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Socio-Demographics and the Development of Malaria Elimination Strategies in the Low Transmission Setting

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Abstract

This analysis presents a comprehensive description of malaria burden and risk factors in Peruvian Amazon villages where malaria transmission is hypoendemic. More than 9,000 subjects were studied in contrasting village settings within the Department of Loreto, Peru, where most malaria occurs in the country. *Plasmodium vivax* is responsible for more than 75% of malaria cases; severe disease from any form of malaria is uncommon and death rare. The association between lifetime malaria episodes and individual and household covariates was studied using polychotomous logistic regression analysis, assessing effects on odds of some vs. no lifetime malaria episodes. Malaria morbidity during lifetime was strongly associated with age, logging, farming, travel

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history, and living with a logger or agriculturist. Select groups of adults, particularly loggers and agriculturists acquire multiple malaria infections in transmission settings outside of the main domicile, and may be mobile human reservoirs by which malaria parasites move within and between micro-regions within malaria endemic settings. For example, such individuals might well be reservoirs of transmission by introducing or reintroducing malaria into their home villages and their own households, depending on vector ecology and the local village setting. Therefore, socio-demographic studies can identify people with the epidemiological characteristic of transmission risk, and these individuals would be prime targets against which to deploy transmission blocking strategies along with insecticide treated bednets and chemoprophylaxis.

1. Introduction

Global malaria control efforts have increased massively in recent years to levels not seen since eradication efforts in much of the world commenced after World War II.¹ The development of sustainable local malaria control measures, regional elimination programs, and ultimately the holy grail of global eradication, is predicated on the notion that the prevalence of parasitemia in human populations can be effectively monitored and control measures evaluated over space and time.^{2, 3} This static notion of malaria control presupposes forward progress in malaria control, but does not necessarily account for local or regional reintroductions by mobile human reservoirs of malaria that may travel within or between endemic regions for economic, social or other behavior reasons. Here we will suggest that one reason for malaria's intractability is that human behavior allows malaria parasites to move among regions with anophelism thus allowing this disease to maintain its hold on human populations.

In Latin America and the Caribbean, 75 percent of malaria infections are caused by *P. vivax*^{4, 5} and are rarely fatal, while 25 percent are caused by the more lethal *P. falciparum*, the dominant malaria parasite in Africa. *P. vivax* malaria, thought not an intrinsically life threatening disease, has been widely recognized to be understudied and to merit increase research and public policy attention.^{4, 6–11} The global burden of *P. vivax* malaria has been under appreciated and yet the morbidity associated with this infection and its spectrum of disease is largely neglected;^{4, 8, 12} therefore, malaria in the Americas has been widely neglected. A total of 1.06 million new cases of malaria were reported in the Americas in 1997, and 247,229 (23.3%) of these cases were from Peru.¹³ Since then, the number of malaria reported in the Americas decreased from 1,150,103 cases and 348 deaths in 2000 to 882,361 cases and 156 deaths in 2004, reflecting a 23% reduction in the number of cases in the region and a 55% decrease in the overall number of malaria-attributed deaths in that period. The case fatality rate due to *P. falciparum* in the region also decreased from 13 per 10,000 cases in 2000 to 7 per 10,000 in 2004.

In contrast, Peru has had the largest net increase of 26% in malaria cases and the second highest number of malaria cases in the Americas reported from 2000 to 2004.¹³ More than 60% of malaria in Peru occurs in the peri-Iquitos area, the capital city of the Peruvian Amazon Region of Loreto (PARL), mostly along forest fringes and 'new' colonization areas. Malaria transmission intensity in the PARL is typically low (entomological inoculation rate (EIR) < 1 infective bite per year), few *Anopheles* spp. vector mosquitoes are infected with malaria parasites,^{14–17} and mixed infections with *P. falciparum* and *P. vivax* are uncommon. Despite the low EIR and low transmission intensity in the Amazon region, asymptomatic malaria parasitemia is common.^{17–20} Malaria transmission in the PARL is seasonal with an epidemic peak from February to July and similar to other malaria-endemic countries, control measures are based on mainly passive surveillance with sporadic active surveillance

campaigns. These measures are incorporated into general local health services within a partially decentralized National Malaria Program (NMP) of the Ministry of Health (MoH).

During the 1980s and 1990s dramatic changes occurred in malaria transmission (Fig. 1), especially because of optimal environmental conditions for proliferation and spread of malaria vectors (i.e. deforestation), emergence of chloroquine-resistant *P. falciparum*, marked incidence of *P. vivax* malaria, entry of *Anopheles darlingii* into the ecology of the PARL mosquito population,^{15, 16} presence of asymptomatic persistent reservoirs for continuous reinfection¹² and ability of the primary parasite *P. vivax* to cause relapsing cases.

In addition to the well-recognized contributions of deforestation,^{14, 23} human sociodemographic factors and behaviors are likely to be important contributors to the reemergence and local reintroduction of malaria as a public health problem throughout the Amazon region. A major livelihood of people living in the rural areas surrounding Iquitos city is based on agriculture, fishing, logging and harvesting wood for charcoal at sites away from permanent domiciles. People with such work may camp outside for weeks or months, later returning home. These activities directly place people at risk for *Anopheles* mosquito bites, which in the PARL is primarily *An. darlingi*,^{6, 7, 15, 16} and bring people with malaria parasitemia from diverse places together. Collectively, these considerations drive the hypothesis that people often acquire malaria outside their home villages and drive the dispersion of new parasite strains. Taking into account these socio-demographic considerations, we hypothesize that regional malaria control policies must consider how human behavior leads to the movement of malaria parasites. People with such epidemiological characteristics would be prime targets among who to deploy malaria insecticide treated bednets, chemoprophylaxis and/or transmission blocking strategies.

Antimalarial drugs are given free of cost by the Peruvian National Malaria Program (NMP) under a Directly Observed Therapy (DOT) protocol but in many geographically far, hard-to-access villages, enforcement of this policy may be less rigid than in villages closer to Iquitos. In remote places where these human reservoirs of malaria transmission may be frequently traveling, malaria diagnosis is not available. Despite the morbidity and large numbers of malaria cases occurring each year in the PARL, the region is considered hypoendemic (low malaria transmission).^{17–19, 24–26} A comprehensive description of malaria burden and risk factors in Peru, a malaria-hypoendemic region with relatively good access to diagnosis, has not been previously reviewed. Therefore, the present study attempted to describe the occurrence and identify risk factors related to malaria in villages of the PARL, to guide researchers and decision-makers in targeting intervention efforts and to provide additional insight into malaria transmission patterns in the study area.

