Determination of Factors Affecting Dengue Occurrence in Representative Areas of China: A Principal Component Regression Analysis

Xiaobo Liu¹, Keke Liu², Yujuan Yue¹, Haixia Wu¹, Shu Yang³, Yuhong Guo¹, Dongsheng Ren¹, Ning Zhao¹, Jun Yang⁴ and Qiyong Liu*¹

¹ State Key Laboratory of Infectious Disease Prevention and Control, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, WHO Collaborating Centre for Vector Surveillance and Management, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China, ² Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China, ³ The Collaboration Unit for Field Epidemiology of State Key Laboratory of Infectious Disease Prevention and Control, Nanchang Center for Disease Control and Prevention, Nanchang, China, ⁴ Institute for Environmental and Climate Research, Jinan University, Guangzhou, China

Background: Determination of the key factors affecting dengue occurrence is of significant importance for the successful response to its outbreak. Yunnan and Guangdong Provinces in China are hotspots of dengue outbreak during recent years. However, few studies focused on the drive of multi-dimensional factors on dengue occurrence failing to consider the possible multicollinearity of the studied factors, which may bias the results.

Methods: In this study, multiple linear regression analysis was utilized to explore the effect of multicollinearity among dengue occurrences and related natural and social factors. A principal component regression (PCR) analysis was utilized to determine the key dengue-driven factors in Guangzhou city of Guangdong Province and Xishuangbanna prefecture of Yunnan Province, respectively.

Results: The effect of multicollinearity existed in both Guangzhou city and Xishuangbanna prefecture, respectively. PCR model revealed that the top three contributing factors to dengue occurrence in Guangzhou were Breteau Index (BI) (positive correlation), the number of imported dengue cases lagged by 1 month (positive correlation), and monthly average of maximum temperature lagged by 1 month (negative correlation). In contrast, the top three factors contributing to dengue occurrence in Xishuangbanna included monthly average of minimum temperature lagged by 1 month (positive correlation), monthly average of maximum temperature (positive correlation), monthly average of relative humidity (positive correlation), respectively.

Conclusion: Meteorological factors presented stronger impacts on dengue occurrence in Xishuangbanna, Yunnan, while BI and the number of imported cases lagged by...
INTRODUCTION

Dengue fever is a mosquito-borne viral infection causing severe flu-like illness, and sometimes causing a potentially lethal complication called dengue shock syndrome. Globally, the incidence of dengue has increased 30-fold over the past 50 years (1). Driven by climatic and environmental changes (2), globalization, urbanization (3, 4), vector activity, and human behavior change (5), or the combination of these favorable conditions (6, 7), dengue outbreaks have been continuously occurring in southern China such as Guangdong (8–13) and Yunnan (14–17) since 2013, which has posed an important public health threat in China (18–23).

Assessing the impact of some driving factors such as vectors and climate-related features on the occurrence of dengue has become one of hotspots in current research (24–28). For instance, some studies have attempted to explore the influencing factors of dengue occurrence in some representative regions such as Guangdong and Yunnan provinces, and reported the potential dengue-related factors, including temperature, relative humidity, precipitation, sunlight and mosquito density (29–31). However, considering the strong correlations among these multi-dimensional factors, the effect of multicollinearity among independent variables has not been well examined in most previous studies, which could severely distort the model estimation. Principal component regression (PCR) can effectively minimize the multi-collinearity among the factors and has been widely used in the field of biomedicine (32, 33). The pathogenesis of dengue is complex, involving viruses, hosts, human populations, ecological, environmental and social factors and the interactions of these factors. It is therefore necessary to take into account many factors in the model estimation and meanwhile to minimize the possible impact from multicollinearity.

In view of this, this study selected two representative cities or prefectures from two provinces with frequent dengue outbreak in recent years having different ecological, meteorological and socioeconomic characteristics, and then established the PCR model to identify the key factors influencing the occurrence of dengue. The results may provide scientific evidence for the formulation of tailored dengue prevention and control strategies and measures in China in the future.

METHODOLOGY

Research Site

In this study, Xishuangbanna Dai Autonomous Prefecture (hereinafter referred to as Xishuangbanna prefecture) in Yunnan Province and Guangzhou city in Guangdong Province were selected as two representative sites with high-risk of dengue in China based on epidemic situation of dengue in during recent years (Figure 1).

Xishuangbanna prefecture is located at 21°10’ to 22°40’ north latitude, 99°55’ to 101°50’ east longitude. It belongs to the humid tropical area in south of the equator and connects Jiangcheng county and Puer city in the East and West. It is adjacent to Lancang county in the northwest, Laos and Myanmar in the southeast, south and southwest, respectively. Covering an area of 19, 582.45 square kilometers, there were 1.196 million permanent residents in this prefecture in 2019.

Guangzhou, the capital city of Guangdong Province, also known as Sub-provincial City, National Central City and Mega-city, is located at 22°26’ to 23°56’ north latitude, 112°57’ to 114°3’ east longitude. It situates on a slope terrain with higher altitude in the northeast and lower altitude in the southwest. The northern part of the city is a hilly and mountainous area with concentrated forests. Guangzhou is adjacent to the subtropical coast and the equator passes through the south-central part of this metropolis, one of the largest cities in China. A marine subtropical monsoon climate prevails in this area, which is characterized by warm and rainy long summer, abundant light and heat, and a short frost period in winter. The annual average temperature ranges 20–22 °C with the smallest annual average temperature difference. Covering an area of 7,434.4 square kilometers, there were 15.359 million permanent residents in this city in 2019.

