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EPIDEMIOLOGY AND SPATIAL ANALYSIS OF MALARIA IN THE NORTHERN PERUVIAN AMAZON

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Abstract. A retrospective surveillance study was conducted to examine the micro-geographic variation of malaria incidence in three malaria-endemic communities in the Northern Peruvian Amazon. The annual malaria risk rate (per 100) ranged from 38% to 47% for *Plasmodium vivax* and from 15% to 18% for *P. falciparum*. Spatial clusters were found for *P. vivax* in Padre Cocha, Manacamiri, and Zungaro Cocha, and for *P. falciparum* only in Padre Cocha. Spatial-temporal clusters showed that the highest monthly number of *P. vivax* cases varied every year from December to March in 1996–1997 and from February to June in 1998–1999, and for *P. falciparum* from November to April in 1996–1997 and from January to April in 1998–1999. Our results suggest a constant presence of high-risk areas (hot spots) for malaria infection in periods with high or low malaria incidence. Modest targeted control efforts directed at identified high-risk areas may have significant impact on malaria transmission in this region.

INTRODUCTION

The geographic information system (GIS) and global positioning system (GPS) have been widely applied to health and epidemiology for malaria research and control in most sub-Saharan Africa countries.[1–6] Spatial point pattern analysis may help identify high-risk diseases areas, sources of diseases, and high-risk populations.[7] These statistical techniques are based on case events and count data, where known geographic locations (x-y coordinates) of disease cases are commonly represented as points.[8–10] The disease (GIS) mapping can also play an important role in formulating malaria control activities, evaluating changes in malaria transmission over time and allocating resources to control malaria,[1,5,11] especially in high or persistent local malaria transmission areas (hot spots).[12]

In South America, Peru has the second highest number of malaria cases. The Amazonian Department of Loreto has been the epicenter of the malaria epidemic since the early 1990, with most cases in communities near the capital of Iquitos. In 1997, an epidemic year, 103,842 cases of *Plasmodium falciparum* malaria and 54,290 cases of *P. vivax* malaria were reported with an annual malaria incidence rate of 148 per 1,000 inhabitants in Loreto.[13] In this region, malaria transmission is seasonal, with peaks in the rainy season from November to June. The rapid spread of both *Plasmodium* species may be due to the appearance of *Anopheles darlingi* as the main vector, which was first documented in 1995.[14,15]

To date, there have been no published studies applying GIS, GPS, and spatial point pattern analyses to examine the micro-geographic distribution of malaria incidence in the northern Peruvian Amazon. In the present report, a retrospective surveillance approach was used to study the malaria incidence in three malaria-endemic communities near the Amazonian city of Iquitos. We examined 1) the micro-geographic variation of malaria incidence in periods with high or low incidence, 2) the identification of malaria high-risk areas, and 3) the presence of spatial and spatial-temporal clusters of malaria.

MATERIAL AND METHODS

Study sites. The study was conducted in three malaria-endemic communities: Padre Cocha, Manacamiri, and Zungaro Cocha (Figure 1). The communities are located between 5 and 15 km from the center of Iquitos, a city of 450,000 people in the Amazon River basin. Padre Cocha and Manacamiri are only accessible by boat and Zungaro Cocha is only accessible by road. Iquitos has a tropical climate, with an average temperature of 27.5°C (81.5°F) and an average annual rainfall of 4 meters (13.1 feet). The surrounding areas are primarily cultivated land and small secondary growth forests. The residents are predominantly mixed Spanish and American Indian (mestizo) and their major trades are fishing, agriculture, and tourism. *Plasmodium vivax* and *P. falciparum* infections were initially reported in Zungaro Cocha in 1991 and in Padre Cocha in 1994, respectively.[15]

Epidemiologic data. A retrospective surveillance community-based setting approach was performed from 1996 to 1999 for Padre Cocha and Manacamiri and from 1998 to 1999 for Zungaro Cocha. The Loreto Region Ministerio de Salud (Ministry of Health, MINSA), Iquitos has a health post in most communities. Symptomatic residents were initially evaluated for malaria infection at the health posts where a finger stick was performed and a malaria thick blood film was prepared. Smears were microscopically interpreted on site or were sent to the local MINSA referral laboratory in Iquitos. Smear results were recorded in the Health Post Fever Registry (Registro Febriles, Malaria Control Programa) of each community, which is used to locate residents for treatment. Residents diagnosed with malaria receive free treatment in accordance with Peruvian MINSA guidelines. Only a few residents (0.2%) seek treatment outside the communities.[16]

