Spatiotemporal Analysis of the Malaria Epidemic in Mainland China, 2004–2014

Qiang Huang,¹ Lin Hu,¹ Qi-bin Liao,¹ Jing Xia,¹ Qian-ru Wang,² and Hong-Juan Peng^{1*}

¹Department of Pathogen Biology, Guangdong Provincial Key Laboratory of Tropical Disease Research, and Key Laboratory of Prevention and Control for Emerging Infectious Diseases of Guangdong Higher Institutes, School of Public Health, Southern Medical University, Guangzhou, Guangdong Province, China; ²Department of Atmospheric Science, College of Atmospheric Sciences, Chengdu University of Information Technology, Chengdu, Sichuan, China

Abstract. The purpose of this study is to characterize spatiotemporal heterogeneities in malaria distribution at a provincial level and investigate the association between malaria incidence and climate factors from 2004 to 2014 in China to inform current malaria control efforts. National malaria incidence peaked (4.6/100,000) in 2006 and decreased to a very low level (0.21/100,000) in 2014, and the proportion of imported cases increased from 16.2% in 2004 to 98.2% in 2014. Statistical analyses of global and local spatial autocorrelations and purely spatial scan statistics revealed that malaria was localized in Hainan, Anhui, and Yunnan during 2004–2009 and then gradually shifted and clustered in Yunnan after 2010. Purely temporal clusters shortened to less than 5 months during 2012–2014. The two most likely clusters detected using spatiotemporal analysis occurred in Anhui between July 2005 and November 2007 and Yunnan between January 2010 and June 2012. Correlation coefficients for the association between malaria incidence and climate factors sharply decreased after 2010, and there were zero-month lag effects for climate factors during 2010–2014. Overall, the spatiotemporal distribution of malaria in China changed from relatively scattered (2004–2009) to relatively clustered (2010–2014). As the proportion of imported cases increased, the effect of climate factors on malaria incidence has gradually become weaker since 2011. Therefore, new warning systems should be applied to monitor resurgence and outbreaks of malaria in mainland China, and quarantine at borders should be reinforced to control the increasingly trend of imported malaria cases.

INTRODUCTION

Malaria remains one of the most devastating vector-borne diseases, it was estimated that approximately 214 million cases of malaria occurred in 2015, resulting in 438,000 deaths worldwide.¹ To address existing and emerging challenges to achieving a malaria-free world, the Global Technical Strategy for Malaria 2016–2030 was developed by the World Health Organization (WHO) and adopted by the World Health Assembly in May 2015.²

Previously, malaria was the most common parasitic infection in mainland China. Due to the efforts of the Chinese government, malaria cases decreased from 24 million in the early 1970s to 30,000 in the late 1990s, and areas in which malaria were endemic had also substantially decreased. In the early 1990s, *Plasmodium falciparum* was successfully eliminated and cases attributed to *Plasmodium vivax* were significantly reduced in all Chinese mainland territories except the Yunnan and Hainan provinces.³ After 2000, a resurgence of malaria occurred in several parts of China, with approximately 64,178 malaria cases reported in 2006.⁴ Through the implementation of the National Malaria Control Program (NMCP) 2006–2015 and with increasing political and financial support, China has successfully controlled this reemerging threat. Additionally, China has implemented the Action Plan of China Malaria Elimination (APCME) 2010–2020 as a component of their efforts to eliminate malaria and response to the Malaria Eradication Plan and Millennium Development Goals. However, malaria transmission persisted in several regions, such

as the central part of China, border areas of the Yunnan Province, and southcentral mountainous areas of the Hainan Province.⁵ Due to rapid economic development and globalization, malaria elimination in China is further challenged by population mobility resulting from increasing numbers of transient workers and farmers and foreign travelers. More and more imported malaria cases have been detected during the current decade, the majority of which were imported from areas such as Ghana, Angola, Myanmar, and Cambodia.⁶

Spatial statistical analysis techniques, such as spatial autocorrelation, have been integrated into geographic information system software to analyze spatial associations and variations and determine distribution characteristics of communicable disease epidemiology.^{7–9} Moreover, scan statistics have long been used to detect local clusters of cases and evaluate their statistical significance through the application of SaTScan software (Version 9.4, Calverton, MD). In addition, numerous studies had found that malaria cases were strongly correlated with climate factors such as temperature, rainfall, and relative humidity.^{10–18} Identification of the spatiotemporal variations in malaria epidemiology in China is pivotal for the establishment of strategies or measures for disease control at the present stage of malaria elimination.

MATERIALS AND METHODS

Study area. Mainland China is situated in the eastern part of Asia and on the west coast of the Pacific Ocean, extending from latitudes 3°51' to 53°33' north to longitudes 73°33' to 135°05' east with an area of 9,600,000 km² (Figure 1). The central and western region of China consists of a plateau zone and mountainous area, and the eastern part consists of hilly lands and plains. The water bodies in China are abundant, with more than 1,500 rivers and 2,800 lakes and drainage areas of over 1,000 km². China has a complex and diverse continental monsoon climate, with a mean annual rainfall of approximately 800 mm and monthly

* Address correspondence to Hong-Juan Peng, Department of Pathogen Biology, Guangdong Provincial Key Laboratory of Tropical Disease Research, and Key Laboratory of Prevention and Control for Emerging Infectious Diseases of Guangdong Higher Institutes, School of Public Health, Southern Medical University, Number 1023 South Shatai Road, Guangzhou, Guangdong Province, People's Republic of China. E-mail: floriapeng@hotmail.com

FIGURE 1. Location and scale of the study region in mainland China. The study region in mainland China is shown in gray, including 23 provinces, five autonomous regions, and four municipalities. The name of each province/autonomous region/municipality within the study area is labeled.

temperature ranging from -1.5 to 24.9°C throughout the country. Mainland China has a population of approximately 1.36 billion distributed over the 31 province level divisions that include 23 provinces, five autonomous regions, four municipalities but does not include Taiwan, Hong Kong, and Macao.