Keywords: dengue, influencing factors, principal component analysis, mosquito-borne disease, control
Data Collection

Records of dengue cases, the number of imported dengue case, the number of imported dengue case lagged by 1 month [Im1] from Guangzhou city and Xishuangbanna prefecture between 2006 and 2017 were obtained from China Notifiable Infectious Disease Reporting System. All dengue cases were diagnosed according to the China National Diagnostic Criteria for dengue (WS216-2008). Information of dengue cases included gender, age, occupation, date of onset, clinical diagnosis, or laboratory confirmed cases, indigenous or imported cases. The criteria of imported or indigenous cases are as described in previous study (34).

Breteau Index (BI) is an index for surveillance Aedes larvae density and can be calculated by number of positive containers per a hundred houses inspected. At present, it is utilized widely in dengue risk assessment. The BI of high-risk areas in Guangzhou city and Xishuangbanna prefecture from June to October from 2006 to 2017 was obtained from the annual surveillance report of major infectious diseases and vectors in China CDC.

According to the major meteorological factors affecting dengue occurrence in representative areas of China in the previous researches, and also considering the availability of data of different indicators at different time scales, monthly meteorological data from 2006 to 2017 were obtained from the National Meteorological Science Data Sharing Service (http://cdc.nmic.cn/home.do). These indicators include monthly average of temperature (Tmean), monthly average of temperature lagged by 1 month (Tmean1), monthly average of maximum temperature (Tmax), monthly average of maximum temperature lagged by 1 month (Tmax1), monthly average of minimum temperature (Tmin), monthly average of minimum temperature lagged by 1 month (Tmin1), monthly average of relative humidity (Hum%), cumulative precipitation (CP), cumulative precipitation lagged by 1 month (CP1), days of precipitation (DP) in the current month, days of precipitation lagged by 1 month (DP1).

The population data over the study period were retrieved from the Guangdong and Yunnan Statistical Yearbooks. The collected dataset of dengue indigenous and imported cases, the key meteorological index and BI data from June to October during 2006–2017 were integrated for the subsequent principal component regression (PCR) analysis.

Statistical Analysis

Multiple linear regression analysis was firstly utilized to determine the possible multiple collinearities of different variables included in this study. Collinearity diagnostic was carried out, and eigenvalue and condition index were computed. All the analyses were analyzed by SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

The variables concerning dengue occurrence in this study were standardized at first using normalization method. Principal component analysis was adopted to determine the number of principal components of standardized key factors including meteorological factors, mosquito density and imported dengue cases in the last month in the selected regions of Guangdong and Yunnan Provinces in China.

Taking the number of imported dengue cases as dependent variable (y) and principal components as independent variable (x), we then adopted the principal components regression analysis. In detail, according to the determined principal component, the principal component in front order replaces the original independent variable (x) for multiple linear regression analysis to obtain the regression model between the standardized independent variable (x) and the dependent variable (y). The number of principal components was determined by the accumulative contribution rate of these principal components by total initial eigenvalues. Then, the standardized independent variable is reduced to the original independent variables to obtain the regression model of the original independent variable and the independent variable. In this study, the established models are as follows.

a. The structure of established principal component regression model using standardized scores of principal components

\[ Y = b_0 + b_1Z_1 + b_2Z_2 + b_3Z_3 + \ldots + b_pZ_p, \]

where \( b_1, b_2, \ldots, b_p \) are called as principal component contribution rate.

b. The structure of established regression model using original variable:

\[ Y = A + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \ldots + \beta_pX_p, \]

where \( \beta_1, \beta_2, \ldots, \beta_p \) are called as marginal coefficient.

RESULTS

General Situation of Variables in the Research Site From 2006 to 2017

Table 1 presents the general composition of dengue and the influencing factors in Guangzhou city of Guangdong province and Xishuangbanna prefecture of Yunnan province, from 2006 to 2017. Totally, 60 records in Guangzhou city and 60 records in Xishuangbanna prefecture were included in the current analysis. And the minimum value, the maximum value, mean and standard deviation were included.

Since 2013, the number of dengue cases have increased in fluctuation, with the highest in 2014 in Guangzhou (Figure 2A). For the imported dengue cases in prior month, it increased after 2009 and reached the highest in Guangzhou city in 2014 and in Xishuangbanna prefecture in 2017 (Figure 2B).

Figure 3 shows the temporal dynamics of the major factors in Guangzhou city and Xishuangbanna prefecture, 2006–2017.

Multiple Regression Analysis

In Guangzhou city, the findings of multiple linear regression analysis suggested high correlations between Tmean and Tmin (\( r = 0.983 \)), Tmean and Tmax (\( r = 0.953 \)), Tmax and Tmin (\( r = 0.895 \)), Tmean1 and Tmin1 (\( r = 0.968 \)), Tmean1 and Tmax1 (\( r = 0.950 \)), Tmax1 and Tmean1 (\( r = 0.865 \)).

In addition, correlations also existed between DP and Hum (\( r = 0.661 \)), DP and Tmean (\( r = 0.623 \)), DP and CP (\( r = 0.754 \)), as well as DP1 and CP1 (\( r = 0.633 \)).

