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SPATIO-TEMPORAL DISTRIBUTION OF *PLASMODIUM FALCIPARUM* AND *P. VIVAX* MALARIA IN THAILAND

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Abstract. Malaria incidence data at the district level from 1997 to 2002 and total malaria case data from 1965 to 2002 in Thailand were analyzed to determine the spatial and temporal dynamics of *Plasmodium falciparum* and *P. vivax* malaria incidence. Over the 37-year period, there was a 35-fold reduction in the incidence rates of *P. falciparum* malaria (11.86% in 1965 versus 0.34% in 2002) and a 7-fold reduction in *P. vivax* malaria (2.89% in 1965 versus 0.40% in 2002). The incidence ratio of *P. falciparum* to *P. vivax* malaria was reduced from 4.1 to 0.8 during this period. Malaria incidence rate exhibited the most rapid reduction between 1975 and 1985, coinciding with the introduction of a combination of antifolate drugs (sulfadoxine-pyrimethamine). The distribution maps of *P. falciparum* and *P. vivax* malaria incidence rates indicated a high spatial heterogeneity. The Thailand-Myanmar and Thailand-Cambodia border areas, where migration of foreign workers was pronounced, had the highest incidence rates for *P. falciparum*, *P. vivax*, and mixed-species infections. Transition probability analysis based on the malaria incidence rate among Thai residents indicated that there was an overall trend of decrease in the number of malaria cases and the number of high incidence districts between 1997 and 2002. High spatial variation in malaria incidence and local human migration patterns suggest that malaria control measures need to be adjusted according to local environmental and demographic settings.

INTRODUCTION

Malaria is a major public health problem in Thailand.[1,2] Annual reported malaria cases in Thailand have continued to decrease over the past two decades and have disappeared from most of the major cities.[2] However, people in rural areas, especially in villages on the Thailand-Myanmar and Thailand-Cambodia borders and forested mountain areas, remain at great risk.[3–6] In these endemic areas, malaria transmission has been considered to have a close association with the forest and movement of the human population.[1,2,7,8] In particular, the seasonal migration of cross-border laborers has been suspected as a leading cause of malaria transmission in these areas.[2,9] However, little is known about spatial patterns and dynamics of malaria in Thailand.

In Thailand, all four species of human malaria occur, but the vast majority of malaria cases are caused by *Plasmodium falciparum* and *P. vivax* infections. Since the appearance of chloroquine (CQ)–resistant *P. falciparum* strains in the 1960s, multidrug-resistant *P. falciparum* has emerged and spread to most areas of this country.[4,10–12] In contrast, drug resistance in *P. vivax* has not been reported in Thailand.[13] Because malaria caused by these two species is treated with different drug regimens, correct diagnosis of malaria species is essential. The existence of different malaria species presents opportunities for mixed-species infections and cross-species interactions, which could affect the outcome of the disease. Previous cross-sectional studies have provided indirect evidence of cross-species interactions. For example, studies on the Pacific island of Vanuatu found that *P. falciparum* malaria was predominant in the long wet season and *P. vivax* malaria in the dry season.[14,15] More direct evidence of cross-species interactions between *P. falciparum* and *P. vivax* was obtained from a well-designed study in a hyperendemic area of Papua New Guinea, where nonindependent and sequential episodes of *P. falciparum* and *P. vivax* malaria appear to be regulated by parasite density.[16] In Thailand, a clinical follow-up study found that *P. vivax* malaria appeared 15–65 days after the treatment of *P. falciparum* malaria, suggesting an effect of inter-species interactions.[17] However, large-scale, cross-sectional analyses of the relationship between the two malaria species have not been performed.

The history of malaria control strongly emphasizes the implementation of integrated approaches. Geographically based monitoring systems and spatial statistics are an important component of the contemporary malaria integrated management system.[18,19] This novel approach requires the development of models that can be used to monitor and predict large-scale spatio-temporal dynamics of malaria. In this study, we analyzed malaria incidence data on different spatial scales and the association between *P. falciparum* and *P. vivax* malaria. Understanding these spatial processes will help develop statistical models of malaria endemicity, which, in turn, will guide our decisions in malaria case management.

