Epidemiology of dengue and the effect of seasonal climate variation on its dynamics: a spatio-temporal descriptive analysis in the Chao-Shan area on China’s southeastern coast

Qin Zhang,1 Yuliang Chen,2 Yu Fu,3 Tao Liu,4 Qingying Zhang,2 Pi Guo,2 Wenjun Ma4

ABSTRACT

Objective Dengue is a mosquito-transmitted virus infection that remains rampant across the tropical and subtropical areas worldwide. However, the spatial and temporal dynamics of dengue transmission are poorly understood in Chao-Shan area, one of the most densely populated regions on China’s southeastern coast, limiting disease control efforts. We aimed to characterise the epidemiology of dengue and assessed the effect of seasonal climate variation on its dynamics in the area.

Design A spatio-temporal descriptive analysis was performed in three cities including Shantou, Chaozhou and Jieyang in Chao-Shan area during the period of 2014–2017.

Setting Data of dengue cases of three cities including Shantou, Chaozhou and Jieyang in Chao-Shan area during 2014–2017 were extracted. Data for climatic variables including mean temperature, relative humidity and rainfall were also compiled.

Methodology The epidemiology and dynamics of dengue were initiated depicted, and then the temporal dynamics related to climatic drivers was assessed by a wavelet analysis method. Furthermore, a generalised additive model for location, scale and shape model was performed to study the relationship between seasonal dynamics of dengue and climatic drivers.

Results Among the cities, the number of notified dengue cases in Chaozhou was greatest, accounting for 78.3%. The median age for the notified cases was 43 years (IQR: 27.0–58.0 years). Two main regions located in Xixin and Chengxi streets of Chaozhou with a high infection that remains rampant across the tropical and subtropical areas worldwide. However, the spatial and temporal dynamics of dengue transmission are poorly understood in Chao-Shan area, one of the most densely populated regions on China’s southeastern coast, limiting disease control efforts. We aimed to characterise the epidemiology of dengue and assessed the effect of seasonal climate variation on its dynamics in the area.

Conclusion Our study contributes to a better understanding of dengue dynamics in Chao-Shan area.

INTRODUCTION

Dengue is characterised as a serious infectious disease with a variety of clinical symptoms, from mild fever to potentially fatal dengue shock syndrome, and remains rampant across the tropical and subtropical areas in the world.1 Dengue viruses are arthropod-borne flaviviruses, which cause dengue shock syndrome in humans, and previous studies suggest that dengue virus production is immunologically regulated.2 At present, endemic dengue virus transmission is reported in the Eastern Mediterranean, American, Southeast Asian, Western Pacific and African regions.3 Accordingly, Aedes mosquitoes, including Aedes aegypti and Aedes albopictus, serve as the main transmission vector of dengue viruses.4 Studies have documented that the variability in ambient temperature and precipitation have an impact on development rates and habitat availability for Aedes aegypti and Aedes albopictus larvae and pupae.5 There has been
sharp increase in the number of dengue infections over the past few decades, and the disease has a great influence on population health and brings a heavy economic burden to patients, society and government. In China, the areas affected by dengue have expanded, and there has been a gradual increase in the incidence over the recent years. In particular, an extensive outbreak of dengue hit China in 2014, and high risk areas for dengue outbreaks were concentrated in neighbouring provinces including Guangdong, Guangxi and Yunnan of southern China. In fact, during this 2014 outbreak, the number of dengue infections in China reached the highest level over the past 25 years.

In China, dengue cases are notified to the China Center for Disease Control and Prevention (CDC) for the surveillance of spread pattern of dengue epidemic. We previously observed a remarkable spatial-temporal heterogeneity of dengue incidence in Guangdong, the most developed province of southern China, and showed that the dengue epidemic had noticeable seasonal and annual variability. In fact, recent studies suggest that dengue may now be endemic to China, and the dengue outbreaks are strongly related to climatic factors including temperature, rainfall and humidity, which have direct impacts on mosquito abundance. Enjoying a subtropical humid monsoon climate and frequent economic and cultural communication with the Southeast Asian countries, Guangdong has a potential high-risk opportunity for transmission of dengue. In particular, dengue poses a great burden of disease in the Pearl River Delta Region of Guangdong province, and the epidemic characteristics have been well documented.