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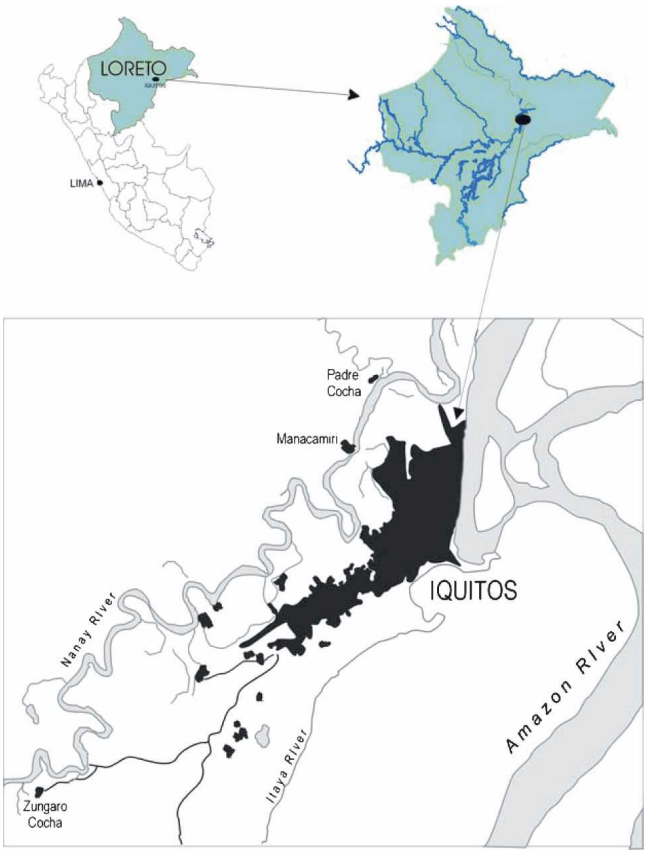

FIGURE 1. Location of Iquitos in Peru and the study sites of Padre Cocha, Manacamiri, and Zungaro Cocha. Dark coloring shows populated areas and the gray areas show rivers. Circles show location and size of the cluster. This figure appears in color at www.ajtmh.org.

Plasmodium falciparum malaria was treated with sulfadoxine/pyrimethamine (SP), 25 mg/kg, and primaquine (PQ), 0.75 mg/kg, administered as single doses. Cases resistant to SP were treated with seven-day courses of quinine and tetracycline or clindamycin. *Plasmodium viv*ax malaria was treated with chloroquine, 25 mg/kg over a three-day period and concurrent therapy with PQ, 0.5 mg/kg/day for 7 days. To minimize bias introduced by recurrent malaria episodes due to treatment failure, all duplicate episodes (cases of *P. falciparum* within 30 days and *P. vivax* within 60 days) were excluded from analyses.

Before initiating this study, verbal inform consent and approval were obtained from the village mayor, health post workers, elders, and heads of households in each community. Afterward, a community-wide census and mapping were performed in Padre Cocha in January 1998, in Manacamiri in September 1999, and in Zungaro Cocha in May 2000. The data from the census were retrospectively cross-linked with the malaria registry (fever registers and treatment logs) for each resident. This was possible because of the low rate of movement of residents into and out of communities.[16]

Geographic information system. All households, streets, and lakes were geocoded using hand-held GPS receivers (ProXR; Trimble, Sunnyvale, CA).[17] To ensure a location error less than one meter, a differential correction was applied using Pathfinder™ Office software, version 1.10 (Trimble). Each household's location was linked to census and epidemiologic information and managed using Arcview GIS software (Environmental Systems Research Institute, Redlands, CA).

Statistical analysis. The malaria risk rate was calculated as the number of new infections divided by the average number of residents at risk. A household with ≥ 8 residents was defined as overcrowded. Residents ≥ 15 years of age were categorized as adults. Chi-square or Fisher exact tests were used to compare differences in proportions and the Student *t*-test or analysis of variance was used to compare difference in means. All statistical analyses were conducted using SAS version 8.1 (SAS Institute Inc., Cary, NC).

