Spatial Patterns of Malaria Reported Deaths in Yunnan Province, China

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Abstract. Malaria has been a heavy social and health burden in the remote and poor areas in southern China. Analyses of malaria epidemic patterns can uncover important features of malaria transmission. This study identified spatial clusters, seasonal patterns, and geographic variations of malaria deaths at a county level in Yunnan, China, during 1991–2010. A discrete Poisson model was used to identify purely spatial clusters of malaria deaths. Logistic regression analysis was performed to detect changes in geographic patterns. The results show that malaria mortality had declined in Yunnan over the study period and the most likely spatial clusters (relative risk [RR] = 23.03–32.06, $P < 0.001$) of malaria deaths were identified in western Yunnan along the China–Myanmar border. The highest risk of malaria deaths occurred in autumn (RR = 58.91, $P < 0.001$) and summer (RR = 31.91, $P < 0.001$). The results suggested that the geographic distribution of malaria deaths was significantly changed with longitude, which indicated there was decreased mortality of malaria in eastern areas over the last two decades, although there was no significant change in latitude during the same period. Public health interventions should target populations in western Yunnan along border areas, especially focusing on floating populations crossing international borders.

INTRODUCTION

Malaria is associated with morbidity, mortality, and economic burden and is responsible for the deaths of nearly 800,000 people each year globally.[1] Malaria burden is a significant public health threat in both highly endemic countries and those with moderate and low transmission.[2] In China, malaria remains a major public health problem,[3,4] especially in the southern part of the mainland.[5] Yunnan Province is located in southern China and suffers from one of the highest malaria morbidity and mortality in China.[4] Malaria outbreaks often occur in Yunnan Province,[6] with more than 80% of the population in this province at risk of malaria infection.[7] Malaria historical records showed that Yunnan Province had the highest number of malaria deaths across the country, and its accumulative malaria deaths account for more than two-thirds of those in the whole of China.[6] A better understanding of the spatial pattern of malaria deaths would help to identify high risk locations and may better support malaria control interventions and resource allocation in this endemic region, in particular by providing a baseline spatial distribution of malaria deaths for the national malaria elimination program (NMEP) in China between 2010 and 2020.

The spatial pattern of malaria is complex because the spatial distribution of the disease is determined by a variety of social, biological, environmental, and cultural factors.[8–11] Understanding the spatial distribution of malaria risk can uncover important information about disease transmission.[12] Geographic information systems (GIS) are a supportive tool to display the spatial variation of disease,[13] to define the distribution,[14,15] seasonality,[16,17] and mortality,[18] and to identify high risk locations of malaria transmission.[19–21] Recently, the spatial scan statistic method has been increasingly used to test whether any clusters can be detected or if the point process is purely randomly distributed.[22] This scan statistic approach has been widely applied in identifying clustering regions and periods in vector-borne diseases like West Nile virus,[23] schistosomiasis,[24] dengue fever,[25] Barmah Forest virus,[26] and malaria.[5,14,27,28] However, little is known about the spatial pattern of malaria deaths. This study investigated the spatial distribution of reported malaria deaths in Yunnan, China, using GIS integrated with spatial analysis approaches. The purposes of this study are three-fold: 1) to determine if malaria deaths were clustered at a county level, 2) to visualize the geographic distribution and seasonal patterns of malaria risk and identify the most likely clusters, and 3) to examine whether the spatial pattern of malaria deaths had changed in Yunnan Province over the last two decades (1991–2010).

METHODS

Study area. Yunnan Province borders Myanmar in the west and Laos and Vietnam in the south with a 4,060 km border (Figure 1). It covers an area of 394,000 km^2 and has a population of 45.9 million as measured in the 2010 census. The province includes 16 prefectures, 128 counties, and over 1,500 townships. Yunnan receives ~1,100 mm of annual rainfall, which occurs mostly between May and October. The seasonal mean temperatures vary from 10 to 15°C, and day temperatures range from 12 to 20°C. The elevation is highly variable, from < 100 m (Hekou county) to over 6,000 m (Deqin county). The complex geographic, ecological, and climatic conditions provide multiple favorable mosquito habitats. Five confirmed anopheles species (*Anopheles minimus*, *Anopheles sinensis*, *Anopheles anthropophagus*, *Anopheles kunmingensis*, and *Anopheles jeyporiensis*) exist and are widely distributed throughout Yunnan Province.[29,30]

Data collection. Malaria is a notifiable infectious disease in China, and cases are identified according to the unified diagnostic criteria issued by the Chinese Ministry of Health. The case of malaria is confirmed by microscope and/or rapid diagnostic test. Patients who are diagnosed with malaria and subsequently died of this disease are recorded as a malaria death.[31] Data on malaria deaths were obtained from the Yunnan