2. Materials and Methods

2.1 Study sites

A retrospective cohort study was carried out in 13 villages of Maynas, province of the PARL in the northeastern region of Peru, all located in one of the main axes of malaria transmission (Fig. 2). Loreto has a population of 964,195 inhabitants and Iquitos is a heavily populated metropolitan area (~60% of Loreto's population), located 120 meters above sea level at latitude 3.44°S and longitude 73.15°W on the bank of the Amazon River. The climate is tropical, with an average temperature of 27.5°C and a mean annual precipitation exceeding 2,500 mm. Monthly rainfalls are greatest in March (310 mm) and lowest in August (150 mm). Iquitos is relatively isolated, accessed only by air or by river and the majority of the population is of mixed Spanish and American Indian ancestry. Iquitos is also a tourist center, and many European and North American visitors pass through the city and surrounding areas on ecotourism expeditions. There are many small villages located on the

banks of the Amazon River and its tributaries, within few hours by boat from Iquitos. People living in these villages are mainly involved in subsistence agriculture, fishing, harvesting wood for charcoal, and logging activities. In each village, composed of several hundreds to a few thousands of people, houses are modest, made of simple wood or concrete block construction with palm thatch or corrugated aluminum roofs, and usually lack running water, and electricity (Fig. 3). Considering the region's geographical isolation from the rest of Peru, health services to people living within the surrounding areas of Iquitos are relatively good and accessible. Four health establishments provide health services to the study villages, described as follows:

Santo Tomas Health Post (STO)—Located 16 km far from Iquitos by road and surrounded by the Nanay River (Fig. 3) it is a referral health center for 3 villages: La Union (147 houses), 13 de Diciembre (35 houses), and Santo Tomas (302 houses). The whole population accounted for approximately 2,650 people.

San Jose de Lupuna Health Post (SJL)—Located 10 km from Iquitos, accessible through Nanay River, is referral for 4 villages: San Pedro (51 houses), Santa Rita (79 houses) (Fig. 2), Fray Martin (34 houses), and San Jose de Lupuna (84 houses), with a whole population of approximately 1,250 people.

Padrecocha Health Post (PAD)—Located 6 km from Iquitos, accessible only through the Nanay River, it is a referral health post for 3 villages: San Andres (28 houses), Nueva Vida (7 houses), and Padrecocha (324 houses), accounting for a population of approximately 1,800.

Mazan Health Center (MAZ)—Located 50 km northeast of Iquitos (40 minutes by speedboat), it is surrounded by the Amazon River to the south and the Napo River to the north, strategically near the confluence of the Napo and Amazon rivers. There is a small road of 3.4 km that crosses the portion of land between the 2 rivers and connects both rivers. Its geographic situation allowed Mazan to mediate commerce between all villages located in margin of the Napo River and Iquitos city through a fluvial wharf designed to attend boats of up to 60 tons of movement and lifting capacity of up to 50,000 tons to the year. Three villages surrounding the health center were part of the study: San Jose, Puerto Alegre, and Mazan, totalizing around 4,200 people.

There is one malaria diagnostic laboratory (microscopy) in each of these four health establishments, responsible for providing diagnostic services and complete treatment against malaria 6 days a week. Malaria diagnosis in these areas follows standard procedures as defined by the MoH in Peru. Standard malaria therapies are: chloroquine for 3 days (10mg/kg on days 1 and 2, and 5mg/kg on day 3), plus primaquine for 7 days (0.5 mg/kg/day) for *P. vivax* malaria; mefloquine (12.5 mg/kg/day for 2 days) plus artesunate (4 mg/kg/day for 3 days) for *P. falciparum* malaria.

2.2 Study population

It was composed by individuals of all ages living in the study sites; if a mother was not available, only the father would answer the questionnaire on behalf of children if they were too young to do so. The overall population comprised roughly 9,700 inhabitants, and 9,195 (95%) subjects participated in the study. Inhabitants who did not participate in the study were due to not finding an adult in their house to answer the questionnaire.

2.3 Data collection procedures

Ten health promoters from the study villages, 2 laboratory technicians and 1 experienced field nurse applying questionnaires were trained on the purpose of each item of the study questionnaire. Individual and household interviews recorded information on characteristics such as demographics, socioeconomic status, occupation, travel history and lifetime exposure to malaria. In the Mazan area questionnaires were applied during May-June 2006; in the other areas during December-February 2007. Households were visited up to 3 times to find an adult to answer the questionnaire. The assembly of the cohort, and follow-up to determine the outcome variable (lifetime malaria episodes), has all happened in the past and was obtained by reviewing malaria program registries in the health establishments of the study areas; then it was complemented by self-reported lifetime malaria episodes at the time of questionnaire.

2.4 Laboratory procedures

To estimate malaria prevalence we performed examinations which routinely are thick blood smears; briefly, in the field 2 thick blood smears were taken, air-dried and stained with giemsa. Well-trained lab technicians examined 100 high-power fields of the thick blood smear for identification of malaria parasites. Treatment was provided for every subject with a positive smear and according to the Peruvian MoH.

2.5 Definition of malaria outcome

The outcome was '*Lifetime malaria episodes*', both types of malaria in the region (*P falciparum* and *P vivax*) were used, and it was categorized as: never, some (1 to 3 episodes), or several (≥ 4 episodes).

2.6 Potential risk factors

Variables selected explored as indicators of exposure to malaria in this study were: gender, health post, age, education, job, travel history and household variables. Health Posts were MAZ, STO, SJL, and PAD. Age was categorized as <5 , $[5-15]$, $[15-45]$, ≥ 45 years old because it nicely divided the data into 4 groups and also treated as a continuous variable with increments of 10 years for more meaningful results. Education was categorized as Technical-Superior, Secondary, Primary, Illiterate, and Under school age. Job was categorized as Commerce-taxi, Logger, Fishing, Agriculture, Housewife, Student, Unemployed, Woodcutter for charcoal, Urban Redevelopment Program building), and Others. Whether travel to rural areas outside of the home village was categorized as a yes/no question: jobs considered as requiring going outside village were Logging, Fishing, Agriculture, and Woodcutter for charcoal. Travel history was categorized as a yes/no question regarding if the subject traveled or not, travel to Iquitos was excluded because transmission is less likely to occur in this city. Three definitions of travel were used, 'T1' was limited to the month previous to the census and of at least 3 days-duration and ≥ 10 km as determined by location of place visited using determined by river used to travel, type of transportation, near village of place visited and duration of trip. 'T2' referred to month previous to census but considered any distance & duration. 'T3' referred to any of the last 4 or less malaria episodes for ≥ 10 km and staying out of village at least for 3 days; for subjects with never malaria, T3 referred to lifetime travel of such characteristics. Living with a logger or agriculturist was categorized as yes for people who live in the same house with at least one logger or agriculturists. Household variables such as exterior / interior wall materials (brick, cement, wood calamine, etc), location of kitchen (exterior, interior), roof material (calamine, palms), rate of bednets per beds, possessions (radio, television, etc). All household variables were not significantly associated with outcome; therefore, tables are not shown for these variables.