Data sources. Data for malaria cases from each month and province between 2004 and 2014 were obtained from the Data-center of China Public Health Science (<http://www.phsciencedata.cn/Share/en/data.jsp>). Malaria cases for whom data were obtained consisted of both clinically diagnosed and microscopically confirmed cases, as defined by the 2006 Diagnostic Criteria for Malaria (WS 259-2006).¹⁹ Population data for each division were acquired from the National Bureau of Statistics of the People's Republic of China (<http://data.stats.gov.cn>). Monthly meteorology data (2004–2014) were obtained from China meteorology data sharing service system and included temperature, rainfall, and relative humidity data from 160 monitoring stations throughout China.

Data management. Monthly average temperature (AT), average rainfall (AR), and average relative humidity (AH) were calculated from 2004 to 2014. Malaria cases and population of each province were geocoded and matched to polygons, and the coordinates of centroids (X , Y) for each

province were computed using ArcGIS 10.2 and exported for scan statistics in SaTScan 9.4. Additionally, raw malaria incidence was adjusted by applying the empirical Bayes smoothing method in Geoda 1.6 (Version 1.6, Tempe, AZ) to account for the variance instability of the raw rates.²⁰ All spatial analyses were based on the WGS 1984 World Mercator coordinate system.

Spatial autocorrelation analysis. Global Moran's I was used to assess the degree of similarity observed between a certain location and its adjacent units, which was referred to as spatial autocorrelation; rejecting the null hypothesis implied a nonrandom spatial pattern.²¹ The first step for the spatial autocorrelation analysis was to choose a spatial weight matrix to define the proximity relationship between each location and its neighboring region, and "Contiguity edges corners" (Queen contiguity) was used to define this spatial relationship within global Moran's I statistics, the w_{ij} was defined with Equation A in Supplemental Table 1, the global Moran's I was defined with Equation B in Supplemental Table 1.

Local indicators of spatial autocorrelation include two common methods—the local Moran's I and G_i^* statistics, which have been widely applied to identify outliers and interpret spatial nonstationarity or hot spots in local region.²² Of the two, the local G_i^* statistic has been applied more

FIGURE 2. Malaria incidence and distribution among populations in mainland China, 2004–2014. (A) Annual malaria incidences during 2004–2014. Annual incidence of malaria increased from 2.89 per 100,000 individuals in 2004 to a peak of 4.60 per 100,000 individuals in 2006 and then dramatically decreased to 0.21 per 100,000 people in 2014. (B) Frequencies of malaria cases by origin during 2004–2014. The proportions of imported cases, which ranged from 16.2% to 45.7% of total cases, were less than those of indigenous cases until 2010; however, following 2010, the ratio reversed, with the proportion of imported cases increasing from 70.9% in 2011 to 98.2% in 2014. (C) Distribution of malaria cases by age group, the proportion of cases in the “≤5 years” and “6–19 years” age groups gradually decreased from 4.5% and 23.5% in 2004 to 0.3% and 1.4% in 2014, respectively; the proportion of cases in the “≥55 years” age group sharply decreased from 24.8% in 2009 to 4.2% in 2014; the proportion of cases in the “20–50 years” age group increased from 60.6% in 2004 to 94.0% in 2014. (D) Distribution of malaria cases by occupation. “Farmer and Worker” (farmer, physical worker, and technical worker) accounted for between 71.2% and 79.6% of total cases during 2004–2014. The proportion of malaria cases that were “Children and Student” reduced from 21.9% in 2004 to 1.1% in 2014, and the proportion of malaria cases that were “Traveler” (commercial people, sailor, and long-distance driver), “Public servant,” and “Unemployed” gradually increased from 0.8%, 2.0%, 3.3% in 2004 to 5.3%, 4.0%, 18.3% in 2014, respectively. This figure appears in color at www.ajtmh.org.

frequently, as it is effective even in datasets in which there is no global spatial autocorrelation.²³ The local G_i^* statistic, which is also known as hot spot analysis, and the spatial relationship between location i and j were weighted by distance, with the bigger distance indicated with a smaller w_{ij} value (0–1), and we selected the “inverse distance” spatial weight matrix to define the spatial relationship. The G_i^* (d) statistic was calculated with Equation C (Supplemental Table 1).

Moran’s I ranges from -1 to $+1$, with approaching -1 indicating that neighboring areas tend to have dissimilar attribute values, approaching 1 indicating that a cluster exists across the study areas with high similarity, and value of zero indicates the null hypothesis of random distribution of malaria incidence. A positive $Z_{G_i^*}$ revealed a high value clustering (hot spot), and a negative $Z_{G_i^*}$ indicated a low value clustering (cold spot).

Scan statistics analysis. Scan statistics were used to detect spatial and temporal heterogeneity within the malaria

epidemic in China. The basic premise of scan statistics is to set a scanning window that varies in size and location. The spatial scanning window is usually a circle covering geographic regions, whereas the temporal scanning window is a time span moving throughout the studied time frame, and the space-time scanning window is a cylinder whose base and height represent the spatial areas and time span, respectively. A log likelihood ratio (LLR) was constructed using the observed and expected cases inside and outside each window. The scanning window with the highest LLR was the most likely cluster. Statistical significance was tested with the Monte Carlo method, and the simulated dataset was set to 999. The likelihood function for a specific window was proportional to^{24,25} Equation D in Supplemental Table 1.