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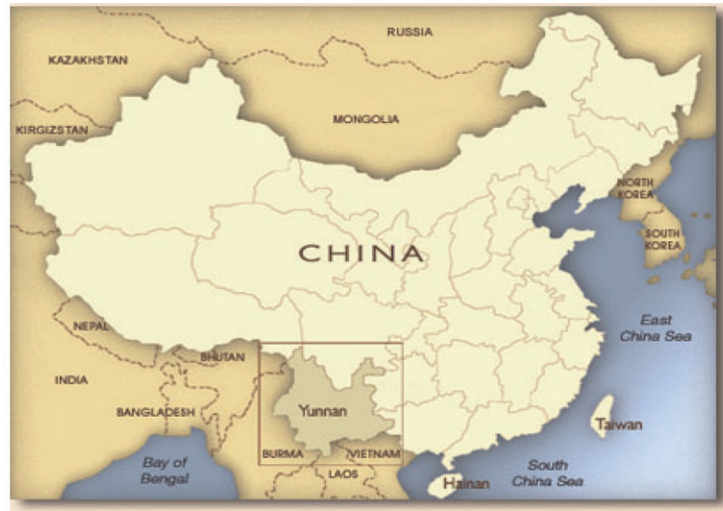
http://kangyunfriends.org/projects/Pingbian/Yunnan_map.jpg

FIGURE 1. Location of Yunnan Province in China.

Center for Disease Control and Prevention (Yunnan CDC), where routine surveillance is undertaken for all notifiable infectious diseases assessed by the National Notifiable Diseases Surveillance System (NNDSS). The malaria deaths were classified according to the International Classification of Diseases, ninth version (ICD-9) (ICD-9: 084). In NNDSS, malaria information includes cases and deaths, and has been accessible on the NNDSS website since 2005. This surveillance system covers health facilities at a township level. Surveillance data are regularly reported to China CDC classified by county, prefectural, provincial, and national level. This study included 128 counties. Demographic data at the county level were obtained from the annual book of the Yunnan Bureau of Statistics. Although malaria deaths observed in Yunnan including *Plasmodium vivax*

and *Plasmodium falciparum*, the dataset we obtained did not separate different parasites. In the current study, malaria deaths were assembled by season (spring, summer, autumn, and winter), between January 2001 and December 2010, and by the year between 1991 and 2010. Malaria mortality is expressed as the number of deaths caused by malaria per 100,000 population per year for each county between 1991 and 2010.

Data management and geocoding. Data on malaria deaths in each county were coded using the county's name and code, and linked to the corresponding polygon on a digital boundary map of Yunnan Province in ArcGIS 9.3 (ESRI Inc., Redlands, CA). The dataset included 528 deaths over a 20-year period. Among these, 506 (96%) deaths were successfully geocoded. The remaining 22 (4%) deaths could not be geocoded, mainly because of the changes in the counties' administrative boundaries. For example, Wanding county was combined with Ruili county in 1999; and Lijiang county was divided into Gucheng county and Yulong county in 2004. We kept the old administrative boundaries of the county map for the dataset by splitting the combined county and/or combining the divided counties. The data on disease and population were geocoded and matched with the boundary map over a 20-year period (1991–2010). The latitude and longitude of the capital location of each county were considered using a geographic coordinates file. All records were assigned to county capital coordinates. Case files, population files, and coordinate files were generated in text format as source files for spatial analysis. The results of the SaTScan software (version 9.1, Martin Kulldorff, Boston, MA) were linked to the boundary map using county codes for mapping purposes in the ArcGIS software.

Data analysis. We divided the dataset into four groups, each consisting of a 5-year period for ease of analysis. Period 1: 1991–1995; Period 2: 1996–2000; Period 3: 2001–2005; and Period 4: 2006–2010. For the purpose of seasonal analysis, we grouped the dataset into spring (March–May), summer (June–August), autumn (September–November), and winter (December–February) for the period 2001–2010.

Spatial cluster analysis. Spatial cluster analysis was performed to detect spatial clusters or high risk locations for malaria for four periods (1991–2010) and four seasons (2001–2010) using SaTScan software. The "purely spatial analysis" was applied to test whether malaria mortality was distributed randomly over space, and if not, to evaluate the statistical significance of malaria clusters. A likelihood ratio test was calculated to determine clusters by testing whether there was an equal risk within and outside a particular area. The statistical significance of clusters was explored by means of 9,999 Monte Carlo replications with P values < 0.01. In the data analysis, a discrete Poisson model was used, as it was assumed that the number of malaria deaths in each county was Poisson distributed. Cluster analysis was performed with the maximum spatial cluster size of 50% and 25% of the population at risk in the spatial window, respectively. The maximum spatial cluster size of 50% of the population at risk was applied to avoid pre-selection bias as described in the SaTScan User Guide (version 9.0). The outcomes of cluster relative risk (RR) for purely spatial cluster analysis were input and linked in the ArcGIS software for visualization.

Dynamic dispersion of malaria mortality. To identify whether the pattern of malaria mortality had changed and whether these changes varied with latitude and longitude of county in the four periods (1991–2010), logistic regression models were applied with the dichotomous variable defined as whether an increase of malaria deaths occurred in each county between these four periods. A county with an increase of malaria deaths was assigned to "1" and a decrease (or no change) of deaths assigned to "0" between any two time periods. The latitude and longitude of the counties' capitals were included as predictor variables. Odds ratios (ORs) were calculated, representing the change in odds of malaria mortality between two periods caused by a 1 unit increase in x (longitude or latitude). That is[32]

$$\mathrm{OR} = e^{\beta} = \frac{\mathrm{odds}(x+1)}{\mathrm{odds}(x)} \quad \left(\mathrm{odds}(x) = \frac{\pi(x)}{1-\pi(x)}\right),$$

$$\pi = \frac{e^{\alpha + \beta_1 x_{longitude} + \beta_2 x_{latitude}}}{1 + e^{\alpha + \beta_1 x_{longitude} + \beta_2 x_{latitude}}}.$$

1) If OR = 1, the odds and probability are the same at all latitudes and longitudes, which means no changes in malaria mortality between two periods by increasing longitude or latitude. 2) If OR > 1, the odds and probability increase as longitude or latitude increases, which means increasing of malaria mortality between two periods by increasing longitude or latitude. 3) If OR < 1, the odds and probability decrease as longitude or latitude increases, which means decreasing of malaria mortality between two periods by increasing longitude or latitude. All these analyses were conducted using SPSS (PASW Statistics, version 18, Chicago, IL).