2.7 Data analysis and statistical procedures

Data were analyzed using SAS v.9.1. Since our outcome is not just dichotomous but consists of 3 categories, then polychotomous logistic regression was used for analysis.²¹ In particular, this tool allowed us to assess effects on odds of several vs. never and some vs. never malaria episodes lifetime. First, we performed polychotomous logistic regression for each variable independently as univariate analysis; second, we performed polychotomous logistic regression for all variables together as a multinomial analysis. The significance level for all hypothesis testing was set at $p \leq 0.05$ and confidence intervals accordingly.

2.8 Ethical considerations

This study was approved by the Ethical Committees of Universidad Peruana Cayetano Heredia and Asociación Benéfica Prisma in Lima, Peru, by the Peruvian Amazon Region Directorate of Health and the Institutional Review Boards of the University of California San Diego and the Johns Hopkins Bloomberg School of Public Health.

3. Results

3.1 Description of study population

The study population consisted of 9,195 individuals, 14%, 17%, 29%, and 40% were from SJL, PAD, STO, and MAZ, respectively (Table 1). A total of 53% were male and 13% younger than 5 years old, with a mean age of 24.4 years, and ranging from <1 to 92 years. The median monthly family income (S/.483 New Soles or \$146 U.S. dollars) was under the Peruvian minimum, which was S/.550 New Soles (\$167 U.S. dollars) in 2007 (Table 1). A homogeneous pattern of behaviors regarding health care service use was observed in the study population. All individuals who reported having had at least one malaria episode referred had used the MoH laboratories for malaria diagnosis and treatment. Approximately one third of the population (33.9%) reported not having experienced at least one episode of malaria during his (her) lifetime. Proportion of individuals reporting never *P falciparum* (68.6%) was almost twice the proportion of individuals reporting never *P vivax* (38.5%). The median number of malaria episodes during lifetime was 3.0. The study population reported a mean time living in malaria endemic areas of approximately 17 years with a median of 12 years, and 32% had lived in these areas for less than 5 years. Use of individual protective measures against mosquito bites was rarely reported, except for regular work clothes.

Considering people ≥ 18 years old (5,033 or 55% of the population): The majority had attended school a mean of 7.1 years and 4.8% never went to school; 43.3%, 45.4% and 6.5% attended primary school, secondary school and technical or professional studies, respectively. Considering people < 18 years old, 32.4% of individuals were under age to go to school (< 6 years old) and 67.6% were on age to go to school from which 2.1% never went to school. The seven most reported past occupations were housewife (31.2%), agriculture (13.5%), commerce (8.2%), logging (7.5%), fishing (4.7%), woodcutter/coal (2.4%), mototaxi (2.2%) and crafts (3.4%). 27.3% referred routinely going outside village for job purposes. People with never malaria was equally represented by children < 5 years old (29.6%), 5–15 years old (33.7%), ≥ 15 years old (36.7%). The group of several malaria episodes lifetime was composed mainly of 15–45 years old subjects (57%), 56.2% males and 43.8% females.

The prevalence of malaria during the study period is shown in Table 2. Among 5556 blood smears examined, 205 cases of malaria parasitemia were identified: 172 of *P vivax*, 33 of *P falciparum* and none mixed infections. Overall, malaria prevalence during the study visit was 3.7% and a ratio of *P falciparum* to *P vivax* of 1:0.19. Most (66.13%) of the study

population had been previously exposed to malaria with 86.4%, 85.2%, 76.4% and 50.3% for each health establishments PAD, SJL, STO, and MAZ, respectively. The annual parasite index (API) was calculated from the number of parasitologically confirmed cases of malaria yearly from 2002 to 2007 (Table 3) as it relates to the average yearly population in the villages during the year. These high rates are comparable with hyperendemic areas where there are multiple annual malaria episodes per child, plus occasional cases among adults. In the study villages as in most of the Peruvian Amazon Region the distribution of malaria cases is entirely different of that observed in African and Pacific Hyperendemic areas of malaria. On average from 2002 to 2007, in the health establishments' study villages the majority of the cases occur in adults (≥ 15 years old): San Jose de Lupuna (52.3%), Santo Tomas (69.2%), Padrecocha (66.2%), and Mazan (70.3%). This is the same for most of the health establishments in Loreto where overall we had 57.9%, 52.8%, 57% and 59.4% of the malaria cases in adults from 2002 to 2007, respectively. More than 80% of the cases from 2002 to 2007 were reported during the first 25–35 epidemiologic weeks yearly (Table 3).

3.2 Risk factors for malaria lifetime—Univariate/Multivariate analysis

The total number of lifetime malaria episodes was found to be positively associated with age (categorized and continuous), gender, health establishment, job, travel history (T1, T2 and T3), job outside village, education, and living with a logger or agriculturist, based on univariate analysis (Table 4). Considering that there were three types of travel history and to avoid colinearity issues, we selected T3 for travel history for multivariate modeling using polychotomous logistic regression (Table 5). Variables in the multivariate analysis included the following: age, gender, education, job, health establishment, travel history (T3), and living with a logger or agriculturist. After adjustment, age, health establishment, type of job, travel history and living with a logger or agriculturist remained significantly associated with the number of lifetime malaria episodes; gender was borderline significant for some vs. never malaria but not significant for several vs. never malaria, and education was not significant.

3.2.1 Age—The odds of some malaria episodes (relative to never) increase by a factor of 1.2 for every 10 years increase in age after adjusting for gender, education, health establishment, job type, travel history, and living with a logger or agriculturist; with a 95%CI from 1.2 to 1.3. The odds of several malaria episodes (relative to never) increase by a factor of 1.6 for every 10 years increase in age after adjusting for gender, education, health establishment, job type, and travel history; with a 95%CI from 1.5 to 1.7. The odds of some malaria episodes (relative to never) are 2.9 times higher for 15 or older years old subjects than for less than 15 years old subjects after adjusting for gender, education, health establishment, job type, travel history, and living with a logger or agriculturist; with a 95%CI from 1.2 to 2.0. The odds of several malaria episodes (relative to never) are 3.0 times higher for 15 or older subjects than for subjects less than 15 years old after adjusting for gender, education, health establishment, job type, travel history, and living with a logger or agriculturist; with a 95% CI from 2.2 to 4.2.