In Xishuangbanna prefecture, the results of multiple regression analysis showed high correlations between Tmean and Tmin (\( r = 0.949 \)). In addition, correlations also existed between Tmean and Tmax (\( r = 0.783 \)), DP and Tmean (\( r = 0.767 \)), DP and CP (\( r = 0.755 \)), and DP1 and CP1 (\( r = 0.645 \)).
After principal component analysis, multiple linear regression analysis was adopted to avoid possible multiple collinearities. The eigenvalues, contribution variance and cumulative contribution of the variance of components in Guangzhou city and Xishuangbanna prefecture are shown in Table 2. Based on the above findings, multiple collinearities existed among some variables in both Guangzhou city and Xishuangbanna prefecture. Therefore, principal component analysis was adopted to avoid possible multiple collinearities. The eigenvalues, contribution variance and cumulative contribution of the variance of components in Guangzhou city and Xishuangbanna prefecture are shown in Table 2.

### Table 1: Comparison of the dengue and the influencing factors in two research sites, 2006–2017.

| Research sites          | Variable | N  | Minimum value | Maximum value | Mean  | Standard deviation |
|-------------------------|----------|----|----------------|---------------|-------|--------------------|
| Guangzhou city, Guangdong | Im       | 60 | 0              | 19790         | 713.30 | 3364.26            |
|                         | Im1      | 60 | 0              | 59            | 3.95  | 6.64               |
|                         | Bt       | 60 | 2              | 13            | 5.33  | 1.91               |
|                         | Tmean (°C) | 60 | 23             | 31            | 27.46 | 1.86               |
|                         | Tmeant1 (°C) | 60 | 25             | 31            | 27.71 | 1.38               |
|                         | Hum (%)  | 60 | 58             | 87            | 77.26 | 6.35               |
|                         | Tmin (°C) | 60 | 19             | 28            | 24.34 | 1.95               |
|                         | Tmin1 (°C) | 60 | 22             | 28            | 24.69 | 1.29               |
|                         | Tmax (°C) | 60 | 28             | 35            | 32.11 | 1.71               |
|                         | Tmax1 (°C) | 60 | 29             | 35            | 32.19 | 1.57               |
|                         | CP (mm)  | 60 | 1              | 835           | 233.62 | 198.47             |
|                         | CP1 (mm) | 60 | 37             | 835           | 299.43 | 165.62             |
|                         | DP (d)   | 60 | 2              | 24            | 14.03 | 5.85               |
|                         | DP1 (d)  | 60 | 7              | 25            | 16.48 | 4.50               |
| Xishuangbanna prefecture, Yunnan | Im       | 60 | 0              | 672           | 56.57 | 151.94             |
|                         | Im1      | 60 | 0              | 41            | 2.65  | 7.04               |
|                         | Bt       | 60 | 0              | 52            | 10.66 | 10.94              |
|                         | Tmean (°C) | 60 | 22             | 26            | 24.73 | 1.03               |
|                         | Tmeant1 (°C) | 60 | 24             | 27            | 25.15 | 0.57               |
|                         | Hum (%)  | 60 | 77             | 91            | 83.62 | 3.42               |
|                         | Tmin (°C) | 60 | 19             | 23            | 21.91 | 1.10               |
|                         | Tmin1 (°C) | 60 | 20             | 23            | 22.10 | 0.76               |
|                         | Tmax (°C) | 60 | 28             | 33            | 30.68 | 0.95               |
|                         | Tmax1 (°C) | 60 | 29             | 34            | 31.24 | 1.025              |
|                         | CP (mm)  | 60 | 23.6           | 555.9         | 222.40 | 128.98             |
|                         | CP1 (mm) | 60 | 48             | 556           | 238.82 | 113.69             |
|                         | DP (d)   | 60 | 5              | 28            | 18.75 | 5.97               |
|                         | DP1 (d)  | 60 | 11             | 28            | 20.03 | 4.45               |

**Principal Component Analysis**

Based on the above findings, multiple collinearities existed among some variables in both Guangzhou city and Xishuangbanna prefecture. Therefore, principal component analysis was adopted to avoid possible multiple collinearities. The eigenvalues, contribution variance and cumulative contribution of the variance of components in Guangzhou city and Xishuangbanna prefecture are shown in Table 2.

**Principal Component Regression Analysis in Guangzhou City**

After principal component analysis, multiple linear regression model was established using dengue cases as dependent variable and Z value as the independent variable.

**Principal Component Regression Analysis in Xishuangbanna Prefecture**

Similarly, after principal component analysis, multiple linear regression model was established in with dengue cases as dependent variable and Z value as the independent variable.

**DISCUSSION AND CONCLUSION**

Guangzhou city (12, 35) and Xishuangbanna prefecture (17) are two representative regions of dengue outbreak with different dengue vectors during recent years in China (21). The actual number of dengue cases may be underestimated in the current notification system because of numbers of undetected cases with...
subclinical infections and atypical symptoms (36). Therefore, identifying the key factors influencing the occurrence of dengue in the two high-risk areas in this study is of great significance for the scientific control of dengue in the future.

At present, many studies focused on the influencing factors relevant to the local transmission, even outbreaks of dengue in representative regions of mainland China, including the two cities or regions in this study (7). Usually, dengue outbreaks...
are the consequence of the combination of many favorable conditions (6, 8). Unfortunately, some key factors were neglected in most previous studies, and the complex collinearity among the studied factors was also not well considered in these researches. Therefore, it is difficult to reveal the true contribution of different influencing factors. Furthermore, inconsistent conclusions existed in different reports due to different study periods and regions selected.