RESULTS

Descriptive analysis. Five hundred and six (506) malaria deaths were used in the analysis over the 20-year period (1991–2010) in Yunnan Province. Table 1 shows the summary statistics for malaria deaths at the county level for the four periods. Malaria deaths decreased from 157 in the period of 1991–1995 to 49 in 2006–2010. The highest number of deaths was reported from the same location—Yingjiang County (in western Yunnan) in all four periods. Figure 2 shows the temporal pattern of annual malaria mortality and incidence rates. There was a clear downward trend for both malaria mortality and incidence rates in Yunnan between 1991 and 2010. The highest malaria mortality was 0.12/100,000 people in 1999, and the lowest was 0.01/100,000 people in 2009.

Figure 3 indicates the seasonal distribution of malaria deaths in two periods (2001–2005 and 2006–2010) with a peak in summer (March to May). There was a clear declining trend over the period of 2001–2010.

Figure 4 shows temporal changes of geographic distribution of malaria mortality in Yunnan Province in the four periods. The temporal pattern indicates the highest malaria mortality (above 1/100,000) occurred in four counties and did not

TABLE 1

Descriptive statistics of malaria deaths at a county level in Yunnan Province ($N = 506$)*

Period	Total deaths	Mean	SD	Minimum	Maximum
1991–1995	157	0.25	0.974	0	12
1996–2000	146	0.23	1.049	0	18
2001–2005	154	0.25	0.818	0	5
2006–2010	49	0.08	0.407	0	6

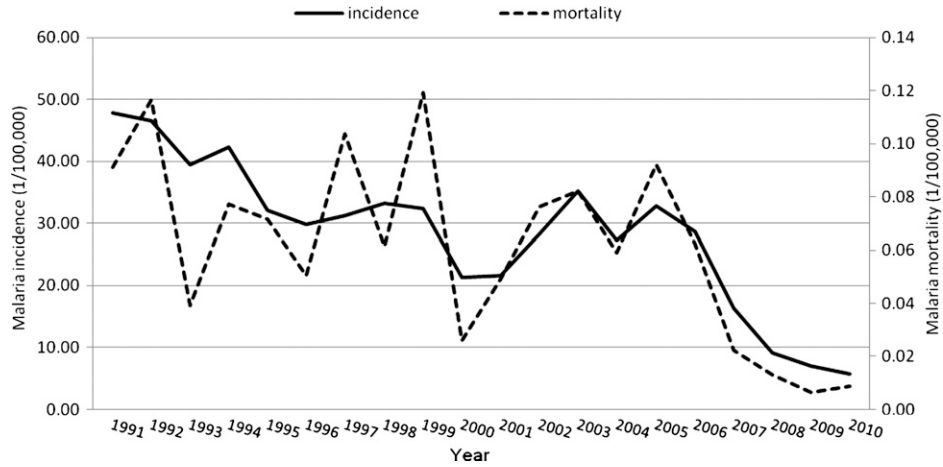*Mean, SD; Minimum and Maximum are for per year and per county.

FIGURE 2. The epidemic patterns of annual malaria mortality and incidences in Yunnan, 1991–2010.

change in the western (3 counties) and north-western (1 county) parts of Yunnan for period 1, period 2, and period 3, respectively; however, in period 4 mortality was < 1/100,000 in all counties. Malaria mortality ranged from 0.1 to 1.0/100,000 in 25 counties in period 1 and continued to decrease to 20, 18, and then 13 counties in the subsequent three periods. Malaria mortality under 0.1/100,000 varied between 8 and 15 counties

within the 20-year period. There were no malaria deaths in the majority of the counties over the last two decades.