MATERIALS AND METHODS

Malaria incidence data. The Malaria Control Program of the Department of Communicable Disease Control, Ministry of Public Health of Thailand, was responsible for monitoring and implementing the malaria control programs and archiving the malaria incidence data. Malaria incidence refers to the number of symptomatic clinical malaria episodes (confirmed by microscopy) occurring in the population within a specific year. This study analyzed countrywide malaria incidence dynamics from 1965 to 2002. District-level malaria incidence data covering 926 districts from 1997 to 2002 were compiled from the records at district malaria clinics and hospitals. The recorded number of foreigner malaria cases at the district level was collected from 1990 to 2001. A more detailed analysis was focused on the Mae Sod District in Tak Province where monthly malaria case data were available for three malaria clinics from 2000 to 2002. These clinics, located in Mae Sod, Mae Kasa, and Mae Kuedlong, are approximately 10 km apart. This dataset was further categorized by the origin of the patients (local residents versus foreigners). For all

clinical data, patient information was excluded. Malaria cases from the two most prevalent parasite species (*P. falciparum* and *P. vivax*) were further divided and used for the subsequent temporal and spatial analyses.

Historical demographic data of Thailand for the period of 1965–2002 were obtained from the National Statistics Office of Thailand and Asia-Pacific Economic Committee.[20,21] Countrywide malaria incidence rate was calculated based on malaria incidence and population data.[22] The district-level population census of 2000 was used to generate the map of malaria incidence rate (number of cases per 100 population) for the year 2000. The population growth rate from 1997 to 2002 at the provincial level was used to estimate district-level population of years other than 2000, assuming that all districts in a given province had the same population growth rate.[20] At the provincial level, the annual total malaria cases were summarized and malaria incidence rates were calculated. Clinic-level malaria incidence rate was calculated using the number of malaria cases at each malaria clinic in Mae Sod district and population data of 2003 at each designated town where the clinic is located.

Spatio-temporal autocorrelation analysis. Spatial analysis is a statistical technique for describing the spatial variations exhibited by the response process of a given phenomenon.[23–25] A spatial autocorrelation statistic is used to quantify the degree of association of a response variable with adjacent points or areas. In this study, we used Moran's *I* statistic to calculate the autocorrelation of malaria incidence rates for sets of points (centroid of each district) that are spatially adjacent in different distance classes.[23] Moran's index *I* is defined as

$$I = \frac{n}{S_0} \frac{\sum_i \sum_{j \neq i} w_{ij}(x_i - \bar{x})(x_j - \bar{x})}{\sum_i (x_i - \bar{x})^2}$$

where x_i is the malaria incidence rate of district *i* of a given year and $\bar{x}$ is the mean incidence rate for all districts, w_{ij} is the weight factor that defines the spatial relationship between district *i* and district *j*, and

$$S_0 = \sum_i \sum_{j \neq i} W_{ij}.$$

The correlogram $I(d)$ quantifies the correlation between locations separated by distance d.[26] This is constructed by setting the weight w_{ij} to 1 if the distance between districts *i* and *j* falls within the tolerance interval $[d - d_0, d + d_0]$, 0 otherwise. Values of Moran's *I* range from 1 to –1, with an expected value of $-1/(n-1)$, where *n* is the number of localities. To calculate the distance matrix, the universal transverse mercator coordinate of each district was generated using the centroid coordinates method of ArcView.[27]

Transition probability analysis. Transition probability models, which describe temporal transition of a variable from one nominal value (or state) to another, have been used to characterize outbreak patterns of infectious diseases from historical data.[28–30] In this study, we used the multistate Markov-chain models to quantify the transition of districts from one class to another.[31] We categorized the malaria incidence rates into five classes: 0 cases (class 1), > 0 to < 0.1 cases (class 2), ≥ 0.1 to < 1 cases (class 3), ≥ 1 to 5 cases (class 4), and > 5 cases (class 5) per 100 population. The transition probability was calculated based on the six-year district-level malaria incidence data (1997–2002).