Based on the previous research, a total of 13 potential influencing factors, including climatic factors, indigenous and imported dengue cases, and mosquito larvae density (BI), were included and analyzed systematically using principal component regression analysis to avoid the possible multiple collinearity and confounding bias (33).

In Guangzhou, a region of dengue epidemic area dominated by *Aedes albopictus* (37), we observed multiple collinearity among variables. Specifically, high correlations existed among monthly maximum, minimum and mean temperatures, and these indicators lagged by 1 month, respectively with correlation coefficient higher than 0.85. In addition, correlations also existed among DP, and humidity, DP and Tmin, and DP and CP, DP1 and CP1, with the correlation higher than 0.60. Similar correlations existed for Xishuangbanna prefecture, where *Ae. aegypti* is the dominated vector for dengue transmission.

In this study, the established PCR model in Guangzhou revealed that the key contributing factors for the occurrence of dengue included BI (positive correlation), and Im1 (positive correlation). Dengue is transmitted by the biting of *Aedes* mosquito. Therefore, as one of a major indicators of mosquito density, BI is regarded as a promising and direct index for dengue early warning worldwide (38). As far as we know, the dengue case is the source of infection and transmission of dengue involving two incubation periods: an internal incubation period (3–15 days) of the dengue case and an external incubation period (3–15 days) in the body of *Aedes* mosquito. Furthermore, as an international metropolis, Guangzhou has a large number of floating populations from other domestic provinces and also

### TABLE 2 | The eigenvalues, contribution variance and cumulative contribution of variance of components in Guangzhou city and Xishuangbanna prefecture, 2006–2017.

| Research sites Component | Variance | Contribution of variance (%) | Cumulative contribution of variance (%) |
|--------------------------|----------|-----------------------------|----------------------------------------|
| Guangzhou city, Guangdong | 4.577    | 35.211                      | 35.211                                  |
|                          | 3.704    | 28.489                      | 63.701                                  |
|                          | 1.258    | 9.676                       | 73.376                                  |
|                          | 1.106    | 8.506                       | 81.882                                  |
|                          | 0.812    | 6.243                       | 88.125                                  |
|                          | 0.653    | 5.027                       | 93.152                                  |
|                          | 0.341    | 2.623                       | 95.775                                  |
|                          | 0.282    | 2.173                       | 97.947                                  |
|                          | 0.166    | 1.273                       | 99.22                                   |
|                          | 0.054    | 0.414                       | 99.635                                  |
|                          | 0.04     | 0.310                       | 99.945                                  |
|                          | 0.005    | 0.037                       | 99.982                                  |
|                          | 0.002    | 0.018                       | 100.00                                  |
| Xishuangbanna prefecture, Yunnan | 4.102    | 31.557                      | 31.557                                  |
|                          | 3.025    | 23.270                      | 54.827                                  |
|                          | 1.500    | 11.540                      | 66.367                                  |
|                          | 1.272    | 9.788                       | 76.155                                  |
|                          | 1.016    | 7.818                       | 83.473                                  |
|                          | 0.753    | 5.793                       | 89.765                                  |
|                          | 0.482    | 3.711                       | 93.476                                  |
|                          | 0.318    | 2.445                       | 95.921                                  |
|                          | 0.229    | 1.765                       | 97.687                                  |
|                          | 0.191    | 1.473                       | 99.159                                  |
|                          | 0.082    | 0.631                       | 99.791                                  |
|                          | 0.021    | 0.159                       | 99.950                                  |
|                          | 0.006    | 0.050                       | 100.00                                  |

1. Im1, the number of imported dengue cases lagged by 1 month; 2. BI, Breteau index; 3. Tmean, monthly average of temperature (°C); 4. Tmean1, monthly average of temperature lagged by 1 month (°C); 5. Hum, monthly average of relative humidity (%); 6. Tmin, monthly average of minimum temperature (°C); 7. Tmin1, monthly average of minimum temperature lagged by 1 month (°C); 8. Tmax, monthly average of maximum temperature (°C); 9. Tmax1, monthly average of maximum temperature lagged by 1 month (°C); 10. CP1, days of precipitation lagged by 1 month; 11. DP , days of precipitation; 12. DP1 and CP1, with the correlation higher than 0.60. Similar correlations existed for Xishuangbanna prefecture, where *Ae. aegypti* is the dominated vector for dengue transmission.

### TABLE 3 | Model parameter test in Guangzhou city, Guangdong province, 2006–2017.

| Model | R   | R² | Adjusted R² | Error of standard estimation | F     | p   |
|-------|-----|----|-------------|------------------------------|-------|-----|
| 1     | 0.881 | 0.776 | 0.725 | 2537.58 | 11.899 | <0.001 |

### TABLE 4 | T test results of partial regression coefficient of the model in Guangzhou city, Guangdong province, 2006–2017.