Purely spatial analysis. SaTScan statistics identified purely spatial clusters of malaria deaths. Figure 5 shows the statistically significant spatial clusters and geographic distribution of the raw dot density of malaria deaths in the four periods. These four maps reveal that overlay regions of both spatial
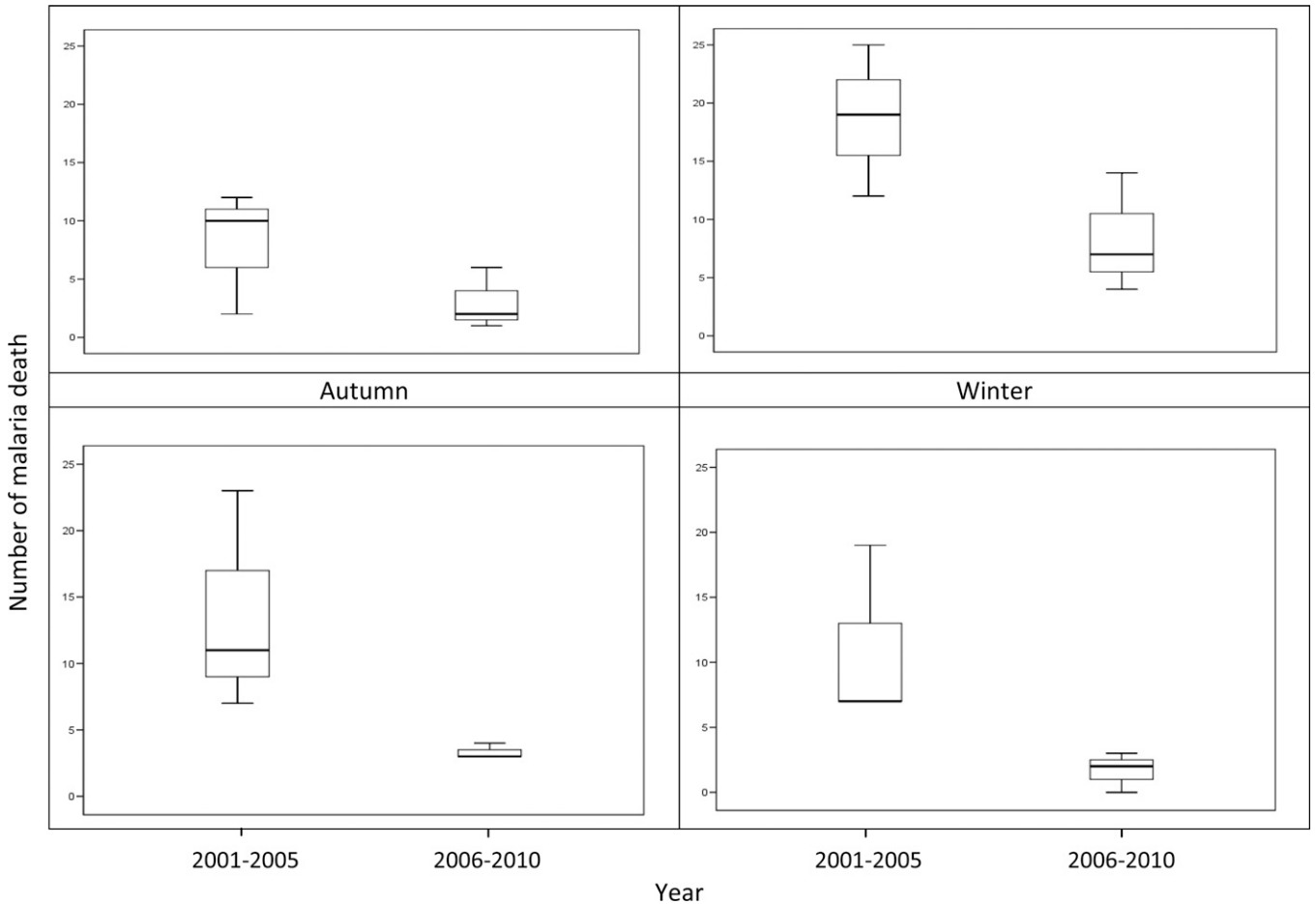

FIGURE 3. Boxplots of the seasonal distribution of malaria deaths during 2001–2010, Yunnan, China The boxplot displays the values of the 25th, 50th, and 75th percentiles.
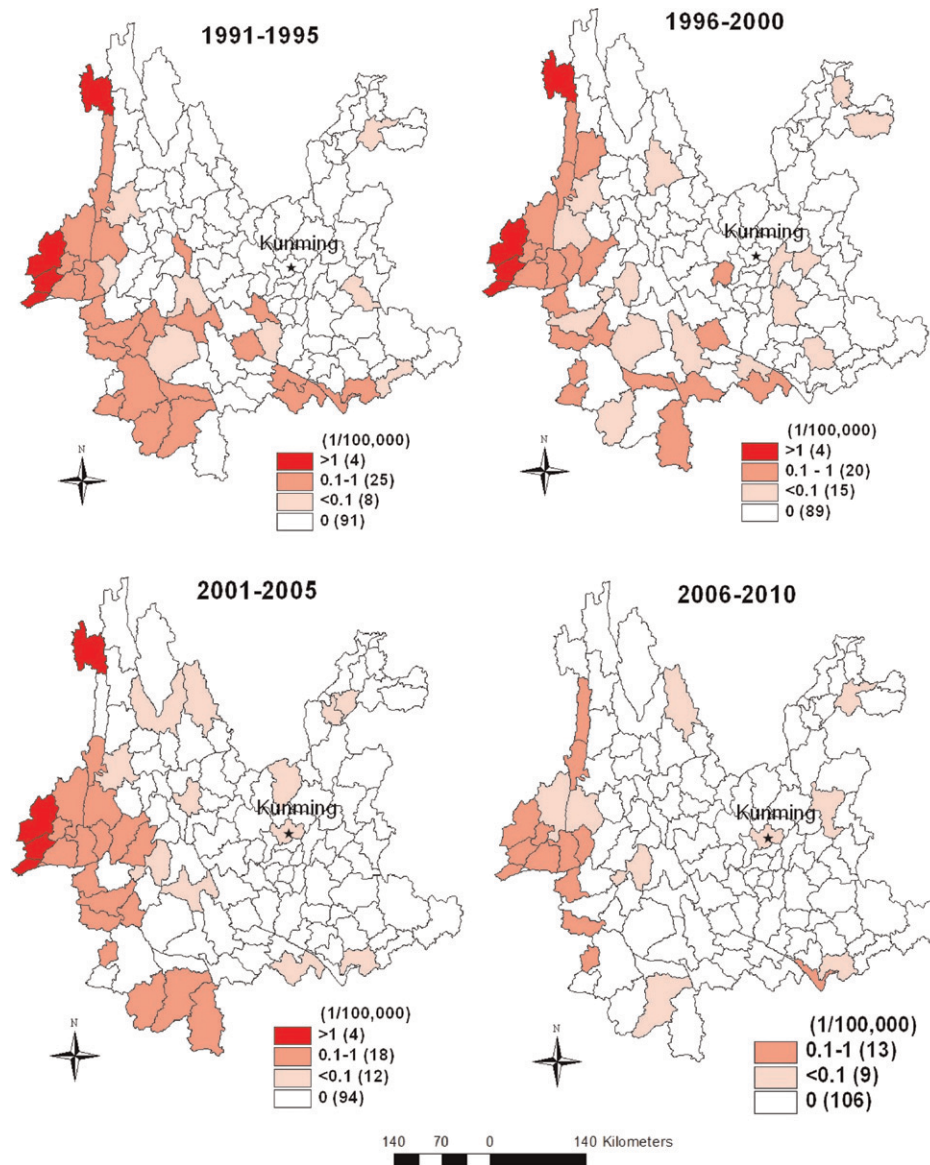
FIGURE 4.   Choropleth maps showing changes of malaria mortality in Yunnan Province in four periods. (The number in the parentheses denotes how many counties in each category. Red color: malaria mortality above 1/100,000; Light red: malaria mortality ranged from 0.1 to 1/100,000; Pink: malaria mortality under 0.1/100,000; White: counties without malaria deaths.)