3.2.2 Gender—The odds of some malaria episodes (relative to never) are 1.2 times higher for male subjects than for female subjects after adjusting for age, education, health establishment, job type, travel history, and living with a logger or agriculturist; with a 95%CI from 1.0 to 1.4. The association between several malaria episodes (relative to never) and gender was not significant after adjustment.

3.2.3 Health establishment—From univariate analysis we chose Mazan as the reference category. *Padrecocha*: The odds of some malaria episodes (relative to never) were 10.1 times higher for subjects living in Padrecocha than for subjects living in Mazan after

adjusting for age, gender, education, job type, travel history, and living with a logger or agriculturist; with a 95%CI from 7.2 to 14.2. The odds of several malaria episodes (relative to never) are 40.6 times higher for subjects living in Padrecocha than for subjects living in Mazan after adjusting for age, gender, education, job type, travel history, and living with a logger or agriculturist; with a 95%CI from 27.6 to 59.6. *San Jose de Lupuna*: The odds of some malaria episodes (relative to never) were 12.8 times higher for subjects living in San Jose de Lupuna than for subjects living in Mazan after adjusting for age, gender, education, job type, travel history, and living with a logger or agriculturist; with a 95%CI from 10.2 to 16.2. The odds of several malaria episodes (relative to never) were 127.1 times higher for subjects living in San Jose de Lupuna than for subjects living in Mazan after adjusting for age, gender, education, job type, travel history, and living with a logger or agriculturist; with a 95%CI from 97.8 to 168.8. *Santo Tomas*: The odds of some malaria episodes (relative to never) were 8.6 times higher for subjects living in Santo Tomas than for subjects living in Mazan after adjusting for age, gender, education, job type, travel history, and living with a logger or agriculturist; with a 95% CI from 7.3 to 10.2. The odds of several malaria episodes (relative to never) were 39.2 times higher for subjects living in Santo Tomas than for subjects living in Mazan after adjusting for age, gender, education, job type, travel history, and living with a logger or agriculturist; with a 95% CI from 31 to 49.

3.2.4 Occupation—People working in commerce or mototaxi (are inside village boundaries in the market or small grocery stores, not at home, driving on the roads of these villages or going to Iquitos) were used together as a reference category. *Agriculture*: The odds of some malaria episodes (relative to never) were 3.2 times higher for subjects working on agriculture than for subjects working on commerce/mototaxi after adjusting for age, gender, education, travel history, and living with a logger or agriculturist; with a 95% CI from 2.0 to 5.2. The odds of several malaria episodes (relative to never) were 4.5 times higher for subjects working on agriculture than for subjects working on commerce/mototaxi after adjusting for age, gender, education, travel history, and living with a logger or agriculturist; with a 95% CI from 2.7 to 7.4. *Housewife*: The odds of some malaria episodes (relative to never) were 1.7 times higher for housewives than for subjects working on commerce/mototaxi after adjusting for age, gender, education, travel history, and living with a logger or agriculturist; with a 95%CI from 1.3 to 2.4. The odds of several malaria episodes (relative to never) were 1.7 times higher for housewives than for subjects working on commerce/mototaxi after adjusting for age, gender, education, travel history, and living with a logger or agriculturist; with a 95% CI from 1.2 to 2.3. *Logging*. The odds of some malaria episodes (relative to never) were 2.6 times higher for subjects working on logging than for subjects working on commerce/mototaxi after adjusting for age, gender, education, travel history, and living with a logger or agriculturist; with a 95% CI from 1.5 to 4.6. The odds of several malaria episodes (relative to never) were 5.0 times higher for subjects working on logging than for subjects working on commerce/mototaxi after adjusting for age, gender, education, travel history, and living with a logger or agriculturist; with a 95%CI from 2.8 to 9.0.

3.2.5 Travel history (T3)—Iquitos as a destination was not considered as traveling regardless of time. In the multivariate analysis we used only T3 for travel history: it referred to the month before one of the last four malaria episodes; and for subjects with never malaria, it referred to lifetime travel to further than 10 km and/or for at least 3 days. The odds of some malaria episodes (relative to never) were 31.1 times higher for subjects who traveled than for subjects who did not travel (as defined by T3) after adjusting for age, gender, education, health establishment, job type, and living with a logger or agriculturist; with a 95% CI from 24.7 to 39.2. The odds of several malaria episodes (relative to never) were 57.8 times higher for subjects who traveled than for subjects who did not travel (as

defined by T3) after adjusting for age, gender, education, health establishment, job type, and living with a logger or agriculturist, with a 95%CI from 49.9 to 76.1.

3.2.6 Living with a person working on logging or agriculture—The odds of some malaria episodes (relative to never) were 1.8 times higher for subjects who lived with a logger or agriculturist than for subjects who did not live with a person working on such activities, after adjusting for age, gender, education, health establishment, job type, and travel history; with a 95%CI from 1.6 to 2.1. The odds of several malaria episodes (relative to never) were 2.2 times higher for subjects who lived with a logger or agriculturist than for a subject who did not live with a person working on such activities, after adjusting for age, gender, education, health establishment, job type, and travel history; with a 95%CI from 1.9 to 2.6.

4. Discussion

From 1880 to 1945, the Amazon was the epicenter of the 'rubber boom', an important period in the socio-economic history of countries with Amazon territories such as Peru, Brazil, Colombia and Ecuador, triggering the migration process, wealth and socio-cultural transformations. During that period all study areas were established with internal migration and colonization with malaria-naïve people from the Peruvian Andes. In 1954, an eradication campaign was launched in the Americas which in 1955 became worldwide, and in Peru the National Service for Malaria Eradication (NSME) was formed. In 1970 with the entrance of a military government which believed that the solution to rural poverty was not in the development of public health but in agrarian reform, the NSME was eliminated and the malaria control budget fell drastically. Other political factors that contributed to the reemergence of malaria were the discontinuation of the U.S. financial help for malaria eradication worldwide.

Few studies have focused on associated risk factors for malaria in communities originating from frontier settlements in the Amazon Basin of Peru. An insightful analysis of frontier malaria in Amazonia comprises three stages: epidemic, transition and endemic.²⁷ The first stage is characterized by high malaria rates and the inefficacy of traditional control measures, whereas the transition period is marked by declines in malaria rates that are partially explained by improved health infrastructure and reduced mobility of settlers. Malaria transmission becomes less intense and more stable in the final stages. Our study provides an example of how heterogeneous is the pattern of malaria due to different individual and group sociodemographic and behavioral characteristics.