Spatial analysis. The spatial scan statistic test was applied[18,19] to detect spatial clusters (excess of cases in a specific area) and spatial-temporal clusters (excess of cases that are close in both space and time) by *Plasmodium* species. This method imposes a circular window moving across the map, defining a set of zones containing different households with different number of cases and household-sizes. As the circular window is placed at each household, the method creates a large number of distinct geographic circles, with different sets of household's areas within them, and each is a possible candidate for cluster. The scan test reports the relative risk of each significant cluster found, which is estimated as the number of cases divided by the expected number of cases within the cluster. Clusters are determined by computing maximum likelihood ratios. The simulated *P* value of the statistic was obtained through Monte Carlo simulations, 9,999 for spatial cluster analysis and 999 for spatial-temporal analysis. Attributable risks (excess risk of malaria disease associated with the clusters detected) were also estimated.

A surface analysis of cumulative malaria risk by year at the

TABLE 1
Demographic characteristics of Padre Cocha, Manacamiri, and Zungaro Cocha, Peru, 1996–1999

Feature	Padre Cocha	Manacamiri	Zungaro Cocha	*P*
Study period	1996–1999	1996–1999	1998–1999	–
No. persons	1,668	1,052	706	–
No. males (%)	838 (50.2)	571 (54.3)	367 (52.0)	0.112
No. adults (%)*	883 (52.9)	545 (51.8)	370 (52.4)	0.615
Mean age in years (range)	19.6 (0–81)	23.2 (0–85)	22.2 (0–86)	0.121
No. households	310	143	148	
Mean residents per household (range)	5.5 (2–20)	7.3 (1–25)	5.8 (1–16)	0.001
Overcrowded households (%)	67 (21.6)	56 (39.2)	30 (20.3)	< 0.001
Traditional structures of households† (%)	130 (41.9)	131 (91.6)	70 (47.3)	< 0.001

* Adults, were residents ≥ 15 years of age.
† Traditional structure of households; sleeping quarters of wood and thatched roof.

TABLE 2

Blood smear examinations and malaria detection slide positivity by *Plasmodium* species in Padre Cocha, Manacamiri, and Zungaro Cocha, Peru, 1996–1999.

Years	Padre Cocha			Manacamiri			Zungaro Cocha		
	No. slides examined	*P. vivax* no. (%)	*P. falciparum* no. (%)	No. slides examined	*P. vivax* no. (%)	*P. falciparum* no. (%)	No. slides examined	*P. vivax* no. (%)	*P. falciparum* no. (%)
1996–1999	9,390	4,412 (47)	1,417 (15)	3,433	2,083 (61)	643 (19)	1,904	1,016 (53)	346 (18)
1996	1,545	1,261 (82)	274 (18)	974	799 (82)	144 (15)	–	–	–
1997	1,659	1,064 (64)	599 (36)	864	544 (63)	312 (36)	–	–	–
1998	2,539	1,295 (51)	223 (9)	706	594 (84)	116 (16)	1,465	648 (44)	280 (19)
1999	3,647	792 (22)	321 (9)	889	146 (16)	71 (8)	439	368 (84)	66 (15)
P value for trend		< 0.0001	< 0.0001		< 0.0001	< 0.0001			

household level was performed using the inverse distance weighted (IDW) interpolator model[20] using ArcView spatial analyst version 1.0 (Environmental Systems Research Institute). The IDW weighs the contribution of each input (control) point by a normalized inverse of the distance from the control point to the interpolated point. It assumes that each input point has a local influence that decreases with distance, and weights the points closer to the processing points more than those farther away. A specified number of points within a specified radius are used to determine the output value for each location. The threshold to define risk areas was based on the distribution of the single value of malaria risk (less than the mean = low risk, between the mean and the mean plus half the SD = moderate risk, and higher values = high risk).

RESULTS

Demographics. A total of 3,426 residents were distributed among 601 households in the three communities (Table 1). The mean age was 21.7 years (range = 0–86 years), and 51% of the residents were adults. No significant differences between communities by sex, age, or adulthood status were observed. The mean number of residents per household ranged from 5.5 to 7.3 and household overcrowding was significantly different between communities ($P < 0.001$). Fifty-five percent of the houses were made of traditional structure (sleeping quarters of wood and thatched roof). The rest of the houses were made of brick and concrete with aluminum roofs.