clusters and dot density are consistent. A most likely cluster was identified in the western part of Yunnan in the four periods. A secondary cluster was identified only significantly in period 1 (1991–1995).

Table 2 shows the results of purely spatial analysis detected in Yunnan in the four periods (1991–2010). The results for the total population, radius of cluster, number of counties, and malaria deaths in cluster, log likelihood ratio, and relative risk were very similar using either 50% or 25% of the population at risk as the maximum cluster size. The results for the maximum spatial cluster size of 50% of the population were applied and reported in Table 2. In period 1, a most likely cluster encompassed 8 counties (RR = 24.41, $P < 0.001$) and a secondary cluster included 22 counties (RR = 2.33, $P < 0.01$), which were observed in the western and southern parts of Yunnan, respectively. In a total of 157 deaths, 127 were detected in cluster regions. For the other three periods, a most

likely cluster was observed (RR = 30.83, $P < 0.001$ for period 2; RR = 32.06, $P < 0.001$ for period 3; RR = 23.03, $P < 0.001$ for period 4) with death numbers of 93, 126, and 32 in the cluster region for period 2, 3, and 4, respectively.

Table 3 displays the spatial clusters of malaria deaths by season between 2001 and 2010. This table indicates that autumn (June to August) had the highest relative risk (RR = 58.91, $P < 0.001$), followed by summer (RR = 31.91, $P < 0.001$). Spring (March to May) and winter (December to February), had similar relative risks to each other (RR = 24.07, $P < 0.001$). Seasonal clustering counties ranged from 8 to 10 and the radius of the cluster is < 100 km. For all seasons, the geographic location of the most likely cluster is identified in the western part of Yunnan along the China–Myanmar border (Figure 6).