| Model | Non standardized partial regression coefficient | Standardized partial regression coefficient | t     | P    |
|-------|-------------------------------------------------|---------------------------------|-------|------|
|       | Partial regression coefficient | Standard error | Partial regression coefficient |       |      |
| 1 Constant | 713.300 | 327.600 | 2.177 | 0.034 |
| REGR factor score 1 for analysis 1 | −856.454 | 330.365 | −0.256 | −2.592 | 0.012 |
| REGR factor score 2 for analysis 1 | −54.908 | 330.365 | −0.016 | −0.166 | 0.869 |
| REGR factor score 3 for analysis 1 | −177.541 | 330.365 | −0.053 | −0.537 | 0.593 |
| REGR factor score 4 for analysis 1 | 2103.971 | 330.365 | 6.369 | 0.000 |

### TABLE 5 | Model parameter test in Xishuangbanna prefecture, Yunnan province, 2006–2017.

| Model | R   | R² | Adjusted R² | Error of standard estimation | F     | p   |
|-------|-----|----|-------------|------------------------------|-------|-----|
| 1     | 0.898 | 0.806 | 0.778 | 137.748 | 3.557 | <0.01 |

In this study, the established PCR model in Guangzhou revealed that the key contributing factors for the occurrence of dengue included BI (positive correlation), and Im1 (positive correlation). Dengue is transmitted by the biting of *Aedes* mosquito. Therefore, as one of a major indicators of mosquito density, BI is regarded as a promising and direct index for dengue early warning worldwide (38). As far as we know, the dengue case is the source of infection and transmission of dengue involving two incubation periods: an internal incubation period (3–15 days) of the dengue case and an external incubation period (3–15 days) in the body of *Aedes* mosquito. Furthermore, as an international metropolis, Guangzhou has a large number of floating populations from other domestic provinces and also...
foreign countries. Additionally, the major driving factor of Im1 identified in Guangzhou also confirmed that the risk of local outbreak caused by imported dengue case in this city is relatively high. This finding was in accordance with previous study focusing on Guangzhou city (34).

Temperature is regarded as one of the most important climatic factors for dengue transmission (39). Based on literature review, appropriate temperature could influence the reproduction of vector mosquitoes and dengue viruses, which subsequently impacts the dengue risk (40). Relative humidity can affect oviposition, egg hatching, dispersal range, feeding behaviors, and lifespan of *Aedes* mosquitoes. Our results in Xishuangbanna demonstrated that the top three factors driving dengue occurrences included Tmin1 (positive correlation), Tmax (positive correlation), and Hum (positive correlation). Xishuangbanna prefecture has a much smaller number of floating populations compared to Guangzhou. In particular, Xishuangbanna belongs to the tropical rain forest area, and the suitable meteorological conditions are more conducive to *Aedes* mosquito breeding, favoring the local outbreak of dengue. The findings were consistent with those in the previous investigations conducted in the border areas of Yunnan and Myanmar [BYM] (7). Due to the relatively little evidence in Xishuangbanna prefecture of Yunnan, more future studies are warranted to further explore the key factors driving the local outbreak of dengue in this area.

Overall, our study observed that meteorological factors, especially Tmin1, Tmax, Hum, played key roles in dengue occurrence in Xishuangbanna, Yunnan while mosquito density (BI) and Im1 played important roles for dengue transmission in Guangzhou, Guangdong. For targeted dengue control in Guangzhou city, it is urgent to pay close attention to the dengue epidemic both at home and abroad, track the imported dengue cases timely, and reduce adult mosquito density relying on source reduction of *Aedes* mosquitoes. As for dengue control in Xishuangbanna, it is necessary to include some key meteorological factors when the implementation of dengue early warning and precise control. Furthermore, the difference of dengue determinants in different provinces could be taken into account when formulating tailored dengue precise control and prevention strategy, response mechanism in representative areas of China in the future.

Some limitations should be noticed. First, the impact factors of dengue local transmission and outbreaks are complicated. We have tried our best to include as many risk factors as possible. However, other factors, such as public health control programs (30), new dengue virus strain invasion (41, 42), emerging insecticide resistance in dengue vectors (43, 44), El Nino Southern Oscillation (28), changes of land use and surface water (2), key areas in a city such as “urban villages (UVs)” (3), social media surveillance data (45), air travel data (46), human behavior, other socio-economic indicators (47), are also important for the dengue occurrence and need to be well discussed in future studies. In addition, the exact number of cases of dengue may be underestimated (36) due to the phenomenon of latent infection and mild cases of dengue, which were not included in this study.

**CONCLUSIONS**

Climatic factors and mosquito density are the key drivers on dengue occurrence in representative high-risk dengue areas in China. Meteorological factors such as monthly average of minimum temperature lagged by 1 month, monthly average of maximum temperature and relative humidity, have stronger impacts on dengue occurrence in Xishuangbanna prefecture of Yunnan, while *Aedes* larvae density and the number of imported dengue cases lagged by 1 month have more profound impacts on dengue occurrence in Guangzhou city. The findings may provide scientific evidence for the development of early warning and targeted dengue control strategies and measures in China.

**DATA AVAILABILITY STATEMENT**

The data analyzed in this study is subject to the following licenses/restrictions: Some data could be available based on China CDC’s regulations. Requests to access these datasets should be directed to liuxiaobo@icdc.cn.

**ETHICS STATEMENT**

This study was approved by the Ethics Committee of National Institute for Communicable Disease Control and Prevention, Israel.