Blood smears. A total of 14,727 blood smears were recorded in the health post log books during the study period (Table 2). Sixty-four percent of smears recorded were from Padre Cocha. The slide positivity rate (SPR) was higher for *P. vivax* (51%, range = 16–84%) than for *P. falciparum (*16%, range = 8–36%) for all three communities. The SPRs by *Plasmodium* species showed a decrease by year in Padre Cocha and Manacamiri. Distribution of malaria prevalence showed similar temporal patterns in the three communities (Figure 2).

Malaria risk. The cumulative malaria risk rate (per 100 inhabitants) was 44% (range = 38–47%) for *P. vivax* and 17% (range = 15–18%) for *P. falciparum*. Padre Cocha reported the highest annual risk rate for *P. vivax* (55.7% in 1998) *and P. falciparum* (29.4% in 1997). The risk rate for both *Plasmodium* species decreased in Padre Cocha and Manacamiri in 1999 (Table 3).

In Padre Cocha, the spatial patterns of cumulative malaria risk of *P. vivax* showed two constant high-risk areas located in the northwestern and southeastern parts of the community (Figure 3A). This pattern was similar to that observed for *P. falciparum* (mostly in the northwestern part of the community; Figure 3B). In Manacamiri, the northwestern part of the community showed a high-risk area for malaria for both *Plasmodium* species. This suggests the presence of a constant hot spot over time (Figure 4). In Zungaro Cocha, the smaller community, no specific pattern of high-risk area by *Plasmodium* species was apparent, with malaria disease dispersed within the community (Figure 5).

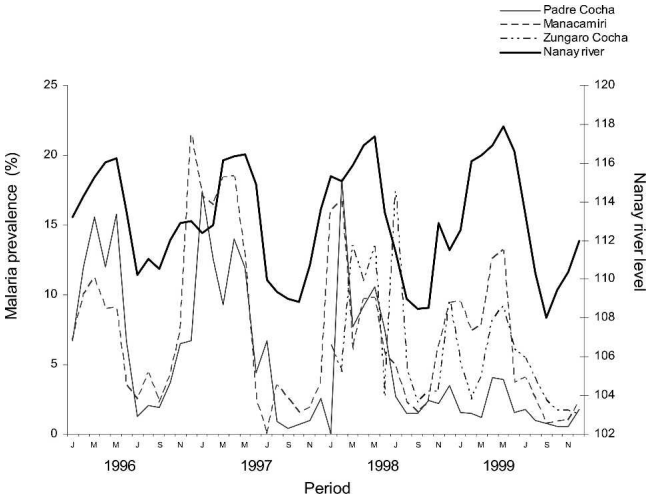

FIGURE 2. Malaria prevalence by community study sites and the Nanay River level, Iquitos, Peru, 1996–1999.

TABLE 3

Annual malaria risk rate by *Plasmodium* species in Padre Cocha, Manacamiri, and Zungaro Cocha, Peru, 1996–1999*

Plasmodium species/year	Padre Cocha Risk rate (95% CI)	Manacamiri Risk rate (95% CI)	Zungaro Cocha Risk rate (95% CI)
P. vivax			
1996	50.8 (48.2–53.3)	54.5 (51.2–57.7)	–
1997	46.5 (44.0–49.0)	43.7 (40.5–46.9)	–
1998	55.7 (53.3–58.2)	43.6 (40.5–46.7)	53.3 (49.4–57.1)
1999	35.6 (33.3–37.9)	12.2 (10.2–14.3)	35.0 (31.5–38.7)
P. falciparum			
1996	16.1 (14.3–18.1)	13.7 (11.6–16.1)	–
1997	29.4 (27.1–31.7)	28.4 (22.6–31.4)	–
1998	11.5 (9.9–13.1)	10.5 (8.7–12.6)	27.3 (23.9–30.8)
1999	15.3 (13.6–17.1)	6.4 (5.0–8.1)	7.8 (5.9–9.9)

* CI = confidence interval.