Changes in the spatial-temporal pattern of malaria deaths. Table 4 indicates that changes of malaria mortality for each county were significantly associated with longitude between
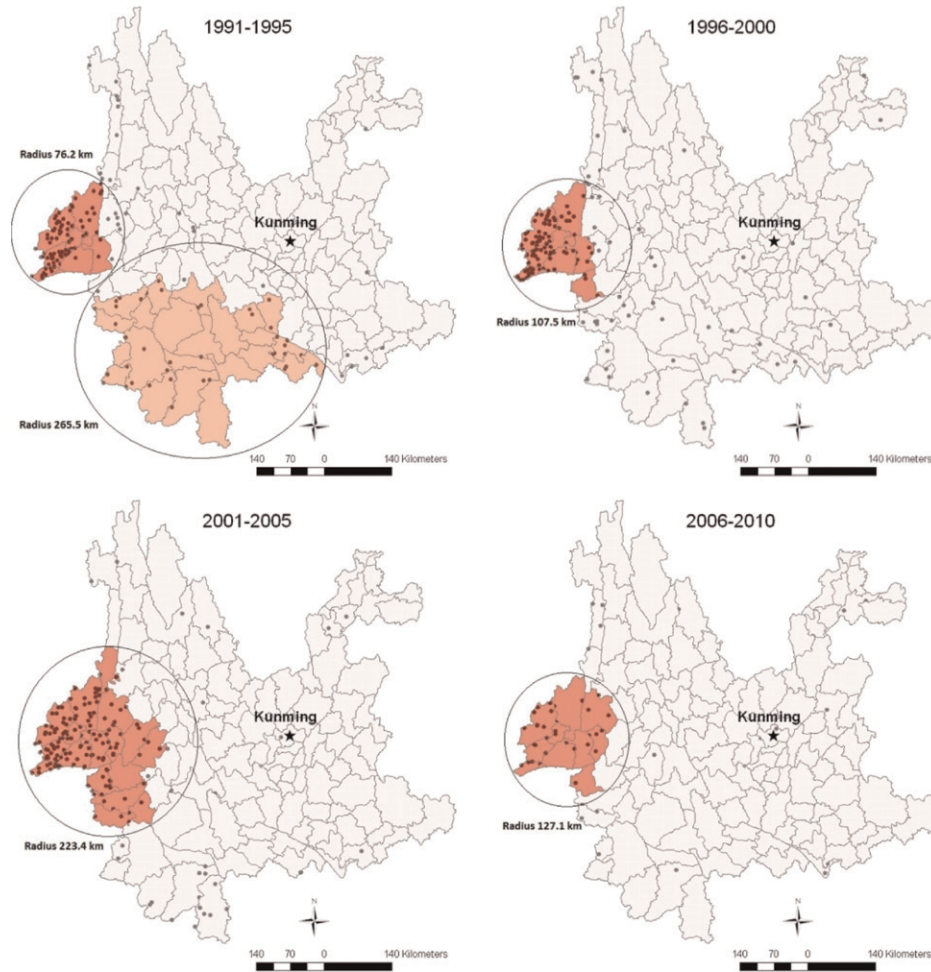
FIGURE 5. Purely spatial clusters and raw dot density map of malaria deaths in Yunnan, 1991–2010 (1 dot = 1 malaria death). (Red color: primary cluster of malaria deaths; Pink: secondary cluster; Light yellow: counties without malaria deaths cluster.)

the periods 1991–1995 and 1996–2000 (OR = 0.743; 95% confidence interval [CI] = 0.585–0.943), the periods 1991–1995 and 2001–2005 (OR = 0.617; 95% CI = 0.464–0.820), and the periods 1996–2000 and 2001–2005 (OR = 0.639; 95% CI = 0.489–0.833). These results suggested that the geographic distribution of malaria deaths was significantly reduced by longitude, which indicated a decreasing trend in mortality in an easterly direction across the province for the last two decades. However, no significant spatial changes by latitude were observed in the study, which indicates that the geographic range of malaria transmission may have not changed significantly with latitude.

Seasonal clusters of malaria mortality were identified in 11 counties in western Yunnan (Figure 6). The temporal malaria mortality of these 11 high risk counties and Yunnan province

ranged from 0.06–1.23/100,000 to 0.01–0.12/100,000 during 1991–2010, respectively (Figure 7). Malaria mortality of 11 cluster counties was 5–12 times higher than that of Yunnan province over a 20-year period.

DISCUSSION

Malaria mortality has continued to decline over the past two decades in Yunnan, China, with the majority of malaria deaths concentrated in western Yunnan. Of importance, high risk locations were identified in the western part of Yunnan, which shares an international border of 1,997 km with Myanmar. The findings imply that malaria remains a serious health threat in this "hotspot" region. We also found that the highest risk occurred in autumn and summer. This temporal pattern

TABLE 2
Spatial clusters of malaria deaths in Yunnan Province, China, 2001–2010

Year	SaTScan statistics	Population	Radius of cluster (Km)	No. of counties in cluster	No. of cluster malaria deaths	Relative risk	P value
1991–1995	Most likely cluster	1,932,528	76.2	8	87	24.41	< 0.001
	Secondary cluster	5,099,408	265.5	22	40	2.33	< 0.01
1996–2000	Most likely cluster	2,173,340	107.5	9	93	30.83	< 0.001
2001–2005	Most likely cluster	5,487,146	223.4	18	126	32.06	< 0.001
2006–2010	Most likely cluster	3,641,948	127.1	11	32	23.03	< 0.001

TABLE 3
Most likely spatial clusters of malaria deaths by season in Yunnan Province, China, 2001–2010

Seasons	Population	Radius of cluster (Km)	No. of counties in cluster	No. of cluster malaria deaths	Relative risk	P value
Spring	3,419,395	98.87	10	23	24.07	< 0.001
Summer	2,223,180	76.24	8	45	31.91	< 0.001
Autumn	1,766,337	94.88	8	42	58.91	< 0.001
Winter	3,419,395	98.87	10	23	24.07	< 0.001

could be related to the rainy season between May and October in Yunnan Province.[33,34] Focused interventions in these months should be more effective in the prevention and control of malaria in Yunnan.

The GIS-based spatial statistical techniques have not been previously applied to analyze high risk clustering in malaria deaths in China. As an epidemic area, Yunnan has a greater number of malaria deaths than any other province in China. In 1995 and 1998, all malaria deaths in China were reported from Yunnan. The results of this study may have several important implications for malaria control policy in China.