Historically, failure to consider population movement contributed to failure of malaria eradication campaigns in the 1950s and 1960s.^{28, 29} As people move, they can increase their risk for acquiring the disease through the ways in which they change the environment.^{30, 31} Such activities can create more favorable habitats for *Anopheles* mosquitoes; at the same time, workers may have increased exposure to the vector. When economic or other needs can no longer be met in a particular environment, people move elsewhere. The 'push factor' could be environmental degradation, population pressure on land, employment, etc. When people believe that a move elsewhere will provide new and attractive opportunities, a 'pull factor' is involved such as better political, economical or social opportunities.^{32, 33}

The Peruvian Department of Loreto remains an important migration destination for people from other cities in Peru (internal migration) and from frontier cities in Colombia and Brazil (external migration). These migration patterns facilitate the movement both of malaria immunes and non-immunes among areas with varying levels of vector density, resulting in a potentially explosive combination for high transmission rates and spread of infection over a

wide area such as occurred in Amazonia in the 1990s.^{6, 7} In terms of spatial dimensions, such human population movements to and from malarious areas are of epidemiologic importance of particular importance in both sustaining and reintroducing malaria. People at high risk for malaria including asymptomatic parasitemia due to acquired clinical immunity over time (e.g. loggers, agriculturists, etc) behave as active transmitters harboring the parasite and transmitting the disease when they move back to areas of low or sporadic transmission, therefore they are likely to be important sources of seasonal epidemics in the region. Since occupational activities are seasonal the same people behave as passive acquirers when exposed to the disease through movement to higher transmission intensity environments; family members and others with low-level or no immunity are often epidemiologically linked to those clinically immune, which increases the risk for disease spread.²⁸

Another sociodemographic feature observed in our study sites is a variable degree of circulation for economic purposes, that is, going between a fixed residence and a site of field labor; such circulation encompasses a variety of movements, usually short-term and cyclical involving no longstanding change of residence.³³ Daily circulation involves leaving a place of residence for up to 24 hours, periodic circulation may vary from 1 night to 1 year, and seasonal circulation is defined by marked seasonality in the physical or economic environment. The study areas exemplify clearly all types of circulation for different activities such as cultivation, logging, fishing, woodcutters for charcoal and tourism. The settlers in the study areas as in most villages in the PARL are highly mobile, moving with daily, periodic and seasonal circulation, from settlements in unstable disease endemic regions to hyperendemic-disease regions of the rainforests. This mobility keeps settlements unstable and at high risk for epidemics through the constant flow of parasitemic laborers.^{34, 35}

Nearly 20% of the Amazon rainforest has disappeared since 1970, which presents a major threat to the world's carbon and climate balance. There is a substantial forest disturbance adjacent to areas set aside for legal logging operations, another important ecological and environmental concern.³⁶ Moreover, between 1999 and 2005, 75% of the rain forest damage was found within 20 km of the roads. However, even within those limits, forests set aside by the government were more than 4 times better protected than areas not designated for conservation.^{27, 36} The Loreto Regional Government is about to build a highway from the frontier river village of Mazan, through the Amazon jungle, to the city of Iquitos. This new road will serve as a bidirectional movement of groups of people identified as developing several malaria episodes lifetime in our study; therefore, we have the opportunity to anticipate, and to study: 1) a potentially huge source of reintroduction of malaria parasites and vectors to areas of Iquitos where there is very low or no transmission but the conditions are most likely favorable and 2) the increasing entrance of non-immune subjects looking for better opportunities.

The analysis of occupational activities allowed us to identify two major groups: 1) subjects with mainly domestic activity, including housewives, students and unemployed adults; and 2) subjects working in agriculture, crafts, harvesting wood for charcoal, logging and fishing (Table 4). When performing the multivariate analysis, agriculturists, housewives, loggers and students remained statistically significant associated with several malaria episodes lifetime (Table 5). The latter analysis defines the main risk group among subjects working in the rain forest or in agricultural activities and its partners at home.

Alongside the Amazon River and its many tributaries, poverty-stricken loggers and agriculturists move deep into the rainforest, in areas where malaria is prevalent, without taking any precaution and for meager wages, making them the mosquitoes' main victims.

Inside villages people who live with a person working in such activities may secondarily acquire malaria.

At least two findings have clear implications for designing appropriate interventions against malaria in our site and other settings with similar endemicity. First, malaria morbidity is clearly associated not only with forest related activities such as logging but also with agriculture activities, sometimes acquired in areas away from villages. Such activities together represent the primary occupation of 21.3% study participants. Because land clearing also leads to changes in relative vector abundance that may favor malaria transmission in such a modified environment, this activity plays a crucial role in maintaining malaria transmission. These circumstances are reminiscent of the well-studied forest-malaria phenomenon in Southeast Asia and call for specific individual and community level interventions to reduce the risk of forest-related malaria in frontier settlements of the Amazon Basin. Second, the probability of having malaria clearly increased with previous history of travel which is of tremendous importance and give us the opportunity for planning and developing a malaria screening site at each point of entrance in villages and regardless of legal issues, health authorities need to coordinate malaria control interventions with logging companies to avoid incomplete treatments without prescription and to deploy basic diagnosis units and surveillance for malaria through the areas of such activities.

Drug treatment kills the asexual stages of *P. falciparum* before they are able to produce gametocytes so appropriate deployment of health services and drug treatment of *P. falciparum* infections can be very effective (until drug-resistance develops). *P. vivax* is less vulnerable to control by these means because mosquitoes will mostly have become infected during a pre-symptomatic period and therefore before drug treatment could have prevented onward transmission of the parasites through mosquitoes.⁶ On the other hand, vector control has historically been the only effective means of malaria control but anti-mosquito abatement programs are difficult to maintain politically and ecologically on a long-term basis,³² particularly because *Anopheles darlingi* is essentially sylvatic and bites not only in a crepuscular (sunset) mode but at various times between dusk and dawn in the Loreto region of Peru (Jan Conn and Marta Moreno unpublished).