In this study, cluster analysis was implemented using a Poisson model. For purely spatial clustering analysis, the maximum spatial cluster size of the population at risk was set to 50%, with the cluster output including the most

FIGURE 3. Distribution of empirical Bayes smoothed annual malaria incidence in mainland China, 2004–2014. The incidences for each province, autonomous region, and municipality have been classified into six levels with six different shades of gray, with a deeper shade of gray indicating higher incidence. The majority of malaria cases were reported between latitudes 18° and 37° north (refer to Figure 1) and located in the southwestern and mideastern regions of mainland China. Both the number and severity of the epidemic areas decreased from 2004 to 2014. Additionally, Anhui, Hainan, and Yunnan had the highest incidence prior to 2010, whereas only Yunnan remained as a high incidence area until 2014.

likely cluster and secondary cluster. For purely temporal clustering analysis, the time aggregation length was set to 1 month, the maximum temporal cluster size was set to 50%, and only the most likely cluster was reported. The space-time retrospective analyses used the same settings as purely spatial and temporal analyses.

Correlation analysis. Spearman correlation analyses were used to evaluate the association between monthly malaria incidence and climate data using IBM SPSS 19.0 (Armonk, NY). In this study, AT_0 , AT_1 , and AT_2 represented the ATs of the current month, the past month, and the month before last, respectively; additionally, AR_0 , AR_1 , and AR_2 represented the ARs of the current month, the month before, and the month before last, respectively; AH_0 , AH_1 , and AH_2 represented the AH of the current month, the past month, and the month before last, respectively.

RESULTS

Descriptive analysis of the malaria epidemic in China. A total of 259,239 malaria cases were reported from 2004 to 2014 in 32 provinces, with an average annual incidence of 1.69 per 100,000 people. The malaria incidence increased from 2.89 per 100,000 individuals in 2004 to the incidence peak of 4.60 per 100,000 individuals in 2006, and then dramatically decreased to 0.18 per 100,000 people in 2012, 0.29 per 100,000 people in 2013, and 0.21 per

100,000 people in 2014 (Figure 2, Supplemental Table 2). Notably, the proportions of imported cases, which ranged from 16.2% to 45.7% of total cases, were less than those of indigenous cases until 2010; however, following 2010, the ratio reversed, with the proportion of imported cases increasing from 70.9% in 2011 to 98.2% in 2014. Interestingly, the proportions of cases in the “ ≤ 5 years” and “6–19 years” age groups gradually decreased from 4.5% and 23.5% in 2004 to 0.3% and 1.4% in 2014, respectively. The proportion of cases within the “ ≥ 55 years” age group sharply decreased from 24.8% in 2010 to 4.2% in 2014; throughout the study period, the majority of the cases were concentrated in “20–50 years” age group, ranging from 60.6% in 2004 to 94.0% in 2014. Additionally, the majority of malaria cases were used as “Farmer and Worker” (farmer, physical worker, and technical worker), which accounted for 71.2–79.6% of the total cases during 2004–2014; the proportion of cases among “Children and Student” reduced dramatically from 21.9% in 2004 to 1.1% in 2014, and the proportion cases among of “Traveler” (commercial people, sailor, and long-distance driver), “Public servant,” and the “Unemployed” gradually increased from 0.8%, 2.0%, 3.3% in 2004 to 5.3%, 4.0%, 18.3% in 2014, respectively (Figure 2, Supplemental Table 2).

According to the spatial empirical Bayes smoothed annual incidences of malaria, malaria cases were predominantly reported between the latitudes 18° and 37° north

TABLE 1

Global Moran's I value for malaria incidence from 2004 to 2014 in mainland China

Year	Incidence (1/100,000)	I	Z	P value
2004	2.888	-0.030	0.115	0.298
2005	3.051	-0.050	-0.153	0.379
2006	4.603	-0.057	-0.225	0.432
2007	3.551	-0.048	-0.166	0.393
2008	1.995	-0.040	-0.090	0.395
2009	1.062	-0.021	0.125	0.364
2010	0.554	0.100	1.514	0.079
2011	0.304	0.063	1.410	0.086
2012	0.182	0.155	2.767	0.012
2013	0.288	0.082	2.054	0.043
2014	0.214	0.169	2.158	0.022

The value of $Z(I)$ statistics represents the statistic value of global Moran's I .

and in the southwestern and mideastern regions of mainland China (Figure 1 and 3). Both the number and intensity of epidemic areas has decreased from 2004 to 2014. Additionally, although Anhui, Hainan, and Yunnan were the highest incidence areas prior to 2010, only Yunnan remained an area of high incidence until 2014.

Spatial autocorrelation analysis. The global Moran's I at the province level (Table 1) indicated that between 2012 and

2014, statistically significant autocorrelation existed between the study areas, which revealed that spatial associations in malaria incidence existed across the entire study area. However, the Moran's I values from 2004 to 2009 were negative ($P > 0.05$), indicating a random distribution of malaria incidence across the overall area. Moreover, a weak spatial autocorrelation was identified from 2010 ($Z = 1.514$, $P = 0.079$) to 2011 ($Z = 1.410$, $P = 0.086$).

Local G_i^* statistics were used to detect hot spots using the output of $Z_{G_i^*}$ values and P values for specific locations (Supplemental Table 3, Figure 4). From this analysis, 16 hot spots (with 99% confidence) were identified during 2004–2014, including Hainan (2004 and 2006–2009), Anhui (2006–2010), Yunnan (2005, 2010–2012, and 2014), and Guangxi (2013). Three hot spots (with 95% confidence) were identified in Hainan and Anhui (2005) and Yunnan (2009).