Statistical analysis. Correlation analysis was used to measure the correlation between incidence rates of *P. falciparum* and *P. vivax* malaria at both the country and district levels.[32] The Student's *t*-test was used to test differences between the national average and province/district-level incidence rates, between clinic-level *P. falciparum* and *P. vivax* malaria incidence rates, and between clinic-level foreign and Thai malaria case numbers. The chi-square test with Yates' correction for continuity was used to test the association between *P. falciparum* and *P. vivax* at the clinic level.

RESULTS

Trend of countrywide malaria incidence. Malaria incidence rates in Thailand showed an overall tendency of decline over the past four decades (Figure 1A). During this period, there was a 35-fold and 7-fold reduction in the incidence rates of *P. falciparum* malaria (11.86% in 1965 versus 0.34% in 2002) and *P. vivax* malaria (2.89% in 1965 versus 0.40% in 2002), respectively. Meanwhile, the incidence ratio of *P. falciparum* malaria to *P. vivax* malaria was reduced from 4.1 to 0.8. The most rapid reduction in malaria incidence rates occurred between 1975 and 1985. We further found a significant correlation between the incidence rates of malaria caused by the two most prevalent parasite species, *P. falciparum* and *P. vivax* ($R = 0.83$, $P < 0.001$). Therefore, despite temporal fluctuations, both species had similar trends of decline, although annual *P. falciparum* malaria case numbers have decreased at a faster pace since the early 1980s. It is interesting to note that the fluctuations of malaria incidence rates, especially *P. falciparum* malaria, were closely associated with the changes of antimalarial drugs imposed by the national drug policies of Thailand (Figure 1).[4,13,33]

In Thailand, increasing proportions of malaria cases were from cross-border migratory foreign workers, and these cases were especially concentrated in districts bordering Cambodia and Myanmar. In the past 12 years, foreigner malaria case numbers remained relatively constant (Figure 1B), suggesting that cross-border seasonal labor may play an important role in malaria transmission in Thailand. Indeed, the provinces with the highest incidence rate border Myanmar and Cambodia. Population movements in these areas, together with the high drug pressure, were considered responsible for the development and spread of mefloquine-resistant *P. falciparum* in western Thailand.[34]

District-level patterns of malaria incidences. At the district level, *P. falciparum* and *P. vivax* malaria exhibited similar spatial patterns and temporal dynamics. Analysis of data from 1997 to 2002 showed a mean correlation of 0.82 (range = 0.77–0.88, $P < 0.01$) between the two species. Correlograms of district malaria incidence rates showed significant spatial autocorrelation up to 100 km (Figure 2), indicating that malaria incidences in Thailand were not randomly distributed, but rather occurred as clusters among adjacent districts. Despite the overall decrease in malaria cases during this period, the extent of spatial clustering, as measured by the spatial autocorrelation, did not change dramatically.

Based on malaria incidence rates, we divided the districts of Thailand into five classes (Figure 3). Class 1 represents malaria-free areas, whereas class 5 is the area with highest inci-

