The Participation of Secondary Clinical Episodes in the Epidemiology of Vivax Malaria during Pre- and Post-Implementation of Focal Control in the State of Oaxaca, Mexico

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Abstract. The participation of vivax malaria secondary clinical was researched in a retrospective cohort of 33,414 confirmed cases occurring between 1994 and 2005 in the state of Oaxaca, Mexico. Secondary episodes occurred in 23.4% of all primary cases. An increase in secondary episodes was associated with primary cases occurring during the dry seasons (risk ratio [RR] = 1.68, 95% CI: 1.45–1.96). The incidence of secondary episodes peaked at an older age, occurred similarly in men and women mostly during low mosquito abundance, and had a uniform distribution among localities. A reduction in secondary episodes was associated with the administration of an increased dose and early administration of primaquine (RR = 0.32, 95% CI: 0.26–0.38). However, limitations to distinguish relapses from re-infections impede assessment of the new treatment effect on relapses and its contribution to malaria control in the area. These findings highlight the need for new therapeutic schemes to radical cure of *P. vivax* infections and operational research aimed at parasite pool elimination.

INTRODUCTION

*Plasmodium vivax* strategy for survival as dormant forms in the liver of patients and the production of gametocytes during pre-symptomatic blood infection add difficulty to the control of its transmission. The resulting chronicity of the infection, manifested in symptomatic and asymptomatic relapses, enable *P. vivax* parasites to persist under unstable environmental conditions that determine seasonal mosquito abundance.1–3

*Plasmodium vivax* is responsible for more than 99% of malaria cases in Mexico, and the frequency of secondary episodes is estimated at 20% to 30%, similar to that observed in other parts of the world.4–7 After the last epidemic outbreak that occurred in the 1980s, malaria is under control in most parts of the country, but persists in residual foci located on the coast of the Pacific Ocean. The main residual focus is located in the state of Oaxaca, which concentrated more than 42% of the 118,602 malaria cases occurring in the country between 1994 and 2005 (records of the National Program for Vector Borne Diseases of the National Center for Disease Surveillance and Control, NCDS/C).

Until 1998, malaria vector control consisted of DDT indoor spraying, and one dose of chloroquine was administered to presumptive malaria (febrile) patients at the time of blood sampling for diagnosis. A complete treatment with chloroquine and primaquine was administered once the diagnosis was confirmed. Starting in 1999, a new control strategy (named focal control) was progressively introduced. This includes environmental management of mosquito breeding sites and home improvements,8 and a single increased dose of primaquine plus the same dose of chloroquine administered to febrile patients at the time of blood sampling, followed by two monthly doses (chloroquine and primaquine) upon confirmation of the diagnosis. After the introduction of the focal control, the incidence of malaria cases in Oaxaca decreased from 5.11 cases/1,000 inhabitants in 1998 to 0.2 cases/1,000 inhabitants during the period 2000–2005 (Table 1).

In this work, we describe the main characteristics of the epidemiology of malaria before and after the introduction of focal control in the State of Oaxaca, including a decrease in the proportion of malaria secondary clinical episodes in patients treated with the new therapeutic scheme. The limitations in separating relapses from re-infections make it difficult to assess the effect of the new treatment scheme on relapses and its contribution to malaria control in the area.

MATERIAL AND METHODS

Design. The protocol of the study was approved by the Ethics Committee of the National Institute of Public Health, Mexico. This was a population-based retrospective longitudinal observational study of a cohort that included all *P. vivax* malaria cases detected and confirmed by the Malaria Control Program (MCP) of the state of Oaxaca between 1994 and 2005. Malaria incidence was calculated using the 1995, 2000, and 2005 population census (Table 1) and National Population Counts (National Institute of Geography and Information) to calculate the annual population at risk. The secondary clinical episode incidence was calculated using the primary cases in the year as population at risk. This made it possible to estimate relative risks instead of odds ratios.

Study site. The study population included residents of six sanitary jurisdictions, of which the Pochutla-Coast region (Sanitary Jurisdiction IV) and the Loxichas and Central Valley regions (Sanitary Jurisdiction I) concentrated the greatest malaria incidence (Figure 1). Malaria transmission is seasonal and peaks are reached during the dry seasons when there is an abundance of the main vector *Anopheles pseudopunctipennis.*9

Detection of malaria cases. Malaria cases were detected and diagnosed by the State’s Malaria Control Program surveillance system. In this system, passive detection of malaria cases is carried out in established community posts. In addition,
MCP technical personnel are active in searching for febrile cases and doing blood sampling. They also collect thick blood samples, gather the forms where cases are recorded at the diagnostic posts, and deliver them to the jurisdictional headquarters laboratory. Diagnosis is carried out by microscopic observation of parasites in the blood samples stained with Giemsa.