Spatial scan statistics analysis. According to the output of the purely spatial scan statistics analysis (Supplemental Table 4, Figure 5), 11 most likely clusters were detected in Hainan (2004), Anhui (2005–2009), Yunnan (2010–2012 and 2014), and Guangxi (2013). Additionally, 14 provinces were identified as secondary clusters from 2004 to 2014, including Yunnan (2004–2006, 2009, and 2013), Hainan

FIGURE 4. Hot spots and clusters of malaria identified in mainland China, 2004–2014. Local G_i^* and purely spatial scan statistical analyses were used. Different star forms represent different magnitudes of Z (G_i^*) value, the “J” and “H” represent hot spots with 95% and 99% confidence, respectively; most likely and secondary clusters are shaded deep and light gray, respectively. Sixteen hot spots (with 99% confidence) were identified during 2004–2014, including Hainan (2004 and 2006–2009), Anhui (2006–2010), Yunnan (2005 and 2010–2012 and 2014), and Guangxi (2013); three hot spots (with 95% confidence) were identified in Hainan and Anhui (2005), and Yunnan (2009). Eleven most likely clusters were detected in Hainan (2004), Anhui (2005–2009), Yunnan (2010–2012 and 2014), and Guangxi (2013); 14 provinces were identified as secondary clusters from 2004 to 2014, including Yunnan (2004–2006, 2009, and 2013), Hainan (2007, 2008), Guangxi (2009, 2012), Anhui (2010, 2011, and 2014), Henan (2014), and Hubei (2014). Both hot spots and spatial clusters were predominately located in Anhui, Yunnan, and Hainan. The malaria purely spatial clusters were roughly concurrent with the outputs of hot spot analysis for both locations and clustering classes.

FIGURE 5. Identified clusters of malaria using purely temporal scan statistics analysis in mainland China, 2004–2014. The temporal clusters of each year were shown with different kinds of lines, the “@” represented the peak of malaria incidence in each temporal cluster, and the number inside the “parentheses” represented the month of cluster duration. The lengths of the temporal cluster duration identified during 2004–2011 were 5 months or more, most of the cases clustered in May–October in 2004 and 2008–2010, June–October in 2005 and 2007, July–November in 2006, and April–September in 2011; the peak of malaria incidence in each temporal cluster mainly presented in July or August from 2004 to 2010. Subsequently, the temporal cluster periods were 3 months (May–July) in 2012, 2 months (June–July) in 2013, and then 4 months (May–August) in 2014; the peak of incidence appeared earlier in June from 2011 to 2014. Furthermore, the peaks of temporal clusters during 2010–2014 had been less obvious than that during 2004–2009. This figure appears in color at www.ajtmh.org.

(2007, 2008), Guangxi (2009, 2012), Anhui (2010, 2011, and 2014), Henan (2014), and Hubei (2014). Both the hot spots and spatial clusters were predominately located in Anhui, Yunnan, and Hainan. It was notable that the results of the purely spatial cluster analysis were roughly concurrent with the output of hot spot analysis for both the locations and clustering of malaria cases.

Temporal scan statistics analysis. Purely temporal scan statistics analysis was performed using the monthly malaria case data from 2004 to 2014 (Figure 5, Supplemental Table 5). The duration of the temporal cluster identified during 2004–2011 was more than 5 months, most of the cases clustered in May–October (in 2004 and 2008–2010), June–October (in 2005 and 2007), July–November (in 2006), and April–September (in 2011); the peak of incidence in temporal cluster mainly presented in July or August from 2004 to 2010. Subsequently, the duration of temporal cluster shortened to 3 months (May–July) in 2012, 2 months (June–July) in 2013, and then 4 months (May–August) in 2014; the peak of incidence appeared earlier in June from 2011 to 2014. Furthermore, the peaks of temporal clusters during 2010–2014 had been less obvious than that during 2004–2009.

Space-time scan statistics analysis. Because the global spatial autocorrelation analysis suggested a random distribution of malaria incidence during 2004–2009 and weak and significant correlations between neighboring districts during 2010–2011 and 2012–2014, respectively, a space-time scan statistics analysis was conducted and identified spatial and temporal clusters of malaria during two time frames: 2004–2009 and 2010–2014. Two most likely clusters and two secondary clusters were detected (Table 2). One of the most likely clusters was identified in Anhui during the time frame from July 1, 2005, to November 30, 2007, and the other most likely cluster was detected in Yunnan during the time frame from January 1, 2010, to June 30, 2012. Two secondary clusters were identified from January 1, 2004, to August 31, 2006, in Yunnan, and from May 2010 to November 2010 in Anhui, Henan, and Hubei. All clusters are indicated on the map in Figure 6.

Correlation analysis between malaria incidence and climate factors. Given the heterogeneity between the spatial autocorrelations for malaria incidence identified in this study between 2004 and 2014, the correlations between monthly malaria incidence and meteorological data were

TABLE 2
Spatiotemporal scan statistics analysis of malaria cases from 2004 to 2014 in mainland China

Year	N	Cluster time frame	Location/radius (km)	Observed cases	Expected cases	RR	LLR	P value
2004–2009	1 ^A	July 1, 2005–November 30, 2007	Anhui/0	76,746	4,247.78	26.93	16,3121.41	< 0.001
	1 ^B	January 1, 2004–August 31, 2006	Yunnan/0	36,552	3,837.37	11.18	52,225.93	< 0.001
2010–2014	1 ^A	January 1, 2010–June 30, 2012	Yunnan/0	3,706	355.51	12.47	5,628.67	< 0.001
	3 ^B	May 5, 2010–November 30, 2010	Henan/484.5	2,698	380.32	8.01	3,105.57	< 0.001

N = number of cluster; A = most likely cluster; B = secondary cluster; RR = relative risk; LLR = log likelihood ratio.

calculated using Spearman correlation analysis with SPSS 19.0 software for two time periods: 2004–2009 and 2010–2014 (Table 3). To analyze the lag effect of climate factors on malaria incidence, meteorological variables for monthly AT (AT₀, AT₁, and AT₂), monthly AR (AR₀, AR₁, and AR₂), and monthly AH (AH₀, AH₁, and AH₂) were included.