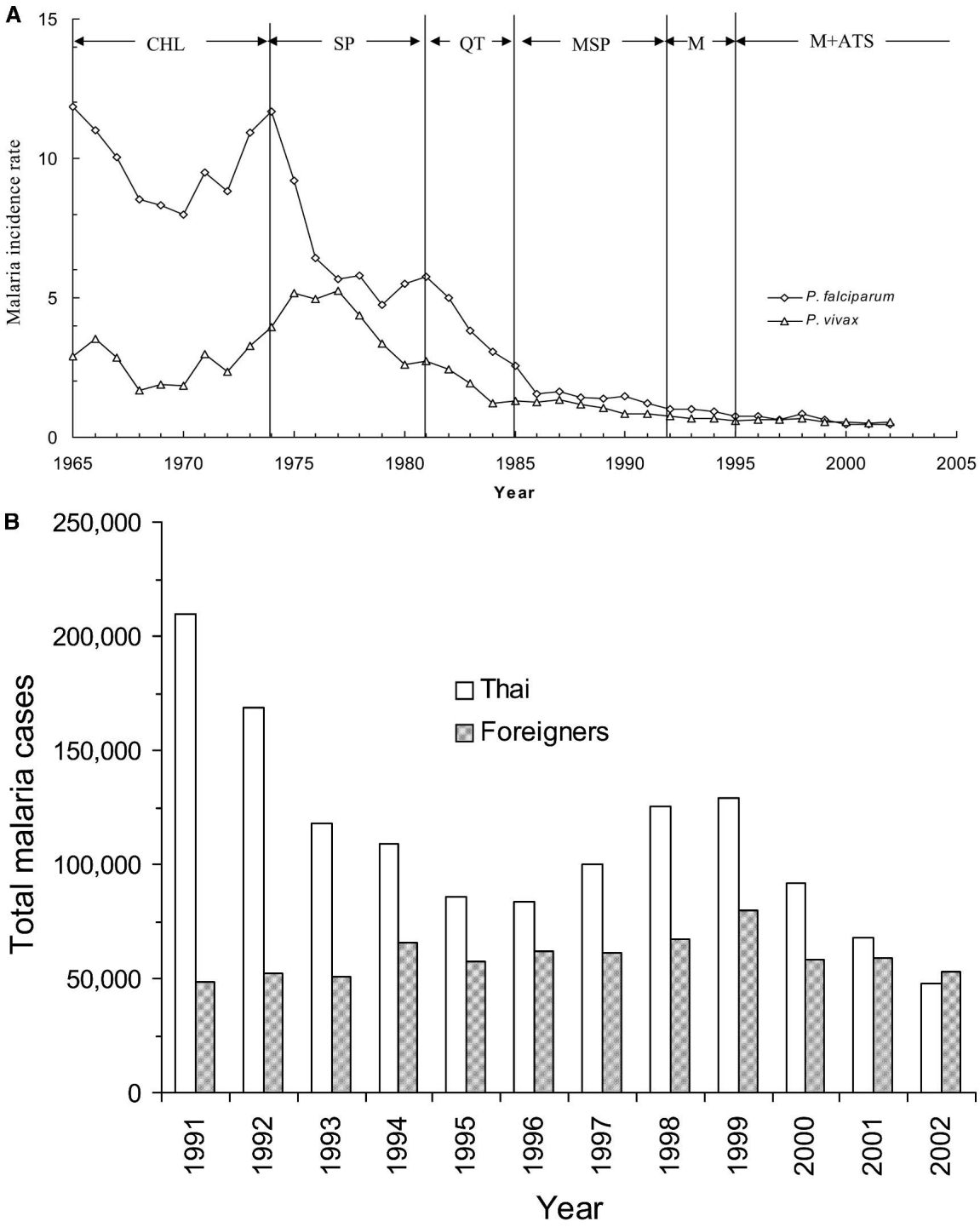

FIGURE 1. **A**, Dynamics of malaria incidence rate (number of cases per 100 population) among Thai residents and antimalarial drug policy changes in Thailand from 1965 to 2002 and **B**, malaria incidence among Thai residents and foreigners diagnosed and treated in Thailand from 1991 to 2002. CHL = chloroquine; SP = sulfadoxine-pyrimethamine; QT = quinine-tetracycline; MSP = mefloquine plus SP; M = mefloquine; ATS = artemisinin.

dence rates. The areas in class 5 are located mainly along the Thailand-Myanmar and Thailand-Cambodia borders (Figure 3). To test the persistence of the malaria status of each class, we performed transition probability analysis. The results demonstrated that class 1 districts had the highest probability (85%) of remaining malaria free, whereas the most endemic districts in class 5 had a 54% probability of remaining in this class (Table 1). As for the probability of malaria incidence rate reduction, districts in class 5 showed a 46% probability of changing to lower classes. In general, the result of the transition matrix reflected an overall trend of decline in malaria incidence rates in terms of the number of total cases and the districts with the highest incidence rates (i.e., in classes 4 and 5) from 1997 to 2002.

