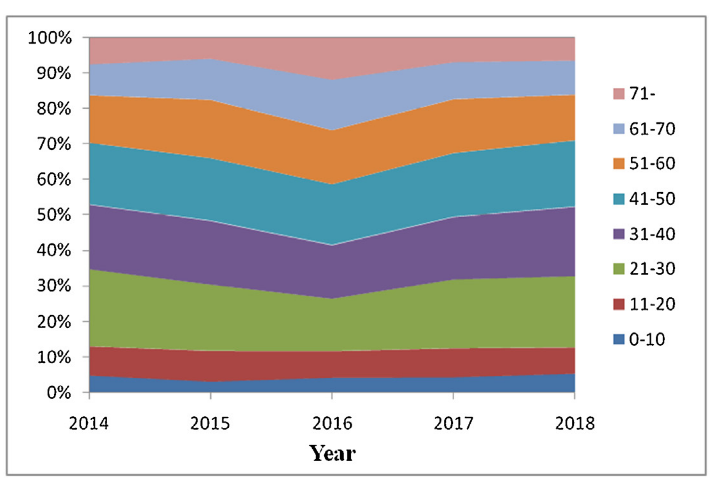

Figure 7. Population analyses of indigenous dengue cases. A. Yearly career rates. B. Yearly sex rates. C. Yearly age rates.

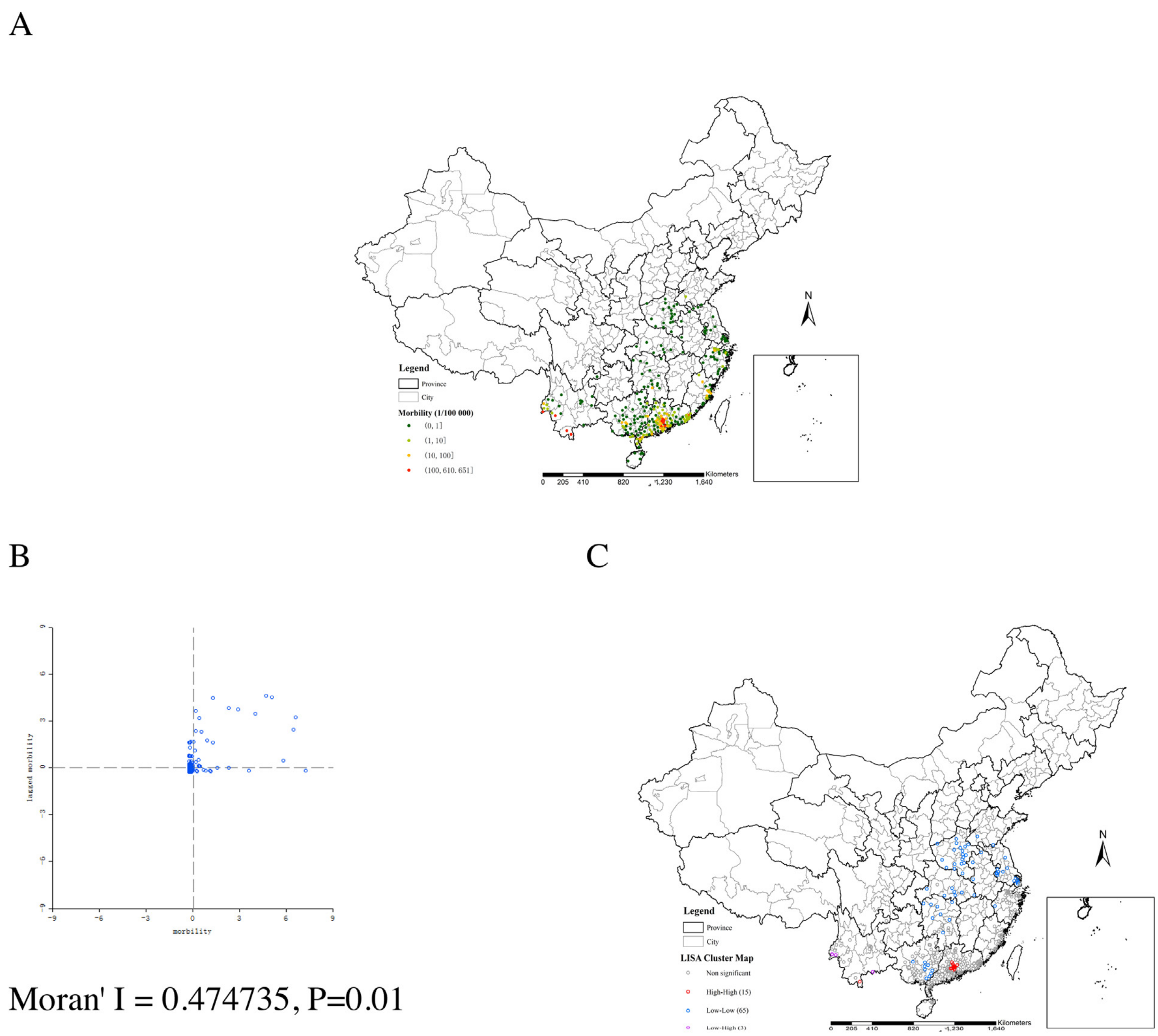

Figure 8. Spatial autocorrelation analyses of indigenous dengue cases. A. Indigenous dengue morbidity in five years. B. Global Moran's I. C. the LISA accumulative map.