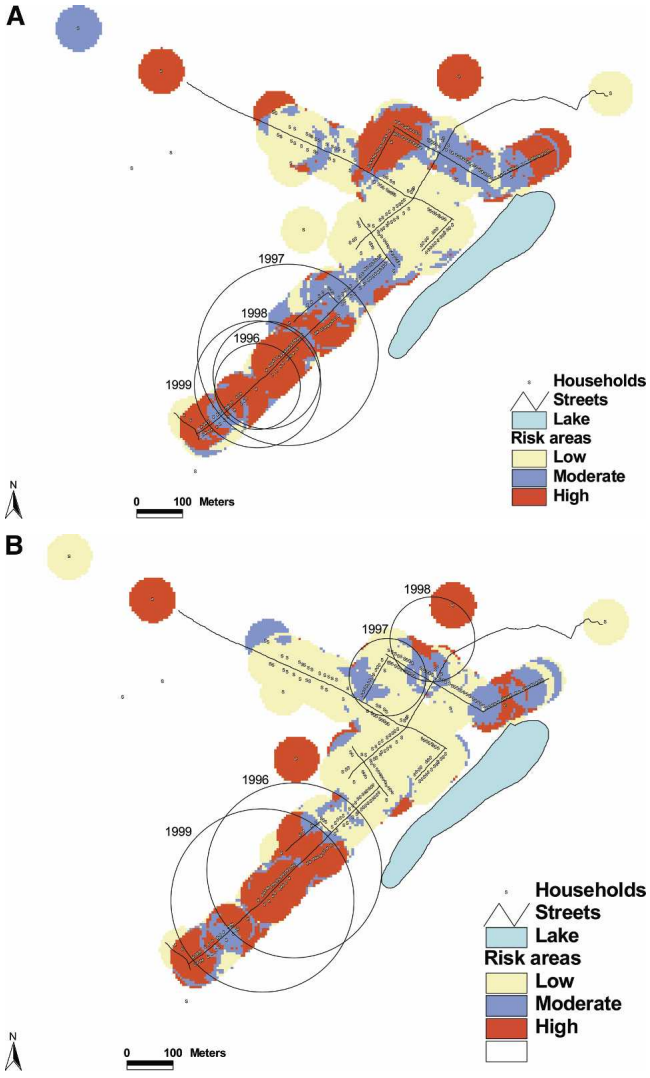

FIGURE 3. **A**, Household malaria risk patterns of *P. vivax* in Padre Cocha, Iquitos, Peru, 1996–1999. Circles show the location and size of the cluster. **B**, Household malaria risk patterns of *P. falciparum* in Padre Cocha, Iquitos, Peru, 1996–1999. Circles show location and size of the cluster. This figure appears in color at www.ajtmh.org.

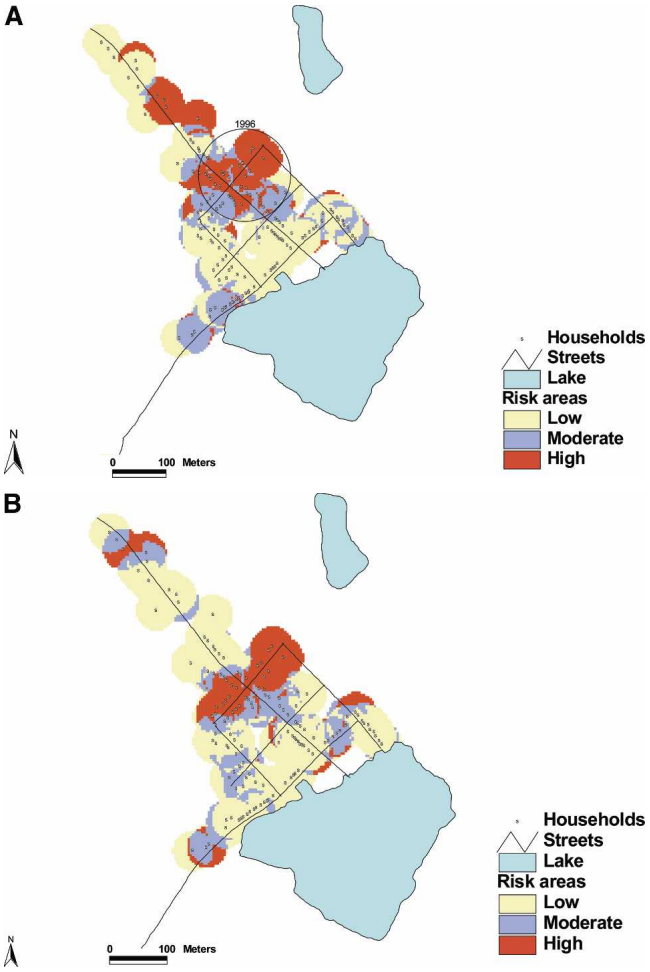

FIGURE 4. **A**, Household malaria risk patterns of *P. vivax* in Manacamiri, Iquitos, Peru, 1996–1999. Circles show the location and size of the cluster. **B**, Household malaria risk patterns of *P. falciparum* in Manacamiri, Iquitos, Peru, 1996–1999. Circles show location and size of the cluster. This figure appears in color at www.ajtmh.org.