Malaria positive samples are registered in a nominal record (Form RNC-L1), which includes patient data (name, age, gender, place of residence, name of parent or guardian in the case of children), dates (onset of symptoms, sampling, and sample observation), treatment (date when treatment began and type of treatment), whether it is a primary or secondary clinical episode, attending health personnel, and locality where the sample was taken. Treatment details are recorded on a separate form (T-1).

Database construction. A database of parasitologically confirmed *Plasmodium vivax* malaria cases was developed from RNC-L1 and T-1 forms. Information was validated and complemented with information from the record of cases by village and collated with the jurisdictional, state, and national records of NCDSIC. Without information on the objectives of the study, a computer technician codified the primary and secondary cases. The information was entered into a Microsoft Excel 2003 spreadsheet (Microsoft Corp., Redman, WA), under supervision and double entry.

**Definition and recording of cases.** A case with a single clinical episode was defined as that of a person living in the area under study with a single record (Form RNC-L1) of malaria by *P. vivax*, without previous history of the disease (before and during the period of study). A case with secondary clinical episode(s) was defined as that of an individual with more than one clinical episode, indicated by repeated records (at intervals of more than 3 weeks) of confirmed *P. vivax* malaria, in two or more occasions. Records of secondary cases were checked for consistency with the corresponding primary clinical episode registry, including, name, gender, place of residence, age, the dates of each event (primary and secondary), and dates of registries.

For each case with secondary clinical episodes, a complementary data record was constructed on the number of clinical events (*R*0, *R*1, *R*E, and *R*3: primary episode, first, second, and third secondary episodes, respectively), interval (in weeks of 7 days) between primary and secondary episodes, week of occurrence within the study period (1994–2005), and dates related to the onset of fever, blood sampling, and beginning of anti-malaria treatment.

**Treatment of malaria cases.** Two anti-malaria treatment schemes were administered during the study period. Between 1994 and 1998, febrile patients suspected of having malaria received one dose of 10 mg. chloroquine/kg of weight at the time of blood sampling, and when *P. vivax* infection was confirmed (mean interval between onset of symptoms and administration of primaquine = 23 days), they received chloroquine (25 mg/kg of weight) distributed into three daily doses (10, 10, and 5 mg/kg of weight) combined with daily 0.25 mg primaquine/kg of weight during 5 days (traditional treatment [TT] scheme) (mean interval between onset of symptoms and administration of primaquine = 20 days).

Based on previous studies on the efficacy of massive administration of a single dose of chloroquine and primaquine to control *Plasmodium falciparum* and *P. vivax* transmission, and the improved effect of intermittent doses to eliminate relapses; starting in 1999, a new therapeutic scheme was progressively introduced (Table 1) that consisted in one single

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**Table 1**

<table>
<thead>
<tr>
<th>Period*</th>
<th>Year</th>
<th>Total cases</th>
<th>Cases with secondary episodes</th>
<th>Cases treated with SRT</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total cases</td>
<td>Cases with secondary episodes</td>
<td>Cases treated with SRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>Population</td>
<td>Incidence per 1,000 habitants</td>
</tr>
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<tr>
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<td></td>
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<td></td>
<td>2004</td>
<td>871</td>
<td>3,553,065</td>
<td>0.25</td>
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<td></td>
<td>2005</td>
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<td>3,553,231</td>
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<td>Total</td>
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<td>33,414</td>
<td>7,817</td>
<td>23.40</td>
</tr>
</tbody>
</table>


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**Figure 1.** Map of the state of Oaxaca depicting the distribution of localities with malaria cases in the six sanitary jurisdictions during the study period 1994–2005.
dose of chloroquine (10 mg/kg of weight) and primaquine (0.75mg/kg of weight) administered to febrile subjects at the time of blood sampling (mean interval between onset of symptoms and administration of primaquine = 3.5 days). If \textit{P. vivax} infection was confirmed, the same treatment was administered on a monthly basis for a period of 3 months, followed by a pause of 3 months, and repeating the scheme three times per year for a period of 3 years. This single-dose-repeated treatment (SDRT) scheme is currently administered to incident malaria cases and to individuals with previous malaria history (in the previous 3 years) and their contacts in localities with active malaria transmission.