The impact of seasonal climatic variation on dengue dynamics in the Chao-Shan area (figure 1), the eastern part of Guangdong province, is poorly quantified. The Chao-Shan area is one of the special regions on China’s southeastern coast. The region has a jurisdiction area of around 10,918 square kilometres, with a very high population density. In addition, it is situated in the intersection part of the Tropic of Cancer and the coastline of the mainland China and has a subtropical oceanic monsoon climate with a mean annual temperature of around 22°C and an abundant precipitation per year. The subtropical oceanic monsoon climate conditions and the increasingly frequent cultural contact with Southeast Asian countries in the Chao-Shan area make it a high-risk area for mosquito-borne infectious diseases. In particular, mosquito vectors such as *Aedes albopictus* are reported as the major vector of dengue virus in the area.

Unfortunately, there are few comprehensive reports on the spatial-temporal epidemic pattern for dengue in the Chao-Shan area. The effects of seasonal climate variation on the dynamics of dengue and the associated disease burden in the region are still unclear. There is

![Location of the Study Sites](http://bmjopen.bmj.com/)

Figure 1 Geographical location of Chao-Shan area including Shantou, Chaozhou and Jieyang cities on China’s southeastern coast.
an urgent need to understand the association between dengue epidemics and seasonal climatic conditions in order to take corresponding protective measures. Therefore, this study aimed to assess the epidemic characteristics of dengue in the Chao-Shan area and the effect of seasonal climate variation on the dynamics of dengue for the period 1 January 2014–31 December 2017.

**MATERIALS AND METHODS**

**Patient and public involvement**

This time series study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (see online supplementary table S1). We obtained the surveillance data of dengue in the study sites and only used the count data for statistical modelling. Patients and or public were not involved because this present study only used the data of the number of dengue cases to construct time series for assessing their associations with meteorological factors. Therefore, no ethics committee approval is required to obtain the data since the count data is presented.

**Dengue case data**

The Chao-Shan area including Shantou, Chaozhou and Jieyang cities is one of the most densely populated regions on China’s southeastern coast. In addition, this area has a subtropical oceanic monsoon climate, geographical position and the frequent culture, economic and trade exchanges with Southeast Asian countries. However, the epidemiological characteristics of dengue and disease burden associated with dengue infections are historically unclear. Therefore, the area was selected as the study site.

From 1 September 2008, all probable, clinic-confirmed and laboratory-confirmed cases of dengue were reported to the Chinese Center for Disease Control and Prevention (China CDC) and diagnosed according to the Diagnostic Criteria for Dengue released by the National Health Commission of China. Probable and confirmed cases were reported online to the China CDC within 24 hours of diagnosis by use of a standardised form including basic demographic information (sex, date of birth and residential address), case classification (probable, clinic-confirmed or laboratory-confirmed), date of symptoms onset and date of diagnosis. Data for dengue cases of Shantou, Chaozhou and Jieyang cities in the Chao-Shan area from 1 January 2014 to 31 December 2017 were available from the Guangdong Provincial CDC. Only indigenous dengue cases were included, and weekly number of dengue cases was calculated for statistical analysis.

**Climate surveillance data**

Daily average values for climatic variables including relative humidity, rainfall (millimetres) and temperature (°C) in the three cities during the study period from 1 January 2014 to 31 December 2017 were obtained from the Guangdong Provincial Climate Bureau. Weekly values of climatic variables were calculated as simple arithmetic means to show the seasonal peaks of dengue in surveillance data and used to assess the potential effect of seasonal variation on the dengue dynamics.

**Statistical analysis**

First, basic characteristics (number, median age, sex ratio and season and year of diagnosis) of dengue cases reported during the study period were described by city. By calculating the interval between the date of onset and the diagnosed date for each dengue case, we estimated the probability density function of the continuous variable of the ‘interval’ and then plot corresponding probability density distributions of the onset to diagnosis of dengue cases for the three cities. The median duration from onset to diagnosis by city was estimated. Each case of dengue has registered current address information. To identify high-risk areas of dengue in the Chao-Shan area, we applied a kernel smoothing method to plot the geographical distribution of cases by street or town.