---

**TABLE 6 | T test results of partial regression coefficient of the model in Xishuangbanna prefecture, Yunnan province, 2006–2017.**

| Model | Non standardized partial regression coefficient | Standardized partial regression coefficient | t | P |
|-------|----------------------------------|----------------------------------|---|---|
|       | Partial regression coefficient | Standard error | Partial regression coefficient |   |   |
| 1     | Constant    | 55.567            | 17.783            | 3.125 | 0.003 |
|       | REGR factor score 1 for analysis 1 | −31.033 | 17.933 | −0.204 | −1.793 | 0.089 |
|       | REGR factor score 2 for analysis 1 | 45.623 | 17.933 | 0.300 | 2.544 | 0.014 |
|       | REGR factor score 3 for analysis 1 | 6.636 | 17.933 | 0.044 | 0.370 | 0.713 |
|       | REGR factor score 4 for analysis 1 | 45.178 | 17.933 | 0.297 | 2.519 | 0.015 |
|       | REGR factor score 5 for analysis 1 | 24.295 | 17.933 | 0.160 | 1.355 | 0.181 |

Some limitations should be noticed. First, the impact factors of dengue local transmission and outbreaks are complicated. We have tried our best to include as many risk factors as possible. However, other factors, such as public health control programs (30), new dengue virus strain invasion (41, 42), emerging insecticide resistance in dengue vectors (43, 44), El Nino Southern Oscillation (28), changes of land use and surface water (2), key areas in a city such as “urban villages (UVs)” (3), social media surveillance data (45), air travel data (46), human behavior, other socio-economic indicators (47), are also important for the dengue occurrence and need to be well discussed in future studies. In addition, the exact number of cases of dengue may be underestimated (36) due to the phenomenon of latent infection and mild cases of dengue, which were not included in this study.

**CONCLUSIONS**

Climatic factors and mosquito density are the key drivers on dengue occurrence in representative high-risk dengue areas in China. Meteorological factors such as monthly average of minimum temperature lagged by 1 month, monthly average of maximum temperature and relative humidity, have stronger impacts on dengue occurrence in Xishuangbanna prefecture of Yunnan, while *Aedes* larvae density and the number of imported dengue cases lagged by 1 month have more profound impacts on dengue occurrence in Guangzhou city. The findings may provide scientific evidence for the development of early warning and targeted dengue control strategies and measures in China.

**DATA AVAILABILITY STATEMENT**

The data analyzed in this study is subject to the following licenses/restrictions: Some data could be available based on China CDC’s regulations. Requests to access these datasets should be directed to liuxiaobo@icdc.cn.

**ETHICS STATEMENT**

This study was approved by the Ethics Committee of National Institute for Communicable Disease Control and Prevention, Israel.
China CDC. No human or animal samples were included in the current study.

AUTHOR CONTRIBUTIONS

XL planned the project and wrote the paper. XL, QL, and YG conducted the field survey. XL, KL, YY, HW, SY, DR, NZ, and JY contributed to data analysis. All authors read and approved the final manuscript.

FUNDING

This research was supported by the National Natural Science Foundation of China (Grant No. 81703280), National Major Science and Technology Projects of China (Grant No. 2017ZX10303404005001), and a Special Project of the Ministry of Ecology and Environment in response to Climate Change “Study on Public Health Problems caused by Climate Change” (Grant No. 202046).

ACKNOWLEDGMENTS

We would like to acknowledge disease prevention and control staff from Guangdong and Yunnan province, for the collection of relevant data. Special thanks to Prof. Peng Bi from the School of Public Health, The University of Adelaide for the revision of the manuscript.