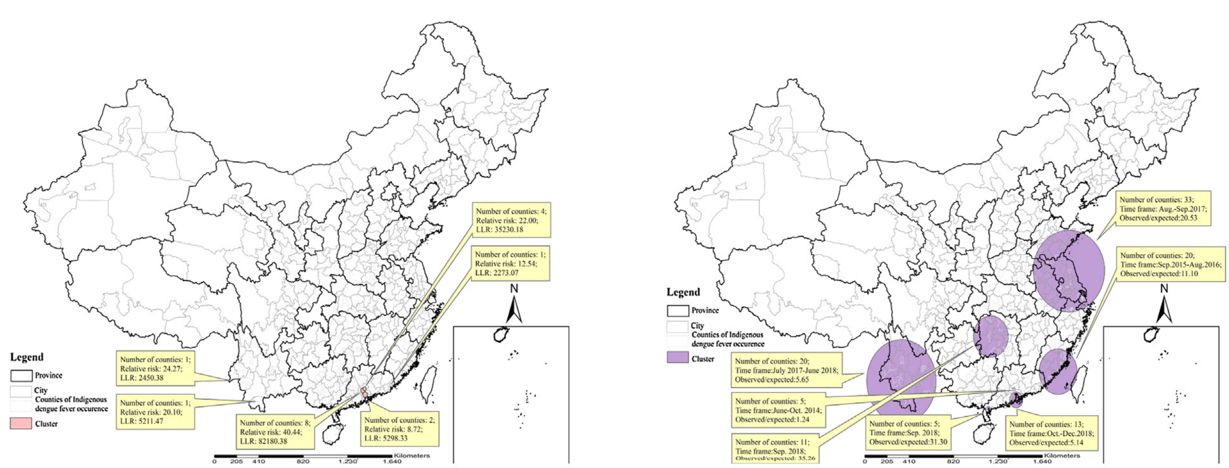

Figure 9. Space-time scan statistic analyses. A. the purely spatial analysis scanning result in 5 years. B. the retrospective space-time analysis scanning result from 2014 to 2018.

Discussion

There were 5 458 imported dengue cases and 59 183 indigenous dengue cases considered in this study. There were seasonal characteristics from August to November for both imported dengue cases and indigenous dengue cases. Dengue fever showed a seasonal pattern. 99.8/100 (99.8%) of indigenous dengue fever cases in continental China occurred from July to November during 2005–2014 (Lai et al., 2015). Imported cases had doubled from 399 to 2112 in 2014-2018. Imported cases in 2017 accounted for about 30/100 (30%) of the total imported cases in 2014-2018. Except for the outbreak of dengue fever in 2014 (Yue et al., 2018), indigenous cases were controlled in 5000 from 2015 to 2018. Compared with the changes of indigenous cases, the counties related to indigenous cases increased dramatically, from 51 to 127 in 2015-2018. Therefore, indigenous cases had been controlled effectively, but had substantial spatial spreading. Spatial spreading of indigenous dengue cases is closely related to economic development, traffic development, population mobility and climate warming, etc., which poses a potential serious threat to public health in China.

Imported cases came from 52 countries in Southeast Asia, Africa, the Americas and Oceania, mainly from Southeast Asia. Dengue fever is endemic in more than 100 countries of Southeast Asia, Africa, Americas, Western Pacific and Eastern Mediterranean regions (Guzman and Harris, 2015). With the movement of people at home and abroad, dengue fever in these regions poses a great threat to China. The main imported dengue source was from Myanmar close to Yunnan border, China, accounting for more than 50/100 (50%) of the total imported cases. Except for Xinjiang Uygur Autonomous Region and Qinghai Province, there were 734 counties in 29 provinces of mainland China with imported cases. The imported cases in Yunnan Province accounted for over 50/100 (50%) of the total imported cases. The imported cases in Ruili City, Dehong Dai Jingpo Autonomous Prefecture, Yunnan Province accounted for about 1/3 of the total imported cases. The rest were mainly distributed along the Southeastern coast in Guangdong, Fujian, Zhejiang and Shanghai, as well as in Beijing and Chongqing. Therefore, imported cases were distributed in borders, coastal areas or developed cities.