Spatial cluster analysis. In Padre Cocha, a significant spatial cluster of *P. vivax* and *P. falciparum* was found in each year (Figure 3). The relative risks of these clusters were higher for *P. falciparum* (range = 1.40–2.56) than for *P. vivax* (range = 1.22–1.51) (Table 4). The attributable risk (AR) was also higher for *P. falciparum* (51%) than for *P. vivax* (30%). The spatial clusters found for *P. vivax* confirmed the presence of high-risk areas in the northwestern part of the community. Two spatial clusters were found in the zones with elevated *P. falciparum* malaria risk (northeast in 1997–1998 and southeast in 1996–1999). The size (number of households) of the spatial clusters indicated an increased over time from 7% to 27% for *P. vivax* and from 4% to 25% for *P. falciparum*.

In Manacamiri, the spatial pattern of malaria risk (Figure 4) suggests the presence of one high-risk area (northwest) for both *Plasmodium* species. One significant spatial cluster was only found for *P. vivax* in 1996, with an AR of 27% ($P < 0.001$). This spatial cluster represented 35% of the total households.

In Zungaro Cocha, the spatial pattern of malaria risk by *Plasmodium* species was not clear through a visual inspection. However, the scan statistic reported the presence of two spatial clusters for *P. vivax* located in the northeastern part of the community in 1998 and 1999 with relative risks of 2.42 (AR = 39%; $P < 0.001$) and 1.61 (AR = 38%; $P < 0.001$), respectively (Figure 5A). No spatial cluster was found for *P. falciparum.*

Spatial-temporal cluster analysis. Significant spatial-temporal clusters for *P. vivax* and *P. falciparum* were found in all years in Padre Cocha (Table 5). The period of occurrence of these clusters has changed over time. In 1996 and 1997, most clusters began from November to February, while in 1998 and 1999 the clusters began in January and February. The relative risks for these clusters ranged from 3.54 to 4.17 for *P. falciparum* and from 2.57 to 3.08 for *P. vivax.* In addition, the size of these clusters varied significantly among years only for *P. vivax* ($P = 0.003$).

In Manacamiri, significant spatial-temporal clusters were found in all years for *P. vivax*, with a relative risk range from