Globally, monthly AT, AR, and AH were significantly associated with malaria incidence during these two time frames ($P < 0.05$); the correlation coefficient for temperature (r_1) decreased from 0.963 (2004–2009) to 0.416 (2010–2014), the correlation coefficient for rainfall (r_2) sharply decreased from 0.839 (2004–2009) to 0.482 (2010–2014), and the correlation coefficient for relative humidity (r_3) decreased from 0.503 (2004–2009) to 0.292 (2010–2014), which were distinctly smaller than temperature and rainfall. Moreover, during 2004–2009, malaria incidence for the current month was most highly correlated with AT₁ and AR₁, indicating a 1-month lag effect of temperature and rainfall on malaria incidence, and there was no lag effect of relative humidity; however, during 2010–2014, AT₀, AR₀, and AH₀ were most highly correlated with malaria incidence ($r_1 = 0.416$, $P < 0.001$; $r_2 = 0.482$, $P < 0.001$; $r_3 = 0.292$, $P = 0.023$), suggesting malaria incidence of the current month

had a weak correlation with AT, AR, and AH of the current month, and there was no lag effect for temperature, rainfall, and relative humidity on monthly malaria incidence.

DISCUSSION

To date, the spatiotemporal analyses of malaria in China have been predominantly focused on the county-level and small-scale geographic areas, which may inform reasonable allocation of public resources²⁶; however, an understanding of malaria macro or provincial level is also imperative, which would contribute to the formulation of general control policies or principles. Based on this need, we described space and time clusters for malaria incidence throughout mainland China and evaluated the correlation between malaria incidence and climate factors to gain a better understanding of the causes of malaria transmission.

According to our results, malaria incidence peaked in 2006, with an annual incidence of 4.60 per 100,000 people, and then dramatically decreased to 0.21 per 100,000 individuals in 2012 and remained at a very low level. These trends indicate that China successfully controlled the resurgence in malaria over the prior 10 years. During this period,

FIGURE 6. Identified clusters of malaria using space-time scan statistics analysis in mainland China, 2004–2014. The areas shaded deep gray indicate most likely cluster locations during the corresponding time frames, and the areas shaded light gray represent secondary cluster locations during the corresponding time frames. The first most likely cluster was located in Anhui during the time frame from July 1, 2005 to November 30, 2007, and the second most likely cluster was detected in Yunnan during the time frame from January 1, 2010 to June 30, 2012. The first secondary cluster was identified from January 1, 2004 to August 31, 2006 in Yunnan, and the second secondary cluster was identified from May 1, 2010 to November 30, 2010 in Anhui, Henan, and Hubei.

TABLE 3
Spearman correlations between malaria incidence and climate factors in two time frames

Year	Temperature	Current month incidence		Rainfall	Current month incidence		Relative humidity	Current month incidence	
		r_1	P		r_2	P		r_3	P
2004–2009	AT ₀	0.826	< 0.001	AR ₀	0.710	< 0.001	AH ₀	0.503*	< 0.001
2004–2009	AT ₁	0.963*	< 0.001	AR ₁	0.839*	< 0.001	AH ₁	0.449	< 0.001
2004–2009	AT ₂	0.673	< 0.001	AR ₂	0.751	< 0.001	AH ₂	0.210	0.076
2010–2014	AT ₀	0.416*	< 0.001	AR ₀	0.482*	< 0.001	AH ₀	0.292*	0.023
2010–2014	AT ₁	0.328	0.005	AR ₁	0.419	< 0.001	AH ₁	0.023	0.861
2010–2014	AT ₂	0.146	0.221	AR ₂	0.284	0.015	AH ₂	–0.215	0.099

AH₀ = current month average relative humidity; AH₁ = last month average relative humidity; AH₂ = last two month average relative humidity; AR₀ = current month average rainfall; AR₁ = last month average rainfall; AR₂ = last two month average rainfall; AT₀ = current month average temperature; AT₁ = last month average temperature; AT₂ = last two month average temperature; r_1 = Spearman correlation coefficient between current month malaria incidence and monthly average temperature; r_2 = Spearman correlation coefficient between current month malaria incidence and monthly average rainfall; r_3 = Spearman correlation coefficient between current month malaria incidence and monthly average relative humidity.

* Represent the strongest correlation coefficient between malaria incidence and climate factors.

two important projects were launched and implemented by the China Ministry of Health, including the NMCP (2006–2015) and APCME (2010–2020).^{3,5} Through these efforts, areas in China in which malaria was endemic were classified into four types, and control strategies and measures with corresponding targets and metrics were implemented accordingly. For example, in class I counties, defined as those with existing indigenous cases and a malaria incidence exceeding 1/10,000 population over past continuous 3 years, targets were set to reduce the incidence to below 1/10,000 population by 2015, eradicate the indigenous cases by 2017, and eliminate the malaria by 2020; in class II counties, defined as counties with indigenous cases identified over past 3 years and an incidence below 1/10,000 population for more than 1 year, targets were to eradicate indigenous cases in all areas except Yunnan by 2015 and eradicate malaria by 2018; in class III counties, defined as those with zero indigenous case reported in past 3 years, the target was to eradicate malaria by 2015; and lastly, in class IV counties, defined as nonendemic areas for malaria.²⁷ The “1-3-7” method of surveillance and control has played a key role in reducing malaria incidence in China by demanding that each case be reported within 1 day, be confirmed and investigated within 3 days, and have specific measures implemented to prevent secondary transmission within 7 days, such as patient treatment and mosquito elimination.²⁸

After 2010, imported cases accounted for more than 70% of total malaria cases in China, which may have resulted from increasing trade activities and international workers.^{29–31} Fortunately, the proportion of malaria cases in the “6–19 year” and “≤ 5 year” age groups was found to have decreased to a very low level, a phenomenon that was also reflected in malaria incidence within the “Children and Student” group. However, the proportion of malaria cases aged 20–54 years and used as “Farmer and Worker” remained high, who have more chance of exposure to the natural environment, or the semi-open village houses and construction sites that provide suitable dwellings for anophelines. Furthermore, the proportions of cases with occupations reported as “Traveler,” “Unemployed,” and “Public servant” increased considerably, serving as a reminder of the importance of education for malaria prevention and control knowledge within these high-risk populations. As malaria transmission has decreased to a very low level in China in present times, it is essential to trace and manage each case of infection, and especially the imported cases,

to prevent the malaria outbreaks, a principal that is also suggested by the WHO.²

Our study showed that the malaria cases of China were clustered between the latitudes 18° and 37° north (Figure 3), which is generally in accordance with the distribution of malaria vectors.³¹ Notably, the scale and severity of the malaria epidemic in China have declined annually, and most recent cases were concentrated in the limited area on the border of China–Myanmar, indicating that inspection and quarantine efforts should be strengthened in border areas.