A total of 231 streets or towns in the Chao-Shan area covering the three cities were included in our dataset. ArcGIS 10.2 (ESRI, Redlands, California, USA) was used to plot the geographical distribution.

Third, to quantify seasonal patterns of dengue epidemic, time series of weekly case counts were plotted by city, and type of cases (probable or confirmed cases), respectively. The periodicity of the time series of dengue case counts, mean temperature, mean rainfall and mean relative humidity was assessed using time-dependent wavelet analysis. The time series data of dengue case counts and climatic factors were analysed by wavelet analysis, and then the wavelet decomposition results were used to calculate power spectrum. By decomposing the time series into the time–frequency domain, wavelet analysis can obtain the significant fluctuation pattern of the time series, that is, the periodic dynamic time pattern. A continuous Morlet wavelet transform on the time series was performed to extract specific frequency components. Then, the temporal periodicity in a time series was inspected with a wavelet plot. A statistical significance test was performed to test the null hypothesis that the signal in a wavelet plot is generated by a stable process of a given background power spectrum (usually white noise) at a certain time with significance level of 95%. The dplR package within R software was used for the Morlet wavelet analysis in this study.

Fourth, in view of the presence of overdispersion in the dengue case data set, a generalised additive model for location, scale and shape (GAMLSS) model with the distribution of the response variable obeying negative binomial distribution was performed to study the association between seasonal characteristics of dengue and climatic variables, including mean temperature, mean rainfall and mean relative humidity. We implemented the Rigby and Stasinopoulos algorithm to estimate the parameters of the models, and the number of cycles of
In order to assess the effects of climatic variables on seasonal dynamics of dengue, we established a set of GAMLSS models where climatic variables were modelled as smooth terms with different df. This was performed by changing the df for the smooth terms of 3 to 1 during model selection. We used the smoothing splines for the smooth terms in the GAMLSS models. We considered temperature, relative humidity and rainfall separately, then with both in model, then with all in model. In addition, some sensitivity analyses by setting df=0 in the smooth terms, where df=0 means the distribution of the response variable is directly modelled as a linear parametric function of explanatory variables, for the three climatic factors considered separately, then both in model, then all in model. As a result, a total of 70 models were generated for comparison and evaluation. As model selection criterion, the Schwartz Bayesian Criterion (SBC) was used here. Models with lower value of SBC are preferred. In addition, we also added the autoregressive term, ln(1+Countlocal cases) in the previous month to account for the autoregressive effect in this study.

The results of the analysis are presented in Table 1. Basic characteristics of dengue cases notified during 2014–17 were shown in Table 1. In total, 2193 probable and confirmed cases of dengue in the Chao-Shan area were reported to the China CDC system, of which 2148 (98.0%) were confirmed (clinic or laboratory confirmed) and 45 (2.1%) were probable, respectively. Among all the reported cases, the proportion (78.3%) of dengue cases reported in Chaozhou was higher than those among Shantou (13.0%) and Jieyang (8.8%). The median age for all notified cases was 43 years (IQR: 27.0–58.0 years), for Shantou cases 35 years (IQR: 23.0–49.0 years), Chaozhou cases 46 years (IQR: 29.0–59.0 years) and Jieyang cases 34 years (IQR: 25.0–50.0 years), respectively. The age distribution among probable and confirmed cases for Shantou and Jieyang cities were similar. The male-to-female ratio was 1:1.1 for all notified dengue cases. The sex distributions among cases for Jieyang were different from those for the other two cities.

For the most recent year 2017 observed, most of the patients were male, irrespective of subgroup analysis results (Figure 2A–C). The median time from illness onset to diagnosis was 6 days (IQR 2.8–8), 3 days (IQR 3–5) and...
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3 days (IQR 1–5) for Shantou, Chaozhou and Jieyang, respectively. The plot of probability density distributions also demonstrated that there was a longer onset-to-diagnosis interval for dengue cases in Shantou (figure 2D).