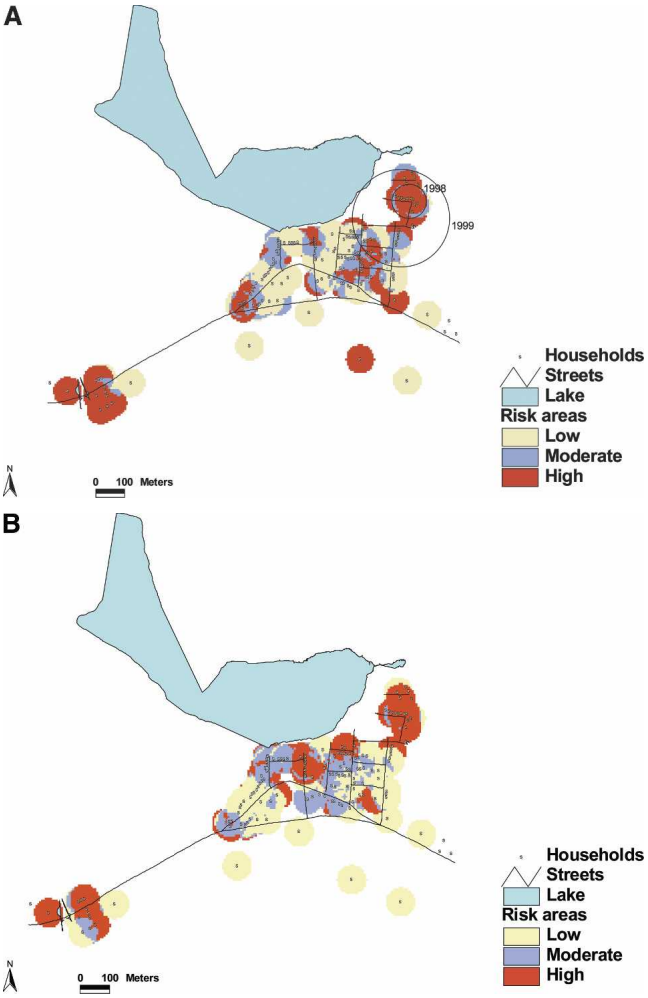

FIGURE 5. **A**, Household malaria risk patterns of *P. vivax* in Zungaro Cocha, Iquitos, Peru, 1998–1999. Circles show location and size of the cluster. **B**, Household malaria risk patterns of *P. falciparum* in Zungaro Cocha, Iquitos, Peru, 1998–1999. Circles show location and size of the cluster. This figure appears in color at www.ajtmh.org.

2.34 to 4.74, and began from January to April. For *P. falciparum,* only two spatial-temporal clusters were found in 1997 and 1998, with relative risks of 3.32 and 4.88, respectively.

In Zungaro Cocha, two significant spatial-temporal clusters were found in the two years of analysis (1998–1999) for *P. vivax*, but only one significant cluster was found for *P. falciparum* in 1998. The time period of these clusters were the same for both *Plasmodium* species (March to May).

DISCUSSION

To our knowledge, this is the first micro-geographic malaria study conducted in a community-based setting in South America. Our findings must be viewed with reference to the changes in malaria over time. Despite these changes, spatial patterns of cumulative malaria risk were observed at the same geographic areas within the communities revealing micro-high risk areas for infection. The consistent micro-high risk areas and spatial malaria clusters found may be explained by the proximity of secondary growth forest and breeding sites, which increases the proximity and accessibility of residents to the breeding habitats and the vector. The average 10-meter fluctuation in the level of the Nanay River causes extensive flooding of the forest during the rainy season, creating potential breeding habitats for *An. darlingi*. A preliminary entomologic analysis showed an association between the abundant presence of adult *An. darlingi* and micro-high risk areas for malaria infection in Padre Cocha, 1998 (Chan AST, unpublished data). In addition, a clear spatial pattern of no malaria infection was observed in the center of each community. This may be due to little vegetation in those areas. Our data was also consistent with the elevated number of malaria cases for *P. falciparum* in 1997,[15] an epidemic year, as well as the clear decrease in malaria cases for both *Plasmodium* species in 1999.

TABLE 4

Spatial cluster analysis by *Plasmodium* species in Padre Cocha, Manacamiri, and Zungaro Cocha, Peru, 1996–1999

Community	Malaria species	Year	Most likely spatial clusters		
			No. cases	Relative risk	*P*
Padre Cocha	*P. vivax*	1996	181	1.51	0.0002
	(Figure 3A)	1997	345	1.22	0.0149
		1998	265	1.34	0.0003
		1999	213	1.41	0.0003
	P. falciparum	1996	101	1.72	0.0001
	(Figure 3B)	1997	134	1.48	0.0016
		1998	23	2.56	0.0349
		1999	136	1.78	0.0001
Manacamiri	*P. vivax*	1996	243	1.33	0.0004
	(Figure 4A)	1997	184	1.21	0.1149
		1998	137	1.34	0.0610
		1999	21	2.36	0.0724
	P. falciparum	1996	28	1.86	0.2468
	(Figure 4B)	1997	35	1.93	0.0562
		1998	7	3.61	0.4491
		1999	7	4.83	0.1361
Zungaro Cocha	*P. vivax*	1998	22	2.42	0.0001
	(Figure 5A)	1999	57	1.61	0.0007
	P. falciparum	1998	24	1.62	0.4087
	(Figure 5B)	1999	3	3.96	0.0951

The MINSA malaria control activities in the communities have included indoor residual house spraying, larviciding of fish culture ponds, and the sporadic distribution of impregnated bed nets. These activities are usually initiated after substantial malaria transmission has already occurred, which may be too late for control measures to significantly reduce transmission.