In contrast to the findings of several studies indicating a strong spatial autocorrelation in malaria incidence at a county or village level in some provinces,^{9,26,29,32} this study identified a strong spatial correlation during 2012–2014, whereas weak correlation existed during 2010–2011; and no correlation in malaria incidence was observed between neighboring regions during 2004–2009 at a provincial scale. This was probably a consequence of the large-scale analysis in this study, which may have concealed the associations between smaller administrative divisions, such as counties or villages. Combining the results of local G_i^* and spatial scan statistical analyses, Hainan, Anhui, and Yunnan were sequentially identified as areas with high incidence clusters during 2004–2009, whereas Yunnan was identified as the predominant cluster after 2011. There were no spatial autocorrelations in malaria incidence prior to 2009, as the majority of malaria cases were located in Hainan, Anhui, and Yunnan; however, a positive spatial correlation emerged during 2010–2014, implying that malaria incidence in China had gradually shifted and clustered in the Yunnan Province, adjacent to Myanmar. Moreover, Guangxi was identified as a hot spot (with 99% confidence) and most likely cluster in 2013, which was predominantly caused by the identification of 1,208 cases (96.56%) imported from Africa.³³

The temporal scan statistics analysis of malaria incidence identified only one most likely cluster in each year. As indicated in Figure 5 and Supplemental Table 5, the cluster period in each year was 5 months or more from 2004 to 2011, whereas shortened to 3 months in 2012, 2 months in 2013, and 4 months in 2014. It is known that climate factors influence the propagation and density of mosquitoes, and agricultural activities may increase the chances of exposure to mosquitoes.^{11,12,16,34} However, with the implementation of APCME since 2010, most of malaria cases were imported, and the imported cases would shorten the temporal cluster periods, which had been shown since 2011.

Because the outbreaks resulted by the imported cases were not as dependent on the local environment factors for mosquitoes breeding as the outbreak resulted by indigenous cases, and the imported malaria cases were also influenced by the seasonal fluctuation of the primary endemic areas, the temporal clusters had shown with shorter duration, earlier presentation, and lower level. Besides, several reasons might also contribute to the changed temporal clusters, for faster and more accurate diagnosis of malaria cases, timely treatment, and continually improved indoor residual spraying and insecticide-treated nets/long-lasting insecticide nets coverage.^{6,28,35,36}

In the spatiotemporal scan statistics analyses, we observed two most likely clusters during 2004–2009, and 2010–2014. One was identified from July 1, 2005, to November 30, 2007, in the Anhui Province. Anhui Province had been an unstable malaria-endemic area for a long time, as being located in the central part of China with the Yangtze River and Huai River flowing through, the temperature and rainfall from April to October are appropriate for mosquitoes' propagation. It had been reported that rainfall was the main factor having impact on malaria incidence in north of Anhui during 1990–2009.¹⁸ This cluster in Anhui may be resulted from several factors, including poor malaria control, the abnormal climate in the central part of China, or expanded paddy fields.^{13,27,37} The other cluster was detected in the Yunnan Province from January 1, 2010, to June 30, 2012; Yunnan Province is situated at southwest of China, adjoin with Myanmar, Vietnam, and Laos (Figure 1), mild temperature and abundant rainfall are suitable for mosquitoes breeding almost the whole year, both *P. vivax* and *P. falciparum* are endemic in this province.^{38,39} Many ethnic minorities are living with the high-risk behaviors for malaria infection, like rubber tapping and farming, and most of them are lack of preventative awareness, like the use of bed nets⁴⁰; besides, the border trade and labor export have been more and more frequent in Yunnan Province with the other southeast Asia countries. Interestingly, Yunnan was one of the secondary clusters presented from January 1, 2004, to August 31, 2006, and the other secondary cluster was located at Anhui, Henan, and Hubei from May 1, 2010, to November 30, 2010. It indicated that the most likely cluster of Anhui had changed into a secondary cluster, and reversely, the secondary cluster of Yunnan had turned into a most likely cluster, which reminds us of the importance of maintaining the vigilance to prevent malaria resurgence. Above all, the clusters had shifted to Yunnan Province in recent years, the screening of high-risk populations such as farmer and worker, and education of antimalaria knowledge should be strengthened with an increased emphasis placed on imported cases.^{30,35,37}

The Spearman correlation analysis results revealed that during 2004–2009, high associations were found between climate factors (temperature and rainfall) and malaria incidence, with correlation coefficients of $r_1 = 0.963$ and $r_2 = 0.839$, respectively; but only a weak association was found between the relative humidity and malaria incidence ($r_3 = 0.503$). There was an apparent declining trend in the association between climate factors and malaria incidence from 2004 to 2014, and especially during 2010–2014 (Table 3). Additionally, we found that the lag effects of monthly average rainfall and temperature on malaria incidence had

gradually reduced from 1 month (2004–2009) to zero month (2010–2014), implying that no lag effect for meteorological factors on monthly malaria incidence was identified in more recent years. This phenomenon may be attributed to the following reasons: imported cases from southeast Asia and Africa changed the epidemic characteristics of malaria, for example, a large number of infected individuals within the incubation period of malaria entered China from abroad and were diagnosed locally,³³ which meant that the imported cases would directly increase the number of cases identified that were not dependent on local climate conditions or mosquitoes density; knowledge and skills of medical staff increased; techniques allowing for earlier diagnosis, including rapid diagnosis tests, were used and increased rates of early diagnosis³⁶; and a more suitable environment increased mosquito density and contributed to the transmission of malaria.⁴¹

In summary, the epidemiological characteristics of malaria in China mainland had changed since 2010, the prevention and control measures should be strengthened in the border area of Yunnan Province, quarantine measures at the borders must be strengthened for the increasing imported cases, especially for the returned laborers. The shortened and earlier presented cluster periods of malaria suggested the antimalaria responses should be implemented ahead of schedule. Additionally, the effect of climate factors on malaria incidence has gradually become weaker; therefore, new warning systems should be constructed to monitor resurgence and outbreaks of malaria in mainland China.