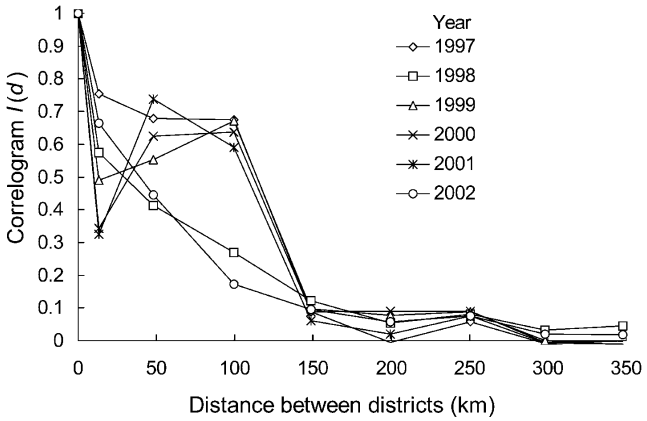

FIGURE 2. Yearly spatial correlograms of malaria incidence rate (cases per 100 population) for the period 1997–2002.

Clinic-level malaria incidence. We have further focused our analysis on three clinics in Mae Sod district in Tak Province. In general, Tak Province had higher malaria incidence rates (5.68 cases per 100 population) than the national average (0.16 cases per 100 population) over the six-year period ($t = 9.36$, degrees of freedom [df] = 5, $P < 0.001$). Data from the three clinics in Mae Sod district showed that malaria incidence rates in Mae Sod (0.67 cases per 100 population) and Mae Kasa (0.32 cases per 100 population) were significantly higher than the national average ($P < 0.05$ for both sites). Despite overall high malaria incidence rates in Tak Province, Mae Kuedlong had significantly lower rates (0.04 cases per 100 population) than the national average ($P < 0.01$). Similar to the nationwide malaria trend, the proportions of *P. vivax* malaria in 2002–2003 had increased and were significantly higher than those of *P. falciparum* malaria. Furthermore, when the relative incidence of each malaria species in these three clinics were compared, we found that there were significantly more *P. vivax* malaria cases in Mae Kasa (*P. falciparum*:*P. vivax* = 282:385, $t = 3.21$, df = 11, $P < 0.01$), whereas the other two clinics did not show such a bias, suggesting that malaria species composition varies on a micro-geographic scale.

One unique feature of malaria epidemiology in Thailand is that the numbers of malaria cases from foreigners have remained relatively constant for the past 12 years. Located at the Thailand-Myanmar border, Mae Sod district represents an area where malaria case numbers from foreign travelers were significantly higher than from local residents (malaria cases in 2000–2001, Thai:Foreigner = 4,420:9,339, $t = 7.02$, df = 23, $P < 0.001$). This indicates that cross-border population movement may contribute tremendously to malaria transmission in this border area. Interestingly, among the foreigner malaria cases, there were significantly more *P. falciparum* than *P. vivax* malaria cases, whereas in local residents malaria cases from the two species were equally abundant. Previously, we have shown that the clear seasonality of malaria incidence in this area, with two peaks occurring in May–July and October–November, is closely associated with the patterns of rainfall.[35] When the malaria case data from foreigners and local residents were analyzed separately, the seasonal peaks were most obvious for the foreigner malaria cases. In contrast, malaria cases in local residents were not markedly seasonal, and the case numbers in the peak months were not significantly different from those in other months.

In Mae Sod, all four human malaria species are present with *P. vivax* and *P. falciparum* as the most prevalent species. Using merozoite surface protein 1 (MSP-1) and MSP-2 polymorphism data, we have previously shown that mixed-strain infection of *P. vivax* malaria in this area was as high as 35% despite its low endemicity.[35] An earlier study in Trad Province of Thailand detected 20% mixed-species infections.[36] However, analysis of the two-year data from three clinics in Mae Sod did not show a significant association between *P. falciparum* and *P. vivax* in either Thai or foreign cases ($P < 0.001$ for each species at each of the three clinics, by chi-square test).[32] For example, less than 2.3% of all malaria cases in Mae Sod district were microscopically diagnosed as mixed-species infections. Such a decrease in mixed species