REFERENCES

1. Ebi KL, Nealon J. Dengue in a changing climate. Environ Res. (2016) 151:115–23. doi: 10.1016/j.envres.2016.07.026
2. Tian H, Huang S, Zhou S, Bi P, Yang Z, Li X, et al. Surface water areas significantly impacted 2014 dengue outbreaks in Guangzhou, China. Environ Res. (2016) 150:299–305. doi: 10.1016/j.envres.2016.05.039
3. Ren H, Wu W, Li T, Yang Z. Urban villages as transfer stations for dengue fever epidemic: a case study in the Guangzhou, China. PLoS Negl Trop Dis. (2019) 13:e0007350. doi: 10.1371/journal.pntd.0007350
4. Qi X, Wang Y, Li Y, Meng Y, Chen Q, Ma J, et al. The effects of socioeconomic and environmental factors on the incidence of dengue fever in the Pearl River Delta, China, 2013. PLoS Negl Trop Dis. (2015) 9:e0004159. doi: 10.1371/journal.pntd.0004159
5. Zhu G, Liu J, Tan Q, Shi B. Inferring the spatio-temporal patterns of dengue transmission from surveillance data in Guangzhou, China. PLoS Negl Trop Dis. (2016) 10:e0004633. doi: 10.1371/journal.pntd.0004633
6. Oidtman RJ, Liu S, Huang Z, Yang J, Siraj AS, Reiner RC, et al. Interannual variation in seasonal dengue epidemics driven by multiple interacting factors in Guangzhou, China. Nat Commun. (2019) 10:1148. doi: 10.1038/s41467-019-09035-x
7. Zheng L, Ren HY, Shi RH, Lu L. Spatiotemporal characteristics and primary influencing factors of typical dengue fever epidemics in China. Infect Dis Poverty. (2019) 8:24. doi: 10.1186/s40249-019-0533-9
8. Wang X, Tang S, Wu J, Xiao Y, Cheke RA. A combination of climatic conditions determines major within-season dengue outbreaks in Guangdong Province, China. Parasites Vect. (2019) 12:45. doi: 10.1186/s13071-019-3295-0
9. Yang Z, Chen B, Wu H, Yang Y, et al. Dengue is still an imported disease in China: a case study in Guangzhou. Infect Genet Evol. (2015) 32:178–90. doi: 10.1016/j.meegid.2015.03.005
10. Sun J, Zhang H, Tan Q, Zhou H, Guan D, Zhang X, et al. The epidemiological characteristics and molecular phylogeny of the dengue virus in Guangdong, China, 2015. Sci Rep. (2018) 8:9976. doi: 10.1038/s41598-018-28349-2
11. Ren H, Zheng L, Li Q, Yuan W, Lu L. Exploring determinants of spatial variations in the dengue fever epidemic using geographically weighted regression model: a case study in the Joint Guangzhou-Foshan Area, China. 2017. Int J Environ Res Public Health. (2017) 14:12. doi: 10.3390/ijerph14121518
12. Zhang Z, Jing Q, Chen Z, Li T, Jiang L, Li Y, et al. The increasing menace of dengue in Guangzhou, 2001-2016: the most important epicenter in mainland China. BMC Infect Dis. (2019) 19:1002. doi: 10.1186/s12879-019-5004-3
13. Zhao S, Musa SS, Meng J, Qin J, He D. The long-term changing dynamics of dengue infectivity in Guangdong, China, from 2008-2018: a modelling analysis. Trans R Soc Trop Med Hygiene. (2020) 114:62–71. doi: 10.1093/trstmh/trza084
14. Wang B, Yang H, Feng Y, Zhou H, Dai J, Hu Y, et al. The distinct distribution and phylogenetic characteristics of dengue virus serotypes/genotypes during the 2013 outbreak in Yunnan, China: phylogenetic characteristics of 2013 dengue outbreak in Yunnan, China. Infect Genet Evol. (2016) 37:7–43. doi: 10.1016/j.meegid.2015.10.022
15. Hu TS, Zhang HL, Feng Y, Fan JH, Tang T, Liu YH, et al. Epidemiological and molecular characteristics of emergent dengue virus in Yunnan Province near the China-Myanmar-Laos border, 2013–2015. BMC Infect Dis. (2017) 17:331. doi: 10.1186/s12879-017-2401-1
16. Wang B, Li Y, Feng Y, Zhou H, Liang Y, Dai J, et al. Phylogenetic analysis of dengue virus reveals the high relatedness between imported and local strains during the 2013 dengue outbreak in Yunnan, China: a retrospective analysis. BMC Infect Dis. (2015) 15:142. doi: 10.1186/s12879-015-0908-x
17. Zhang FC, Zhao H, Li LH, Jiang T, Hong WX, Wang J, et al. Severe dengue outbreak in Yunnan, China, 2013. Int J Infect Dis. (2014) 27:4–6. doi: 10.1016/j.ijid.2014.03.1392
18. Chen B, Liu Q. Dengue fever in China. Lancet. (2015) 385:1621–2. doi: 10.1016/S0140-6736(15)60793-0
19. Lai S, Huang Z, Zhou H, Anders KL, Perkins TA, Yin W, et al. The changing epidemiology of dengue in China, 1990-2014: a descriptive analysis of 25 years of nationwide surveillance data. BMC Med. (2015) 13:100. doi: 10.1186/s12916-015-0336-1
20. Jin X, Lee M, Shu J. Dengue fever in China: an emerging problem demands attention. Emerg Microbes Infect. (2015) 4:e3. doi: 10.1038/emi.2015.3
21. Yue Y, Liu X, Xu M, Ren D, Liu Q. Epidemiological dynamics of dengue fever in mainland China, 2014-2018. Int J Infect Dis. (2019) 86:82–93. doi: 10.1016/j.ijid.2019.06.015
22. Ooi EE. The re-emergence of dengue in China. BMC Med. (2015) 13:99. doi: 10.1186/s12916-015-0345-0
23. Ooi EE. The re-emergence of dengue in China. BMC Med. (2015) 13:99. doi: 10.1186/s12916-015-0345-0
24. Xiang J, Hansen A, Liu Q, Tong MX, Sun Y, et al. Association between dengue fever incidence and meteorological factors in Guangzhou, China, 2005–2014. Environ Res. (2017) 153:17–26. doi: 10.1016/j.envres.2016.11.009
25. Xu L, Suge LC, Chan KS, Zhou J, Yang J, Sang S, et al. Climate variation drives dengue dynamics. Proc Natl Acad Sci USA. (2017) 114:113–8. doi: 10.1073/pnas.1618558114