Received August 30, 2016. Accepted for publication February 8, 2017.

Published online May 1, 2017.

Note: Supplemental tables appear at www.ajtmh.org.

Acknowledgments: We are grateful to the participants in this study and the anonymous reviewers and editors for their comments and valuable inputs.

Financial support: This work was supported by the funding of from the National Natural Science Foundation of China (No. 81271866, 81572012), the Guangdong Province Universities and Colleges Pearl River Scholar Funded Scheme (2014), the Guangdong Provincial Natural Science Foundation Key Project (2016A030311025), and Guangzhou health and medical collaborative innovation major special project (201604020011) to Hong-Juan Peng.

Authors' addresses: Qiang Huang, Lin Hu, Qi-bin Liao, Jing Xia, and Hong-Juan Peng, Department of Pathogen Biology, Guangdong Provincial Key Laboratory of Tropical Disease Research, and Key Laboratory of Prevention and Control for Emerging Infectious Diseases of Guangdong Higher Institutes, School of Public Health, Southern Medical University, Guangzhou, Guangdong Province, China, E-mails: yellowq1992@sina.com, 826308409@qq.com, liaoqibin1991@sina.cn, xj-0730@163.com, and floriapeng@hotmail.com. Qian-ru Wang, Department of Atmospheric Science, College of Atmospheric Sciences, Chengdu University of Information Technology, Chengdu, Sichuan, China, E-mail: 1161327945@qq.com.

REFERENCES

1. World Health Organization, 2014. *World Malaria Report 2014*. Geneva, Switzerland: WHO. Available at: http://www.who.int/malaria/publications/world_malaria_report_2014/en/. Accessed April 18, 2017.
2. World Health Organization, 2015. *Global Technical Strategy for Malaria 2016–2030*. Geneva, Switzerland: WHO. Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R2-en.pdf?ua=1. Accessed April 19, 2017.