There is evidence that a substantial proportion of people 5 years or older in villages around Iquitos have asymptomatic malaria parasitemia, whether *P. vivax* or *P. falciparum*, which is likely the dominant reservoir of continued transmission.¹⁷ We have observed (Vinetz and Gilman, unpublished) that in villages near Iquitos, approximately 4–8% of all people sampled through a cross-sectional active surveillance had malaria parasitemia as determined by light microscopy. Of these, ~2/3 had no symptoms referable to malaria within the prior 2 weeks. These data are mirrored by findings in Brazilian Amazonia^{19, 26} and we and others have commented on the observation that asymptomatic reservoirs of malaria parasitemia are likely to be reservoirs of continuing malaria transmission.³⁷

We have identified target populations for testing and deploying a malaria transmission-blocking vaccine (TBV) to prevent malaria parasites from being transmitted from the only known reservoir, humans, to mosquitoes. Theoretically, TBVs would have the same effect on reducing malaria as eliminating the mosquito vector preventing mosquitoes from becoming infected with the parasite after ingestion of blood from an infected individual. TBVs would not prevent recipients from developing malaria, but the idea is to develop a type of herd immunity within human populations that serve as important reservoirs of transmission. Targeting the people who serve as the most important reservoirs for mosquito infection with a TBV would have the greatest effect on malaria transmission within a population.^{38, 39} Alternative population-based strategies other than TBVs to prevent malaria

transmission could also include radical treatment or malaria chemoprophylaxis of risk groups as described herein, but would be practically difficult to implement.

TBVs are designed to induce an antibody response in humans that will block the parasite's infectivity to mosquitoes, hence spread of parasites between people and reduce the potential for infected returning travelers, migrants and circulators to introduce or re-introduce malaria into a given area. The approach is as follows: 1) Humans are vaccinated with recombinant mosquito/sexual-stage specific protein(s). 2) When a mosquito ingests a blood meal, vaccine-induced antibodies are taken up along with parasites (gametocytes). 3) Ingested antibodies would then interact with parasite surface or secreted proteins within the mosquito midgut, preventing the parasite from infecting the mosquito. If enough people within a population develop such antibodies, malaria transmission can be reduced, possibly even eliminated.³⁹ Additionally, TBVs would reduce the spread of drug- or vaccine-selected mutant parasites by reducing genetic recombination of the parasites within the mosquito. The mosquito stage of malaria parasites is a genetic bottleneck: of the tens or hundreds of gametocytes that enter the mosquito, derived from millions to hundreds of millions of erythrocytic parasites, only a few oocysts ($\sim 10^0 - 10^1$) develop within the mosquito midgut.^{40–42} An effective TBV may extend the useful life of newly developed drugs or other malaria vaccines by reducing the passage of mutant parasites from drug- or vaccine-treated humans to mosquitoes.

This study provides new insights into mechanisms of persistence, introductions, and reemergence of malaria. The considerations discussed there towards new approaches to control malaria based on the considerations of sociodemographic and behavioral factors in the hypoendemic Peruvian Amazon settings. The generalizability of these observations to more intensive transmission settings needs to be determined. This information may help guide decision makers to specify effective control measures targeted to this population and transmission situation. Moreover, it provides measurable evidence of the burden of malaria in this area, especially regarding type of occupation and travel history definitions, which may influence political commitment with regard to this relevant public health problem. Furthermore, this epidemiologic and sociodemographic information is essential for establishing field sites for testing malaria TBVs, which by necessity will need to be deployed on a micro-environmental scale. Population movements that either place people at risk for malaria or cause them to pose a risk to others can not be stopped. However, prevention measures can address the causes of these movements which, in developing countries, are often prompted by need rather than choice. These data support our hypothesis that persons infected with malaria are likely to have contracted it outside the limits of the village. Migratory and circulatory labors appear to be major determinants of human reservoirs of *P. vivax*. Malaria control in such areas could be achieved most efficiently by the deployment of a targeted intervention in high risk groups using a TBV.

Further studies are needed to measure the magnitude of *P. vivax* relapses occurring in the Peruvian Amazon to allow us quantify the burden of this phenomena which is known to cause a cumulative experience of 10–30 episodes of malaria during lifetime.⁶ Further analysis of data generated by this ongoing cohort study is expected to provide additional insights into the phenomenon of frontier malaria in the Amazon Basin.

Limitations

Potentially, the most important source of bias in measuring number of infections lifetime was recall bias. We are not concerned about recall bias because of two reasons: 1) as long as memory failure is equal amongst individuals, recall bias will not occur, and 2) we treated outcome as categorical which we definitively think avoided recall bias.

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Footnote for Abbreviations

PARL	Peruvian Amazon Region of Loreto
EIR	entomological inoculation rate
NMP	National Malaria Program
MoH	Ministry of Health
STO	Santo Tomas Health Post
SJL	San Jose de Lupuna Health Post
PAD	Padrecocha Health Post
MAZ	Mazan Health Center
API	annual parasite index
NSME	National Service for Malaria Eradication
TBV	transmission-blocking vaccine

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Figure 1. Malaria Cases in Peru: 1939–2010. Cases of malaria due to *Plasmodium falciparum* *P. vivax* were not differentiated and reported systematically until 1990. Source: Peruvian Ministry of Health, Lima, Peru

Figure 2. Axes of malaria transmission in Loreto, Peru-2007. Study sites location. Source: Loreto Regional Health Directorate, Iquitos, Loreto, Peru.

Figure 3. Health sites villages as visualized by satellite imaging. a: Padrecocha village. b: Santa Rita. c: Santo Tomas & La Union. d: Santo Tomas. e: Mazan. f: Mazan. g: Typical transportation route between villages. h: Mazan.