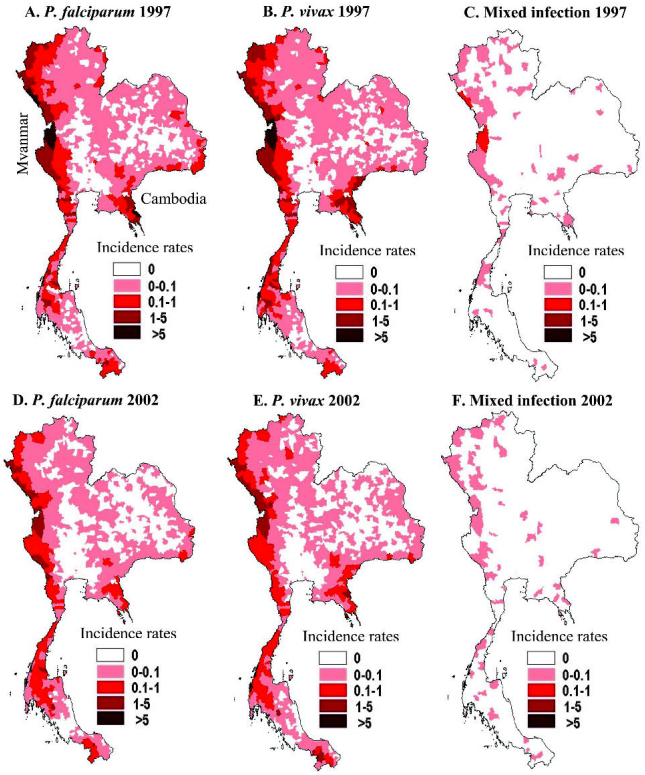

FIGURE 3. Dynamics of spatial distribution of malaria incidence rates (number of cases per 100 population) at the district level between 1997 and 2002. This figure appears in color at www.ajtmh.org.

TABLE 1

Matrix of transition probabilities among the five malaria incidence rate classes

Transition probability	Transitioned class				
	1	2	3	4	5
Initial class					
1	0.85	0.14	0.00	0.00	0.00
2	0.18	0.77	0.05	0.01	0.00
3	0.01	0.24	0.68	0.07	0.01
4	0.00	0.01	0.33	0.60	0.06
5	0.00	0.00	0.00	0.46	0.54

infection rate might be due to the overall reduction in malaria transmission and/or the insensitivity of microscopic examination to detect mixed species infections.

DISCUSSION

In this study, we performed a retrospective analysis of malaria incidence data for the past 37 years in Thailand. Although a gradual decrease in nationwide malaria cases has been observed over this period, there was high spatial heterogeneity in malaria incidence rates across the country. High-incidence regions were concentrated near areas bordering Myanmar and Cambodia. Further analysis of malaria incidence data in Mae Sod district showed great variation in malaria incidence rates and species composition between local and foreign patients. On the Thai side, political stability has fostered a good public health infrastructure. In Mae Sod, there are three government-funded malaria clinics offering free diagnosis and treatment of malaria. On the Myanmar side, such services are not present at this time. As a result, many patients simply cross the border to seek free malaria treatments. Therefore, the significantly higher foreigner case numbers in Mae Sod may have actually resulted from increased human migration and perhaps indicate higher levels of malaria transmission in Myanmar. These foreign malaria cases may have contributed to local malaria transmission, since Thai residents in Tak Province had the highest malaria incidence rates in the country. Given the possibility that migratory foreign workers are an important source of malaria transmission, the change in the patterns of migration could have impacted on the population at risk and the incidence of reported cases. Unfortunately, accurate records on the number of migratory laborers and the patterns of migration are not available. Nonetheless, the results of this retrospective analysis suggest that control of malaria in these high-incidence areas requires close monitoring of malaria in migratory foreigners.