First, the primary spatial cluster identified in this study is concentrated in the China–Myanmar border area, which has the longest border (1997 km), the highest annual parasite incidence rate (API, > 2.3%), and the highest proportion of

P. falciparum reported in positive blood smears (33%)[29] compared with the China–Vietnam and China–Laos border areas. Furthermore, all primary spatial clusters examined in the four periods had no significant geographic changes, which suggest that the primary cluster existed in this border area for two decades. Targeted public health interventions should therefore be focused on this area. It is estimated that there is a floating population of more than 10 million in the border area of Yunnan, and over 6.5 million of them (4 million entries by foreigners and 2.5 million re-entries by Chinese nationals) crossed the international border between China–Myanmar, China–Vietnam, and China–Laos each year and this number keeps growing.[7,34] The migration of people (e.g., refugees and returning workers) from Myanmar has led to a significant number of imported malaria cases and deaths, and
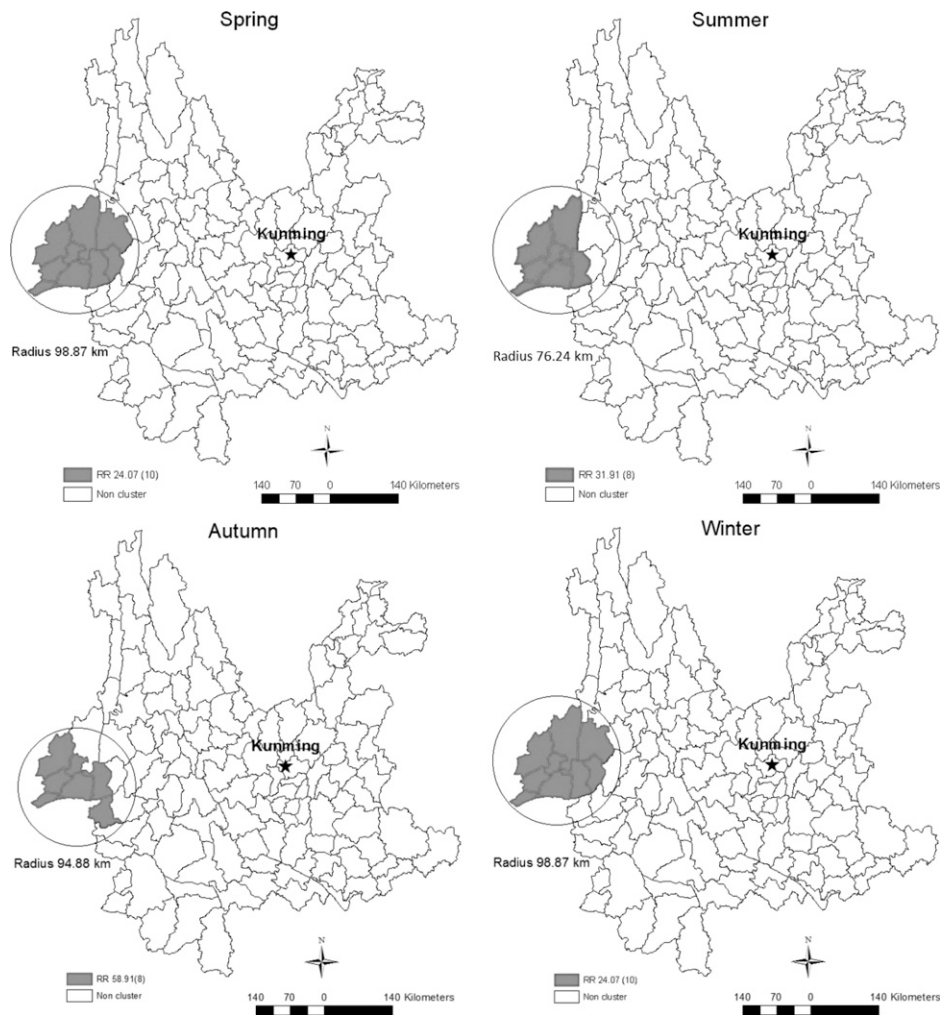

FIGURE 6.   Seasonal clusters of malaria mortality in Yunnan, 2001–2010.

TABLE 4
Changes of malaria mortality for a 1° increase in longitude and latitude, Yunnan Province, China, 1991–2010

Time intervals	Longitude			Latitude		
	OR	95% CI	P value	OR	95% CI	P value
Period 1–Period 2	0.743	0.585–0.943	0.015*	0.879	0.649–1.192	0.407
Period 1–Period 3	0.617	0.464–0.820	0.001**	0.861	0.613–1.207	0.385
Period 1–Period 4	0.869	0.603–1.251	0.449	1.061	0.667–1.689	0.803
Period 2–Period 3	0.639	0.489–0.833	0.001**	0.799	0.576–1.108	0.178
Period 2–Period 4	1.023	0.736–1.424	0.891	1.017	0.674–1.536	0.935
Period 3–Period 4	1.309	0.788–2.175	0.299	1.229	0.719–2.100	0.451

OR = odds ratio; CI = confidence interval; *$P < 0.05$; **$P < 0.01$; Separate odds ratios reported for different intervals defined by the four periods. Period 1 = 1991–1995; Period 2 = 1996–2000; Period 3 = 2001–2005; Period 4 = 2006–2010.

resulted in frequent malaria outbreaks in Yunnan.[7,29] It also has an implication that the identified cluster area could be the dominating source of *P. falciparum* imported into other provinces in mainland China. For example, in 2005 the reported number of *P. falciparum* in Yunnan accounted for 84% of the total *P. falciparum* cases in China (3,497 of 4,146) and 69% (2,413 of 3,497) of these were imported from neighboring countries along the Yunnan border.[35] In 2009, among 23 provinces reporting malaria cases in mainland China, 21 of them reported that all malaria deaths were identified as imported cases.[36] The number of imported *P. falciparum* cases in 2010 increased by over 100% in some inland provinces, such as Jiangsu, Anhui, and Sichuan.[37]