Indigenous cases were distributed in 314 counties, 13 provinces, and were mainly distributed in Yunnan, Guangxi, Guangdong, Fujian and Zhejiang, with the largest number of yearly cases of 12 177 in Baiyun District, Guangzhou, Guangdong Province. Many indigenous cases happened in Jinghong City, Xishuangbanna Dai Autonomous Prefecture, Yunnan Province every year. Indigenous dengue fever emerged gradually from Yunnan Province and the southern provinces to the southeastern coastal provinces, and then to the central and northern provinces every year. Indigenous dengue fever spread from the southwestern border, southern provinces, and southeastern coastal provinces to the central and northern regions in 2014-2018. Dengue fever outbreaks have spread from the southern coastal areas to the relatively northern and western areas (Wu et al., 2010). The regions in the southwestern border, southern provinces and the southeast coastal provinces expanded from 2014 to 2018. There were spatial clustering characteristics for indigenous dengue fever, with high value clusters in Yunnan border and southern Guangdong. Dengue fever was concentrated in Ruili City and Jinghong City of Yunnan Province, and Guangzhou City of Guangdong Province from August to October every year. The cases from August to October accounted for 96.3/100 (96.3%) of the total cases in Guangzhou City in 2014, and areas of high density for dengue fever were located at the district junctions in Guangzhou City (Yue et al., 2018). Dengue fever is transmitted by *Aedes albopictus* and *Aedes aegypti* (Bhatt et al., 2013). The hatching and growth of *Aedes albopictus* and *Aedes aegypti* are directly affected by weather conditions such as temperature and rainfall (Lai, 2011). Yunnan border belongs to the torrid zone, with annual rainfall of 800-1600 mm. The Southern region of Guangdong belongs to the subtorrid zone, with annual rainfall of more than 1600 mm. Most of the other provinces related to indigenous dengue fever belong to the subtorrid zone, with annual rainfall of 800-1600 mm. Indigenous dengue fever also occurred in Shandong and Henan, which belong to the warm temperature zone. With the arrival of summer and autumn, the temperature in central and northern China has gradually increased, the rainfall has increased, mosquito vectors have gradually become active, and dengue fever cases have increased. The rapid economic development at home and abroad which has brought about the flow of people, as well as global warming, are conducive to the occurrence and spread of dengue fever. Therefore, in order to prevent and control dengue fever in mainland China, we should focus on the dynamics of dengue fever in Yunnan border, Guangdong and southeastern coastal areas, and make a good emergency plan for dengue fever. We should pay attention to the development of dengue fever in the central and northern provinces in China, and be alert to the further spatial spread of dengue fever.

About 1/3 of the imported dengue cases are foreigners. By occupation, the top three yearly rates of imported dengue cases were from the categories of Farmer, Businessman, and Student in 2014-2018, which accounted for about 70/100 (70%) of the total. The migration of Farmers, Businessmen, and Students is the main reason for the importation of dengue fever. The rate of male cases was significantly higher than that of female cases for imported dengue, and the population in 21-50 years was the main imported source. By occupation, the top three yearly rates of indigenous dengue cases were from Housework and unemployment, Retiree, and Businessman, which accounted for about 47/100 (47%) of the total. The rate of female cases was a little higher than the rate of male cases for indigenous dengue, and the population in 21-50 years was the main source. In all, 12.9% (12.9/100) of dengue cases were from the Businessman category, and 58.2% (58.2/100) of dengue cases were from individuals 21-50 years old. In order to strengthen the prevention and control of dengue fever, we should strengthen management and registration of the movement of Farmers, Businessmen, and Students. In order to cope with the epidemic of indigenous dengue cases in China, it is necessary to strengthen knowledge of dengue prevention and control among the population that falls into the categories of Housework and employment, Retiree and Businessman.

Conclusion

This research provides valuable information on epidemiological dynamics of dengue fever by statistical method and GIS technology in mainland China, 2014-2018. There were 5 458 imported dengue cases distributed in 734 counties, 29 provinces and 59 183 indigenous dengue cases in 314 districts, 13 provinces, which both show seasonal patterns from August to November. It was easy for Businessmen to be infected with dengue fever. About 58.2/100 (58.2%) of dengue cases occurred in individuals aged 21-50 years. Imported dengue cases, with 50/100 (50%) in Yunnan and mainly from Southeastern Asia, had doubled in these years. In 2014-2018, indigenous dengue cases were clustered in Yunnan border and southern Guangdong, and spread from the southern regions to the central and northern regions. Grasping epidemiological dynamics of dengue fever is helpful to formulate targeted, strategic plans and implement effective public health prevention and control measures.

Author contributions

Qiyong Liu initiated the study. Yujuan Yue collected the data, cleaned the data, performed the analysis and drafted the manuscript. The others revised the manuscript.

Ethics statement

No human or animal samples were included in the research presented in this article; therefore ethical approval was not necessary for this research.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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