26. Guo P, Zhang Q, Chen Y, Xiao J, He J, Zhang Y, et al. An ensemble forecast model of dengue in Guangzhou, China using climate and social media surveillance data. Sci Total Environ. (2019) 647:752–62. doi: 10.1016/j.scitotenv.2018.08.044
27. Wang C, Zhang H, Fan J, Wang F, Liu Q. A study of the dengue epidemic and meteorological factors in Guangzhou, China, by using a zero-inflated Poisson regression model. Asia Pac J Public Health. (2014) 26:48–57. doi: 10.1177/1010539513480195
28. Xiao J, Liu T, Lin H, Zhu G, Zeng W, Li X, et al. Weather variables and the El Nino Southern Oscillation may drive the epidemics of dengue in Guangdong Province, China. Sci Total Environ. (2018) 624:926–34. doi: 10.1016/j.scitotenv.2017.12.200
30. Li MT, Sun GQ, Yakob L, Zhu HP, Jin Z, Zhang WY. The dengue outbreak of 2014 transformed the epidemic characteristics of dengue in Guangdong Province, China. J Infect. (2019) 78:491–503. doi: 10.1016/j.jinf.2019.03.001
31. Liu K, Zhu Y, Xia Y, Zhang Y, Huang X, Huang J, et al. Dynamic spatiotemporal analysis of indigenous dengue fever at street-level in Guangzhou city, China. PLoS Negl Trop Dis. (2018) 12:e0006318. doi: 10.1371/journal.pntd.0006318
32. Lee Y, Ha SY, Park HK, Han MS, Shin KH. Identification of key factors influencing primary productivity in two river-type reservoirs by using principal component regression analysis. Environ Monit Assess. (2015) 187:213. doi: 10.1007/s10661-015-4438-1
33. Liu RX, Kuang J, Gong Q, Hou XL. Principal component regression analysis with SPSS. Computer methods and programs in biomedicine. (2003) 71:141–7. doi: 10.1016/s0169-2607(02)00058-5
34. Sang S, Yin W, Bi P, Zhang H, Wang C, Liu X, et al. Predicting local dengue transmission in Guangzhou, China, through the influence of imported cases, mosquito density and climate variability. PLoS ONE. (2014) 9:e102755. doi: 10.1371/journal.pone.0102755
35. Zhu G, Xiao J, Liu T, Zhang B, Hao Y, Ma W. Spatiotemporal analysis of the dengue outbreak in Guangdong Province, China. BMC Infect Dis. (2019) 19:493. doi: 10.1186/s12879-019-4015-2
36. Jing Q, Li Y, Liu J, Jiang Z, Su W, et al. Dengue underestimation in Guangzhou, China: evidence of seroreversal in communities with no reported cases before a large outbreak in 2014. Open Forum Infect Dis. (2019) 6:ofz256. doi: 10.1093/ofid/ofz256
37. Luo L, Jiang LY, Xiao XC, Di B, Jing QL, Wang SY, et al. The dengue preface to endemic in mainland China: the historical largest outbreak by Aedes albopictus in Guangzhou, 2014. Infect Dis Poverty. (2017) 6:148. doi: 10.1186/s40249-017-0352-9
38. Aryaprema VS, Xue RD. Breteau index as a promising early warning signal for dengue fever outbreaks in the Colombo District, Sri Lanka. Acta tropica. (2019) 199:105155. doi: 10.1016/j.actatropica.2019.105155
39. Morin CW, Comrie AC, Ernst K. Climate and dengue transmission: evidence and implications. Environ Health Perspect. (2013) 121:1264–72. doi: 10.1289/ehp.1306556
40. Teurlai M, Menkes CE, Cavarero V, Degallier N, Descloux E, Grangeon JP, et al. Socio-economic and climate factors associated with dengue fever spatial heterogeneity: a worked example in New Caledonia. PLoS Neglect Trop Dis. (2015) 9:e0004211. doi: 10.1371/journal.pntd.0004211
41. Lin Y, Ma D, Wen S, Zeng F, Hong S, Li L, et al. Molecular characterization of the viral structural gene of the first dengue virus type 1 outbreak in Xishuangbanna: a border area of China, Burma and Laos. Int J Infect Dis. (2019) 79:152–61. doi: 10.1016/j.ijid.2018.11.370
42. Huang L, Luo X, Shao J, Yan H, Qiu Y, Ke P, et al. Epidemiology and characteristics of the dengue outbreak in Guangdong, Southern China, in 2014. Eur J Clin Microbiol Infect Dis. (2016) 35:269–77. doi: 10.1007/s10096-015-2540-5
43. Su X, Guo Y, Deng J, Xu J, Zhou G, Zhou T, et al. Fast emerging insecticide resistance in Aedes albopictus in Guangzhou, China: alarm to the dengue epidemic. PLoS Negl Trop Dis. (2019) 13:e0007665. doi: 10.1371/journal.pntd.0007665
44. Li CX, Kaufman PE, Xue RD, Zhao MH, Wang G, Yan T, et al. Relationship between insecticide resistance and kdr mutations in the dengue vector Aedes aegypti in Southern China. Parasites & vectors. (2015) 8:325. doi: 10.1186/s13071-015-0933-z
45. Liu K, Wang T, Yang Z, Huang X, Milinovich GJ, Lu Y, et al. Using Baidu search index to predict dengue outbreak in China. Sci Rep. (2016) 6:38040. doi: 10.1038/srep38040
46. Findlater A, Moineddin R, Kain D, Yang J, Wang X, Lai S, et al. The use of air travel data for predicting dengue importation to China: a modelling study. Travel Med Infect Dis. (2019) 31:101446. doi: 10.1016/j.tmaid.2019.07.002
47. Yue Y, Sun J, Liu X, Ren D, Liu Q, Xiao X, et al. Spatial analysis of dengue fever and exploration of its environmental and socio-economic risk factors using ordinary least squares: a case study in five districts of Guangzhou City, China, 2014. Int J Infect Dis. (2018) 75:39–48. doi: 10.1016/j.ijid.2018.07.023

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Liu, Liu, Yue, Wu, Yang, Guo, Ren, Zhao, Yang and Liu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.