Both *P. falciparum* and *P. vivax* are prevalent in Yunnan. There was an average decrease in malaria incidence of 4.3% for *P. falciparum* and 5.2% for *P. vivax* per year during 1991–2006 in this province.[3,4] *Plasmodium vivax* is the dominant species in Yunnan.[35] The incidences of *P. vivax* cases were 3–5 times higher than those of *P. falciparum* between 1995 and 2005.[3,4] A further examination of the cluster pattern of malaria deaths caused by different parasites might provide more detailed information to support policy development for malaria intervention in Yunnan province.

Second, the results reveal that the total number of malaria deaths has been gradually decreasing, but there have been no large changes in the locations of the primary cluster over the four periods (RR: 23.02–32.06, $P < 0.001$) (Table 2). This is despite the fact that increased activity through the national

program for malaria control has taken place in this region for decades. The high antimalarial drug resistance in western Yunnan could be one of the key reasons for this persistent cluster. The majority of the population with chloroquine resistance of *P. falciparum* lives in western Yunnan bordering Myanmar. According to 20 years' (1982–2003) of monitoring data, the most chloroquine-resistant *P. falciparum* is observed in Ruili, western Yunnan, which had the highest parasite resistance rate to chloroquine of 100%, 96%, and 83% in the 1982, 1993, and 2003 surveys, respectively. Interestingly, the overall rate of resistant clinical cases decreased from 97% between 1981 and 1983 to 40% between 2005 and 2006.[38] This decline is consistent with the decrease of malaria deaths in Yunnan. In contrast, an association between the emergence of chloroquine resistance and increases in malaria mortality has been observed in Senegal.[39] The use of poorly effective drugs is a major factor likely to result in an increase of malaria deaths.[40] The use of effective antimalarial drugs will be important to decrease clinical cases and to prevent more deaths in Yunnan. Socio-economic factors like economic status, living conditions, and agriculture practices could be related to the persistent cluster in western Yunnan over the past two decades.[4,41] The cross-border migrations from Myanmar and effects of seasonal rains on malaria incidence could also contribute to the spatial patterns observed in this region.[7,29]

Third, Yunnan province is a high malaria-endemic region located south of the 25th parallel north. Malaria endemicity
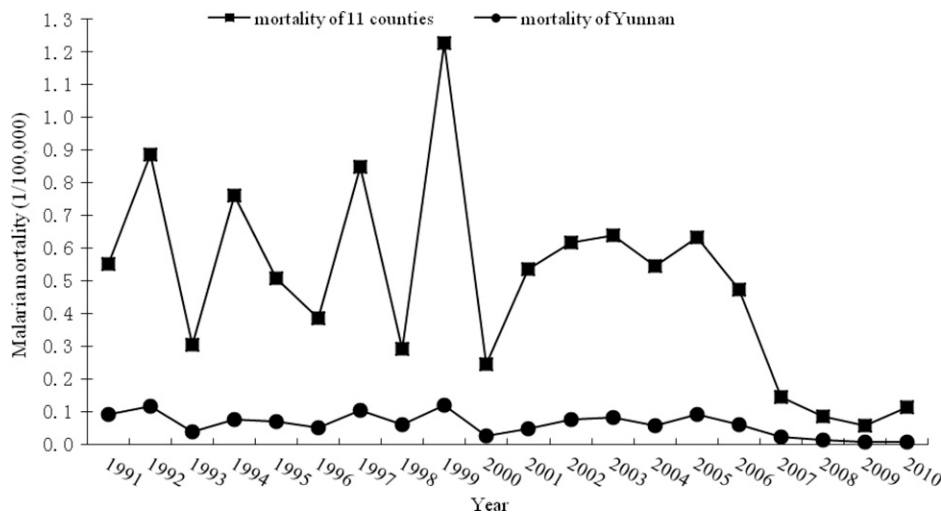

FIGURE 7. Mortality of Yunnan province and 11 cluster counties of western Yunnan.

in this region is historically stable and remains at a high level.[42] Our results suggest that the magnitude of malaria risk and intensity is concentrated in western Yunnan, where 25 distinct ethnic minorities live. People living in this remote, forested, and hilly area generally have a low income and education level, poor knowledge of malaria transmission, and personal protection, and poor access to health facilities. Additionally, plantation agriculture, forest work, and other outdoor activities are common in the border area.[41] Intensive interventions of malaria prevention and control should therefore be implemented in this vulnerable region.

In this study, we identified spatial clusters, seasonal patterns, and geographic variations of malaria deaths in Yunnan Province. The epidemics of *P. vivax* and *P. falciparum* malaria could be different. We did not separate analyses of deaths on parasites caused by a lack of detailed death information on *P. vivax* and *P. falciparum* in this study. Further research should explore the difference in deaths caused by *P. vivax* and *P. falciparum,* and assess the major determinants of malaria risk in this endemic region. In addition, there is a need to evaluate the effectiveness of current malaria elimination program strategies in Yunnan, which launched in 2010.[37]

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