STUDY POPULATION CHARACTERISTICS (N=9,195) BY HEALTH POSTS IN THE PERUVIAN AMAZON REGION OF LORETO, 2007

TABLE 1

Health posts ^a	Mazan	Santo Tomas	San Jose de Lupuna	Padrecocha	Total
Variable					
Study Population	3,715 (40.4%)	2,649 (28.8%)	1,247 (13.6%)	1,584 (17.2%)	9,195
Males	1,965 (52.9%)	1,395 (52.7%)	663 (53.2%)	814 (51.4%)	4,837 (52.6%)
Age 1 (years)					
mean $\pm$ SD	23.4 $\pm$ 17.9	24.3 $\pm$ 18.2	26.5 $\pm$ 20.3	24.7 $\pm$ 17.0	24.4 $\pm$ 18.4
median	18.5	20.1	21.4	21	19.8
Age 2 (years)					
Less than 5	508(13.7%)	372(14.0%)	165(13.2%)	159(10.0%)	1,204(13.1%)
[5–15>	1,038 (27.9%)	609 (23.0%)	289 (23.2%)	384 (24.2%)	2,320 (25.2%)
[15–45>	1,635 (44.0%)	1,271 (48%)	554 (44.4%)	777 (49.1%)	4,237 (46.1%)
45 or older	534 (14.4%)	397 (15.0%)	239 (19.2%)	264 (16.7%)	1,434 (15.6%)
Family income					
Nuevos Soles	686.2	340.2	293.8	332.5	483.1
U.S. Dollars	207.9	103.1	89.0	100.8	146.4
Education ^b					
None	108 (5.8%)	61 (4.2%)	48 (6.8%)	24 (2.4%)	241 (4.8%)
Primary	835 (44.8%)	638 (43.5%)	306 (43.4%)	400 (40.2%)	2,179 (43.3%)
Secondary	752 (40.3%)	698 (47.6%)	311 (44.1%)	524 (52.6%)	2,285 (45.4%)
Tech/Superior	171 (9.2%)	69 (4.7%)	40 (5.7%)	48 (4.8%)	328 (6.5%)
Job ^c					
Loggers	330 (17.0%)	40 (2.7%)	20 (3.0%)	8 (0.8%)	398 (7.8%)
Fishing	37 (1.9%)	89 (6.0%)	16 (2.4%)	100 (10.1%)	242 (4.7%)
Charcoal	0 (0%)	35 (2.3%)	81 (12.0%)	4 (0.4%)	120 (2.4%)
Agriculture	223 (11.5%)	93 (6.2%)	135 (20.0%)	240 (24.1%)	691 (13.5%)
Craftsman	1 (0.1%)	35 (2.3%)	4 (0.6%)	135 (13.6%)	175 (3.4%)
Commerce/Moto	293 (15.1%)	176 (11.8%)	37 (5.5%)	24 (2.4%)	530 (10.4%)
Housewife	590 (30.5%)	467 (31.3%)	238 (35.2%)	296 (29.7%)	1,591 (31.2%)
Unemployed	110 (5.7%)	85 (5.7%)	35 (5.2%)	30 (3.0%)	260 (5.1%)

^aHealth posts (villages) were: Mazan (Mazan, San Jose, Puerto Alegre), Santo Tomas (Santo Tomas, La Union, Nuevo Quistococha), San Jose de Lupuna (San Jose de Lupuna, Santa Rita, San Pedro, Fray Martin and Padrecocha (Padrecocha, San Andres, Nueva Vida).

^bEducation data excluded all subjects younger than 18 years old.

^cJob data excluded school students and under school age subjects.

Health posts ^a	Mazan	Santo Tomas	San Jose de Lupuna	Padrecocha	Total
Urbanity Program	9 (0.5%)	16 (1.1%)	2 (0.3)	6 (0.6%)	33 (0.6%)
Other	344 (17.8%)	456 (30.6%)	109 (16.1%)	153 (15.3%)	1,062 (20.8%)

TABLE 2

MALARIA PREVALENCE IN THE STUDY HEALTH POSTS IN THE PERUVIAN AMAZON REGION OF LORETO, 2007

Health post ^a	Mazan	Santo Tomas	San Jose de Lupuna	Padrecocha	Total
Prevalence (95%CI)^b					
Number of slides	2,546	1,392	786	832	5,556
Any species	2.8% [2.1,3.4]	6.2% [4.9,7.4]	3.9% [2.6,5.3]	2.4% [1.4,3.4]	3.7% [3.2,4.2%]
<i>P. vivax</i>	2.0% [1.5,2.6]	6.2% [4.9,7.4]	2.6% [1.5,3.7]	1.9% [1.0,2.9]	3.1% [2.7,3.6%]
<i>P. falciparum</i>	0.7% [0.4,1.0]	0.00	1.3% [0.5,2.1]	0.48% [0.01,0.95]	0.6% [0.4,0.8%]
<i>P. vivax</i> : <i>P. falciparum</i>	1:0.35	1:0	1:0.5	1:0.25	1:0.19

^a Health posts (villages) were: Mazan (Mazan, San Jose, Puerto Alegre), Santo Tomas (Santo Tomas, La Union, Nuevo Quistococha), San Jose de Lupuna (San Jose de Lupuna, Santa Rita, San Pedro, Fray Martin and Padrecocha (Padrecocha, San Andres, Nueva Vida).

^b CI = Confidence interval (exact binomial). Two cases of mixed (*P. vivax* plus *P. falciparum*) malaria infections were identified and included separately for each malaria parasite species.

TABLE 3

MALARIA CASES AND API^d IN HEALTH ESTABLISHMENT STUDY SITES FROM 2003 TO 2007

Health site	Parasite	2003	2004	2005	2006	2007	2004–2007 (≥80%) ^d
SJL ^b	<i>P. vivax</i>	389	422	660	419	195	EW (2 – 29)
	<i>P. falciparum</i>	65	77	413	234	6	2,326 / 2,880
	API	349.2	383.8	822.8	487.1	152.7	80.8%
MAZ ^b	<i>P. vivax</i>	1,355	1,535	1,560	1,569	1,757	EW (2 – 37)
	<i>P. falciparum</i>	233	507	764	487	873	8,553 / 10,640
	API	324.1	416.7	453.6	362.2	529.3	80.4%
PAD ^b	<i>P. vivax</i>	707	573	1,042	385	280	EW (2 – 27)
	<i>P. falciparum</i>	62	19	56	22	9	2,559 / 3,155
	API	480.6	370	445.7	165.1	146.5	81.1%
STO ^b	<i>P. vivax</i>	944	889	1,204	526	169	EW (3 – 29)
	<i>P. falciparum</i>	78	35	130	49	18	3,276 / 4,042
	API ^c	385.7	348.7	503.4	217	70.6	81%

^a API: Annual Parasite Incidence = confirmed cases during one year /village's population (x 1000)

^b Health unit located in San Jose de Lupuna (SJL), Mazan (MAZ), Padrecocha (PAD) and Santo Tomas (STO)

^c Denominator in STO was obtained from the study census in La Union, Nuevo Quistococha and San Tomas

^d This column indicates the Epidemiological Weeks (EW) interval with at least 80% of the malaria cases considering the last 5 years Source: Health Regional Directorate of Loreto. STO population was calculated from study census

TABLE 4

UNIVARIATE ANALYSIS: EPIDEMIOLOGY OF MALARIA IN THE PERUVIAN AMAZON REGION OF LORETO^a (N=9,195)