In figure 3, a kernel density estimate map from dengue case data with latitude/longitude coordinates shows geographical distributions of dengue cases in the Chao-Shan area. Spatial smoothing with the kernel density estimation produced dengue risk hotspots suggesting that the geographical regions with the greatest number of dengue cases were around Xixin and Chengxi streets in Chaozhou city. Overall, dengue showed annual peaks of activity, a major peak in autumn, consistent among time series of dengue cases in Shantou, Chaozhou and Jieyang (figure 4). Although Chao-Shan area had a seasonal attack of dengue peaking between September and October of each year, we observed that the number of dengue cases increased sharply in 2015 in Chaozhou.

Results of wavelet analysis for time series of notifications of dengue and climatic variables including mean
temperature, mean rainfall and mean relative humidity in Chao-Shan area during the study period were shown in figure 5. It showed that the estimations of local powers for weekly time step examined were the largest at the period of 1 year, suggesting dengue cases showed a significant annual periodicity (figure 5A). In particular, based on the strongest power of the annual periodicity estimated for the time series of climatic variables (mean temperature, rainfall and relative humidity) throughout the study period (figure 5B–D), these factors broadly followed similar periodicity with that of dengue cases.

Based on the results of wavelet analysis, we further analysed the effects of climatic variables on seasonal dynamics of dengue using a framework of GAMLSS by testing different df for the smooth terms during model selection to determine an optimal model (see online supplementary table S2). We found that the model with the variable of mean temperature modelled as a smoothing spline term with $df=1$ had the smallest value of SBC and the best model fit among the 70 kinds of candidate models, suggesting that the effect of mean temperature on dengue dynamics in Chao-Shan area was most obvious. In addition, according to the GAMLSS framework, a significant non-linear partial effect of mean temperature on dengue dynamics have been observed, and the risk of dengue transmission was most when the temperature was between 25°C and 28°C (figure 6).

Figure 3 Geographical distributions of dengue cases in Chao-Shan area from the beginning of 2014 to the end of 2017. Spatial smoothing with the kernel density estimation produced dengue risk hotspots suggested that the geographical regions with the greatest number of dengue cases were around Xixin and Chengxi streets in Chaozhou city.

Figure 4 Temporal dynamics of dengue in Chao-Shan area from the beginning of 2014 to the end of 2017. (A) Weekly time series of number of probable and confirmed dengue cases in Chao-Shan area. (B) Weekly time series of number of probable and confirmed dengue cases by city in Chao-Shan area.
Our study of probable and confirmed cases of dengue reported to the national CDC surveillance system during 2014–2017 gives the first comprehensive estimation of the local burden and epidemiology of the disease in the study sites. Among the three cities covering a jurisdiction area of around 10,918 km², Chaozhou is responsible for the largest proportion of all the notified dengue cases. We recorded a median age of infection at 43 years (IQR 27.0–58.0 years) for all notified dengue cases, and the male-to-female ratio was 1:1.1. Our study suggests that cases of dengue tend to arise in autumn season of the year, presenting a significant annual periodicity of epidemics.

In particular, we found that the effect of temperature on dengue epidemics was most obvious among the climatic factors assessed.

Figure 5  Wavelet analyses for time series of notifications of dengue and climatic variables including mean temperature, rainfall and relative humidity in Chao-Shan area, 2014–2017. Local wavelet power spectrum for dengue cases (A), mean temperature (B), rainfall (C) and relative humidity (D). Solid and bold lines indicate boundary of statistical significance.