3. China Ministry of Health, 2010. Action plan of China malaria elimination (2010–2020). Available at: <http://static1.1.sqspcdn.com/static/f/471029/25390656/1409634767923/China+Action+Plan+of+Chin>. Accessed April 18, 2017.
4. Zhou SS, Wang Y, Tang LH, 2007. Malaria situation in the People's Republic of China in 2006. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi* 25: 439–441.
5. China Ministry of Health, 2006. National Malaria Control Programme (2006–2015). Available at: <http://www.nhfpc.gov.cn/bgt/pw10603/200605/e22e4e380a7443109b85b23fabdd1130.shtml>. Accessed April 18, 2017.
6. Feng J, Xiao H, Xia Z, Zhang L, Xiao N, 2015. Analysis of malaria epidemiological characteristics in the People's Republic of China, 2004–2013. *Am J Trop Med Hyg* 93: 293–299.
7. Fang L, Yan L, Liang S, de Vlas SJ, Feng D, Han X, Zhao W, Xu B, Bian L, Yang H, Gong P, Richardus JH, Cao W, 2006. Spatial analysis of hemorrhagic fever with renal syndrome in China. *BMC Infect Dis* 6: 77.
8. Hinman SE, Blackburn JK, Curtis A, 2006. Spatial and temporal structure of typhoid outbreaks in Washington, D.C., 1906–1909: evaluating local clustering with the Gi* statistic. *Int J Health Geogr* 5: 13.
9. Tsai PJ, Lin ML, Chu CM, Perng CH, 2009. Spatial autocorrelation analysis of health care hotspots in Taiwan in 2006. *BMC Public Health* 9: 464.
10. Yang GJ, Tanner M, Utzinger J, Malone JB, Bergquist R, Chan EY, Qi G, Zhou XN, 2012. Malaria surveillance-response strategies in different transmission zones of the People's Republic of China: preparing for climate change. *Malar J* 11: 1–9.
11. Mabaso ML, Vounatsou P, Midzi S, Da Silva J, Smith T, 2006. Spatio-temporal analysis of the role of climate in inter-annual variation of malaria incidence in Zimbabwe. *Int J Health Geogr* 5: 20.
12. Chaves LF, Koenraadt CJ, 2010. Climate change and highland malaria: fresh air for a hot debate. *Q Rev Biol* 85: 27–55.
13. Zhou SS, Huang F, Wang JJ, Zhang SS, Su YP, Tang LH, 2010. Geographical, meteorological and vectorial factors related to malaria re-emergence in Huang-Huai River of central China. *Malar J* 9: 337.
14. Huang F, Zhou S, Zhang S, Wang H, Tang L, 2011. Temporal correlation analysis between malaria and meteorological factors in Motuo County, Tibet. *Malar J* 10: 54.
15. Komen K, Olwoch J, Rautenbach H, Botai J, Adebayo A, 2015. Long-run relative importance of temperature as the main driver to malaria transmission in Limpopo Province, South Africa: a simple econometric approach. *EcoHealth* 12: 131–143.
16. Diboulo E, Sie A, Diadier DA, Voules DA, Ye Y, Vounatsou P, 2015. Bayesian variable selection in modelling geographical heterogeneity in malaria transmission from sparse data: an application to Nouna Health and Demographic Surveillance System (HDSS) data, Burkina Faso. *Parasit Vectors* 8: 118.
17. Huang F, Zhou S, Zhang S, Zhang H, Li W, 2011. Meteorological factors-based spatio-temporal mapping and predicting malaria in central China. *Am J Trop Med Hyg* 85: 560–567.
18. Gao HW, Wang LP, Liang S, Liu YX, Tong SL, Wang JJ, Li YP, Wang XF, Yang H, Ma JQ, Fang LQ, Cao WC, 2012. Change in rainfall drives malaria re-emergence in Anhui Province, China. *PLoS One* 7: e43686.
19. Hygienic Standards. The Diagnostic Criteria for Malaria (WS 259-2006). Available at: <http://www.freestd.us/soft4/4649603.htm>. Accessed April 18, 2017.
20. Anselin L, 2006. How (not) to lie with spatial statistics. *Am J Prev Med* 30: S3–S6.
21. Moran PAP, 1950. Notes on continuous stochastic phenomena. *Biometrika* 37: 17–23.
22. Ord JK, Getis A, 1995. Local spatial autocorrelation statistics: distributional issues and an application. *Geogr Anal* 27: 286–306.
23. Anselin L, 1995. Local indicators of spatial association—LISA. *Geogr Anal* 27: 93–115.
24. Kulldorff M, 1997. A spatial scan statistic. *Commun Stat Theory Methods* 26: 1481–1496.
25. Kulldorff M, 1999. Spatial scan statistics: models, calculations, and applications. Glaz J, Balakrishnan N, eds. *Scan Statistics and Applications*. Boston, MA: Birkhäuser Boston, 303–322.
26. Wen L, Li C, Lin M, Yuan Z, Huo D, Li S, Wang Y, Chu C, Jia R, Song H, 2011. Spatio-temporal analysis of malaria incidence at the village level in a malaria-endemic area in Hainan, China. *Malar J* 10: 88.
27. Chen Z, Shi L, Zhou XN, Xia ZG, Bergquist R, Jiang QW, 2014. Elimination of malaria due to *Plasmodium vivax* in central part of the People's Republic of China: analysis and prediction based on modeling. *Geospat Health* 9: 169–177.
28. Zhou SS, Zhang SS, Zhang L, Rietveld AE, Ramsay AR, Zachariah R, Bissell K, Van den Bergh R, Xia ZG, Zhou XN, Cibulskis RE, 2015. China's 1-3-7 surveillance and response strategy for malaria elimination: is case reporting, investigation and foci response happening according to plan? *Infect Dis Poverty* 4: 55.
29. Hui FM1, Xu B, Chen ZW, Cheng X, Liang L, Huang HB, Fang LQ, Yang H, Zhou HN, Yang HL, Zhou XN, Cao WC, Gong P, 2009. Spatio-temporal distribution of malaria in Yunnan Province, China. *Am J Trop Med Hyg* 81: 503–509.
30. Zhang L, Feng J, Xia ZG, 2014. Malaria situation in the People's Republic of China in 2013. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi* 32: 407–413.
31. Huang JX, Xia ZG, Zhou SS, Pu XJ, Hu MG, Huang DC, Ren ZP, Zhang SS, Yang MN, Wang DQ, Wang JF, 2015. Spatio-temporal analysis of malaria vectors in national malaria surveillance sites in China. *Parasit Vectors* 8: 146.
32. Xia J, Cai S, Zhang H, Lin W, Fan Y, Qiu J, Sun L, Chang B, Zhang Z, Nie S, 2015. Spatial, temporal, and spatiotemporal analysis of malaria in Hubei Province, China from 2004–2011. *Malar J* 14: 145.
33. Li JH, Lin KM, Wei SJ, Wei HY, Li J, Yang YC, 2015. Effect of malaria surveillance and control of Guangxi Zhuang autonomous region in 2013. *Zhongguo Xue Xi Chong Bing Fang Zhi Za Zhi* 27: 41–44.
34. Dommar CJ, Lowe R, Robinson M, Rodo X, 2014. An agent-based model driven by tropical rainfall to understand the spatio-temporal heterogeneity of a chikungunya outbreak. *Acta Trop* 129: 61–73.
35. Hsiang MS, Gosling RD, 2015. Striding toward malaria elimination in China. *Am J Trop Med Hyg* 93: 203–204.
36. Yin JH, Yan H, Huang F, Li M, Xiao HH, Zhou SS, Xia ZG, 2015. Establishing a China malaria diagnosis reference laboratory network for malaria elimination. *Malar J* 14: 40.
37. Lu G, Zhou S, Horstick O, Wang X, Liu Y, Muller O, 2014. Malaria outbreaks in China (1990–2013): a systematic review. *Malar J* 13: 269.
38. Liu H, Yang HL, Tang LH, Li XL, Huang F, Wang JZ, Li CF, Wang HY, Nie RH, Guo XR, Lin YX, Li M, Wang J, Xu JW, 2015. In vivo monitoring of dihydroartemisinin-piperaquine sensitivity in *Plasmodium falciparum* along the China-Myanmar border of Yunnan Province, China from 2007 to 2013. *Malar J* 14: 47.
39. Liu H, Yang HL, Tang LH, Li XL, Huang F, Wang JZ, Li CF, Wang HY, Nie RH, Guo XR, Lin YX, Li M, Xu JW, 2014. Monitoring *Plasmodium vivax* chloroquine sensitivity along China-Myanmar border of Yunnan Province, China during 2008–2013. *Malar J* 13: 364.
40. Xu JW, Liao YM, Liu H, Nie RH, Havumaki J, 2014. Use of bed nets and factors that influence bed net use among Jinuo Ethnic Minority in southern China. *PLoS One* 9: e103780.
41. Kenea O, Balkew M, Gebre-Michael T, 2011. Environmental factors associated with larval habitats of anopheline mosquitoes (Diptera: Culicidae) in irrigation and major drainage areas in the middle course of the Rift Valley, central Ethiopia. *J Vector Borne Dis* 48: 85–92.