Variables	Some Malaria Episodes			Several Malaria Episodes			P Value
	Odds Ratio	95% CI		Odds Ratio	95% CI		
Age 1 (10yrs)	1.51	1.45, 1.56		1.96	1.88, 2.04		< 0.0001
Age 2 (yrs)							
<5>	1.00 ^b			1.00 ^b			< 0.0001
[5–15>	3.5	2.92, 4.20		6.96	4.96, 9.76		
[15–45>	7.36	6.17, 8.78		32.49	23.46, 44.99		
[45>	9.15	7.23, 11.57		73.1	51.25, 104.27		
Gender							< 0.0001
Female	1.00 ^b			1.00 ^b			
Male	1.53	1.38, 1.70		1.52	1.36, 1.70		
Health Establishment							< 0.0001
Mazan	1.00 ^b			1.00 ^b			
Padrecocha	4.45	3.25, 6.09		10.73	7.78, 14.79		
San Jose de Lupuna	2.79	2.30, 3.37		12.86	10.65, 15.53		
Santo Tomas	2.31	2.05, 2.61		5.38	4.68, 6.18		
Education ^c							< 0.0001
Technical / Superior	1.00 ^b			1.00 ^b			
Secondary	1.56	1.16, 2.12		2.18	1.58, 3.01		
Primary	1.9	1.40, 2.58		3.59	2.60, 4.97		
None	1.64	1.02, 2.63		3.06	1.91, 4.93		
Job ^d							< 0.0001
Commerce / Mototaxi	1.00 ^b			1.00 ^b			
Agriculture	4.46	2.98, 6.67		7.79	5.23, 11.60		
Housewife	1.55	1.21, 2.00		1.88	1.46, 2.44		
Craftsman	3.49	1.48, 8.25		6.22	2.71, 14.27		
Charcoal	5.07	1.91, 13.47		18.06	7.15, 45.66		

Variables	Some Malaria Episodes		Several Malaria Episodes		P Value
	Odds Ratio	95% CI	Odds Ratio	95% CI	
Loggers	6.99	4.38, 11.15	7.65	4.78, 12.25	
Fishing	3.51	1.91, 6.43	6.8	3.79, 12.21	
None	1.65	1.11, 2.45	1.78	1.19, 2.67	
Urbanity Program	0.78	0.24, 2.61	2.83	1.08, 7.42	
Job outside village					< 0.0001
No	1.00 ^b		1.00 ^b		
Yes	3.29	2.56, 4.22	4.72	3.69, 6.03	
Travel history 1 (T1) ^e					< 0.0001
No	1.00 ^b		1.00 ^b		
Yes	2.54	2.05, 3.15	2.79	2.24, 3.47	
Travel history 2(T2) ^e					0.0027
No	1.00 ^b		1.00 ^b		
Yes	1.3	1.118, 1.50	1.15	0.98, 1.35	
Travel history 3 (T3) ^e					< 0.0001
No	1.00 ^b		1.00 ^b		
Yes	8.13	4.26, 15.50	5.57	2.91, 10.63	
Living with L/A ^f					< 0.0001
No	1.00 ^b		1.00 ^b		
Yes	1.238	1.114, 1.376	1.221	1.093, 1.365	

^aDependent variable is malaria episodes lifetime as: never (0), some (1–3) and several (≥ 4). Reference is never.

^bIndicates reference category

^cEducation analysis was performed excluding all subjects younger than 18 years old.

^dJob analysis was performed excluding school students and under school age subjects.

^eIquitos was considered as no travel for T1, T2 & T3. T1 & T2 referred to last month previous to study. T1 for > 10 km or out of village for at least 3 days. T2 for any distance & duration. T3 referred to month previous of at least one of the last four malaria episodes for further than 10km or for at least 3 days. For subjects with never malaria, T3 referred to lifetime.

^fLiving with a person who works on Logging (L) or Agriculture (A).

TABLE 5

MULTIVARIATE ANALYSIS: EPIDEMIOLOGY OF MALARIA IN THE PERUVIAN AMAZON REGION OF LORETO^a (N=9195) *

Variables	Some Malaria Episodes			Several Malaria Episodes			P Value
	Odds Ratio	95% CI		Odds Ratio	95% CI		
Age (10yrs)	1.231	1.149, 1.320		1.576	1.464, 1.697		< 0.0001
Age 2 (yrs)							
<15>	1.00 ^b			1.00 ^b			<0.0001
[15>	1.537	1.17, 2.02		3.015	2.2,4.13		
Gender							0.0168
Female	1.00 ^b			1.00 ^b			
Male	1.167	1.003, 1.358		0.952	0.791, 1.146		
Health Establishment							< 0.0001
Mazan	1.00 ^b			1.00 ^b			
Padrecocha	10.137	7.219, 14.236		40.563	27.6, 59.614		
San Jose de Lupuna	12.832	10.158, 16.211		127.143	95.756, 168.816		
Santo Tomas	8.636	7.337, 10.166		39.189	31.326, 49.025		
Education							0.054
Technical /Superior	1.00 ^b			1.00 ^b			
Secondary	1.13	0.786, 1.625		1.322	0.876, 1.994		
Primary	1.123	0.78, 1.616		1.291	0.855, 1.950		
None	0.975	0.582, 1.635		0.725	0.405, 1.298		
Job							< 0.0001
Commerce / Mototaxi	1.00 ^b			1.00 ^b			
Agriculture	3.212	1.995, 5.174		4.476	2.714, 7.383		
Housewife	1.732	1.263, 2.375		1.659	1.174, 2.343		
Craftsman	1.675	0.679, 4.135		2.14	0.875, 5.238		
Charcoal	1.605	0.587, 4.384		2.208	0.832, 5.859		
Loggers	2.595	1.470, 4.581		4.972	2.746, 9.004		
Fishing	1.164	0.596, 2.273		1.652	0.844, 3.235		
None	1.124	0.69, 1.829		1.133	0.668, 1.923		

Variables	Some Malaria Episodes		Several Malaria Episodes		P Value
	Odds Ratio	95% CI	Odds Ratio	95% CI	
Urbanity Program	0.853	0.201, 3.624	2.701	0.689, 10.582	
Student	1.543	1.117, 2.130	1.074	0.749, 1.540	
Under School Age	0.337	0.075, 1.522	0.692	0.146, 3.294	
Other	1.294	0.928, 1.806	1.161	0.808, 1.667	
Travel history (T3) ^c					
No	1.00 ^b		1.00 ^b		< 0.0001
Yes	31.126	24.717, 39.179	57.818	43.924, 76.107	
Living with L/A ^d					< 0.0001
No	1.00 ^b		1.00 ^b		
Yes	1.798	1.545, 2.091	2.2	1.85, 2.616	

^a The dependent variable is number of malaria episodes during lifetime categorized as never (0), some (1–3) and several (≥ 4). The reference category is never.

^b Indicates reference category.

^c Iquitos was considered as no travel. T3 referred to month previous of at least one of the last four malaria episodes. For subjects with never malaria, T3 referred to lifetime.

^d Living with a person who works on Logging (L) or Agriculture (A).

* Adjusted analysis: Polychotomous logistic regression was performed with all variables in the model.