**DISCUSSION**

This present analysis of spatial distribution patterns of dengue identified two main epidemiological regions corresponding to Xixin and Chengxi streets in Chaozhou city, where dengue peaks in autumn. We found that Chaozhou accounted for around 78% of the total number of dengue cases reported during the study period. We speculated that this may owe to the combined effect of multiple factors including its subtropical monsoonal climate, its industries producing abandoned ceramics that could provide abundant of breeding places for mosquitoes after raining and local residents’ habit of planting flowers at home providing breeding environment for mosquito vectors. Our results indicate that dengue cases showed a significant annual periodicity in Chao-Shan area. Findings from Asia-Pacific countries including Thailand, Laos and the Philippines have shown localised
The GAMLSS is a general framework for fitting semiparametric regression type models where the distribution of the response variable includes highly skew and kurtotic continuous and discrete distribution and allows all the parameters of the distribution of the response variable to be modelled as smooth functions of the explanatory variables. There is more flexibility in identifying those non-linearities using a generalised additive model (GAM)-based approach than traditional linear regression models. By inspecting a scatterplot (data were not shown) between dengue incidence and temperature, we found the relationship was non-linear, so it required the special estimation methods of the non-linear regression procedure. Additionally, the choice of $df$ values is very important when constructing the GAMLSS model. Therefore, we performed a sensitivity analysis by trying different $df$ in the smooth term of the model and determined an optimal model according to the assessment of model fit. Overall, our results revealed a powerful capability with GAMLSS model for catching the appropriate relationship between dengue incidence and temperature.

The associations between dengue seasonality and climatic variables such as temperature, rainfall, relative humidity, sunshine and El Niño-Southern Oscillation (ENSO) indices have been documented in previous studies. In this study, our results reveal that temperature has significantly non-linear effects on epidemics risk and intensity of dengue, with the greatest attributable risk due to temperature estimated at around 25°C. To identify the significantly associated climatic factors with dengue epidemics, we repeated model selections and adopted different climatic factors with different $df$ in the smooth terms of the GAMLSS framework. We found that the variation in daily mean temperature partly drives dengue dynamics, and this climatic factor is closely related to the seasonal fluctuation of dengue incidence in Chao-Shan area. The association between temperature and seasonal dynamics of dengue observed in our study was also reported in previous studies in Guangzhou and Taiwan, which has a similar subtropical humid monsoon climate. The estimated effects of temperature driving the seasonal dynamics of dengue can be partly explained by some mechanisms, for example, temperature effects on the biting rate of mosquitoes, incubation period of pathogens and human exposure to mosquitoes.

Several limitations of this study should be mentioned. First, we did not consider potentially relevant factors, such as mosquito density and other environment elements including vegetation cover, distance to water bodies and so on. The variables may partly influence the relationship between temperature and dengue epidemics estimated in this work. In addition, although the quantitative results derived from this study pointed out that temperature was associated with increased risk of dengue transmission, other factors such as human activities during urbanisation and globalisation were also suggested to be very important in driving the long-term trends. At present, we cannot obtain the data on laboratory test results for various kinds of dengue viruses. Therefore, we cannot...
study the epidemiological features of dengue cases caused by different viruses as well as the age-specific dengue antibody prevalence in the population. Furthermore, our results faced a common challenge for studies using data from surveillance with possible under-reporting or variations in diagnosis practices of cases. This was also suggested from a previous study.33

CONCLUSIONS
In summary, this study represented an initial step to analyse the epidemiological characteristics of dengue in Chao-Shan area, one of the most densely populated regions on China’s southeastern coast and used a statistically rigorous approach for assessing the effects of climatic factors on dengue epidemics. Overall, our results are helpful towards advancing our understanding of the pattern of how climate influences dengue, and useful for the control and prevention of the disease for local government in the study sites.

Author affiliations
1 Good Clinical Practice Office, Cancer Hospital of Shantou University Medical College, Shantou, China
2 Department of Preventive Medicine, Shantou University Medical College, Shantou, China
3 Department of Finance, Zhongnan University of Economics and Law, Wuhan, China
4 Guangdong Provincial Institute of Public Health, Guangdong Provincial Center for Disease Control and Prevention, Guangzhou, China

Contributors QinZ, PG and WM conceived the study, undertook statistical analysis and drafted the manuscript. YC, YF, TL and QinZ collected the data and assisted in the statistical analysis. QinZ, PG, TL, QinZ and WM interpreted the results. QinZ, PG and TL wrote and revised the manuscript. All authors read and approved the final manuscript.

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