Based on malaria incidence rates, 926 districts have been categorized into five classes in our analysis. Spatial autocorrelation analysis showed geographical association of districts to form clusters, suggesting that malaria transmission in one district is directly or indirectly associated with transmission in neighboring districts. This may be due to regional similarities in climatic and environmental factors that are linked to the dynamics of vectors. Although this was not directly tested due to the lack of environmental data, the malaria distribution map showing the concentration of the disease in the forested areas and areas bordering Myanmar and Cambodia favors such a connection. In addition, the clustering of high-incidence districts may be related to socioeconomic factors that affect the effectiveness of vector control programs. An earlier study has clearly shown that malaria is directly linked to poverty in Thailand.[37] We have noted that in certain high-incidence areas, malaria control programs include government-funded free malaria clinics and local vector control efforts (mostly application of residual insecticide). However, the effectiveness of the vector control program on malaria control has not been evaluated. State transition analysis found that each malaria incidence class had a high probability (54–85%) of remaining in the same class. On one hand, this indicates that malaria will persist in Thailand, especially in the rural and border areas, which further stresses the need for a continued and strengthened malaria control program. On the other hand, the results are also encouraging, showing significant improvements of malaria status in the central regions and chances for improvement in the bordering endemic regions.

The Malaria Control Program of the Department of Communicable Disease Control is responsible for monitoring malaria incidence and changes in the national antimalarial drug policies. In the mid 1970s, malaria cases from both parasites were on the increase because the drug used at that time, CQ, became less effective. Consequently, a new combination of antifolate drugs (sulfadoxine-pyrimethamine [SP]), was introduced in 1975. This resulted in a sharp decrease in *P. falciparum* malaria, but *P. vivax* malaria was not greatly affected.[13] Since 1980, the national drug policy has changed four times in response to the drug resistance problem in *P. falciparum*. To date, *P. falciparum* has developed resistance to CQ, SP, and mefloquine in succession, and multidug-resistant parasites have spread to most malarious areas of this country.[38] To deal with multidrug resistance, a mefloquine-artesunate combination became the standard treatment for *P. falciparum* malaria in 1995. Overall, *P. falciparum* responded well to drug changes; each drug change resulted in an immediate sharp decrease in *P. falciparum* malaria cases. Since 1995, the *P. falciparum* malaria incidence rate continued to decrease each year, but the *P. vivax* malaria incidence rate showed only a slight decline. As a result, *P. vivax* became the most prevalent malaria parasite in Thailand at the turn of the century. Such a difference in response to control measures may be directly linked to the intrinsic biologic properties of *P. vivax,* such as early gametocytogenesis and relapse, rather than to differential sensitivity to antimalarial drugs, because recent surveys showed no resistance of *P. vivax* to most antimalarial drugs except SP.[39]

Current treatments for *P. falciparum* and *P. vivax* malaria involve two different combinatory drug regimens to combat multidrug resistance for *P. falciparum* (mefloquine and artesunate) and relapse for *P. vivax* (CQ and primaquine).[13] Recent studies showed that *P. vivax* malaria relapse was reduced to < 5% under the current antimalarial drug policy compared with > 30% in late 1980s.[17,40–42] Therefore, the recent *P. vivax* records may well represent the actual vivax transmission in Thailand. Other studies have shown that the recent drug policy was highly effective and helped stabilize the multidrug resistance problems of *P. falciparum* malaria in Thailand.[6,43–45] However, it must be emphasized that artesunate and other artemisinin combinations are the last drugs in our line of defense in malaria chemotherapy. While significant drug resistance of *P. vivax* has not been detected in Thailand, *P. vivax* malaria still prevails and shows no signs of decreasing. In certain areas, such as Sa Kaeo Province near the Thailand-Cambodian border, *P. vivax* malaria has soared to an unprecedented level in the past few years.[46] Since drug resistance in *P. vivax* has not been detected in this area, the increase in *P. vivax* incidence rates may be related to changes in the composition and abundance of vectors with differential capabilities of transmitting the two malaria parasites.[13,47] If this is true, the malaria control program in Thailand will require an integrated approach combining chemotherapy for the disease and control of the vector.

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