Padre Cocha was the community where most spatial and spatial-temporal clusters were found. In this community, the malaria risk (per 100) of the spatial clusters was higher for *P. falciparum* (range = 49–66%) compared with *P. vivax* (range = 24–38%), and the ratio of female-to-male malaria cases was higher within the spatial clusters when compared with the rest of the community (*P. vivax*, range = 1.2–1.4, *P. falciparum*, range = 0.9–1.2). Although female residents were more likely than males to be infected, the difference was not statistically significant. This finding was similar to that reported by Roper and others.[16]

The spatial-temporal clusters found have confirmed the hypothesis that in recent years the highest monthly number of malaria cases has varied, indicating different temporal patterns. This variation is still unexplained, but one hypothesis is the continuing environmental changes and the recent presence of El Niño in Peru.[21]

TABLE 5
Spatial-temporal cluster analysis by *Plasmodium* species in Padre Cocha, Manacamiri, and Zungaro Cocha, Peru, 1996–1999

Community	Malaria species	Year	Most likely spatial-temporal clusters			
			No. cases	Relative risk	*P*	Time frame (months)
Padre Cocha	*P. vivax*	1996	89	3.08	0.001	Dec
		1997	180	2.57	0.001	Jan–Mar
		1998	153	2.65	0.001	Jan–Feb
		1999	121	2.94	0.001	Mar–May
	P. falciparum	1996	36	4.11	0.001	Nov–Dec
		1997	103	3.54	0.001	Feb–Apr
		1998	25	4.17	0.001	Jan–Feb
		1999	79	3.83	0.001	Feb–Apr
Manacamiri	*P. vivax*	1996	116	2.34	0.001	Feb–Apr
		1997	89	2.66	0.001	Jan–Mar
		1998	60	4.27	0.001	Feb
		1999	20	4.74	0.002	Apr–Jun
	P. falciparum	1996	9	6.39	0.083	–
		1997	44	3.32	0.001	Apr–May
		1998	20	4.88	0.001	Feb–Mar
		1999	10	4.43	0.273	–
Zungaro Cocha	*P. vivax*	1998	66	2.31	0.001	Mar–May
		1999	47	2.90	0.001	Mar–May
	P. falciparum	1998	36	2.45	0.006	Mar–May
		1999	8	5.14	0.414	–

This study had a number of limitations. First, our analysis did not take into account other potential risk factors that may contribute to geographic variation in malaria risk and the presence of disease clustering, such as *Anopheles* distribution, distance from house to stream, land- and water-use patterns, and socioeconomic features.[22,23] However, a study conducted between August 1997 and July 1998 in Padre Cocha reported no association between malaria household incidence and family size, neighborhood population density, or house construction type.[16] Second, malaria incidence may be explained by critical levels of river height and rainfall.[21,24] Climatic factors such as the daily Nanay River level, precipitation, and temperature were analyzed by backward linear regression analysis and showed that only river level was significantly associated with malaria infection, and explained only 28% of the total variation of malaria risk in the communities. Third, smears were microscopically interpreted on site and at the local MINSA referral laboratory in Iquitos; therefore, a misclassification bias may exist. Fourth, the scan statistic imposes a circular window moving across the community area to detect clusters, so that the presence of potential noncircular clusters was not evaluated.

Recent applications of GIS/GPS in malaria control have been reported in India,[25] Madagascar,[26,27] and Thailand.[28] In India, the objective was to develop a model to assist planning and implementation of a suitable malaria control. The location of disease occurrence and information on specific vectors were analyzed in a GIS permitting the development of appropriate preventive action. In Madagascar, GIS has been applied to detect areas at high-risk for malaria outbreak and used in malaria surveillance with the objective of anticipating areas with a concentrated distribution of *An. funestus*. Similarly, in Thailand, GIS/GPS have permitted real-time monitoring and forecasting of the distributions of four malaria species so that control measures may be conducted before mosquitoes emerge as adults and transmit disease.

In summary, our results show the presence of microgeographic variations in periods with high or low malaria incidence, and a constant presence of high-risk areas (hot spots) for malaria infection. Results of this study may lead to a reorientation of malaria control where relatively modest, targeted control efforts directed at identified high-risk areas may have significant impacts.[29] Future research in a wider variety of communities and the application of new spatial cluster methods are required to better understand the microgeographic variation of malaria in this region.

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