**Malaria cases with secondary episodes and associated factors.** The cohort was divided into three periods according to epidemiologic characteristics and the control interventions applied in the study area. 1) 1994–1997, the conventional vector control using indoor DDT spraying and TT treatment was applied; 2) 1998–1999, corresponding to an epidemic outbreak, when intensive anti-vectorial intervention along with an intensification of malaria case surveillance was applied; and 3) 2000–2005, when an alternative “focal control” was implemented, which included management of larval breeding sites and cleaning of vegetation around the houses with the involvement of the community. Most patients were treated with SDRT, but 4% were still treated with TT.

**Data analysis.** An exploratory analysis was conducted to describe the weekly distribution in the 1994–2005 cohort of the total number of primary and secondary malaria cases, and the intervals (in weeks) between the primary and secondary clinical episodes. This analysis included summary measures and central tendencies, and a graphic pattern examination. This was followed by an analysis to explore and describe the distribution of cases with only one (primary) episode and those with secondary episodes.

The distribution of the primary episodes (of both, single primary and with secondary episodes cases) among four seasonal periods (dry: week 50 to week 14 of the following year, transition from dry to rainy: weeks 15 to 23, rainy: weeks 24 to 40, and transition to dry: weeks 41 to 49) was researched. The distribution and the intervals between primary and secondary episodes were researched in relation to patient demographic variables (gender, age, etc.), different climates in the area, week and year, altitude and population density, control intervention periods, and treatment administered during the primary episode (dose and interval between the onset of symptoms and the administration of primaquine).

The variables associated to primary clinical episodes that presented secondary episodes afterwards in a preliminary bivariate analysis with a \( \chi^2 \) value equal or lower than 0.2 were selected and analyzed using a logistic regression model. To evaluate possible collinearity among the independent variables, \( \chi^2 \) tests were applied to evaluate the independence of qualitative variables and the linear correlation coefficient of Pearson for quantitative variables before introducing them to the model. The 1998 and 1999 cases were excluded in view of the elevated likelihood that secondary episodes were caused by re-infections resulting from the high transmission registered during those years. Furthermore, primary cases occurring in 2005 were not included in the analyses because there was no information about their possible secondary episodes occurring after the end of the research period. A multivariate logistic analysis was constructed to research factors and conditions occurring during the primary episodes associated with the risk of presenting later secondary clinical episodes. The following variables were included in the model as independent variables: age and gender of the patient, altitude (masl of up to 250, between 251 and 1,250, and > 1,250), and population in the locality of residence, season (dry, rainy, transition dry-rainy, and transition rainy-dry), week and year of occurrence of the case, interval in days between the onset of the symptoms and the beginning of treatment with primaquine, and administered treatment (TT and SDRT). All analysis were carried out at a 95% confidence level using Stata 9.2 (Stata Corporation, College Station, TX) for descriptive and statistical analysis and Excel for the registration and preparation of data.

**RESULTS**

A total of 33,414 nominal records of patients with confirmed \textit{P. vivax} infection were identified in the Malaria Control Program registry between 1994 and 2005. Of these, a total of 7,817 (23.4%) malaria cases presented secondary episodes (Table 1). Single secondary clinical episodes occurred in 7,236 cases (92.56%) and 581 and 90 patients presented two and three recurrent episodes, respectively.

The greatest proportion (53.1%) of primary episodes (17,744) happened during the outbreak of 1998 (Table 1) and of these, 37.64% presented secondary episodes. This was an atypically high proportion of recurrent episodes compared with the annual frequencies during the study period. The greatest proportion (41.33%) of malaria cases, without taking into account if they presented secondary episodes afterwards, occurred during the dry season, and of these, 33.21% presented secondary episodes (Table 2). On the other hand, the greatest proportion of secondary episodes took place during the rainy season (Table 3). The mean interval between the primary and the first (R1) secondary episode was longer during the 1994–1997 (TT) period (40.05 ± 62.79 weeks) than during the 1999–2005 (SDRT) period (27.52 ± 14.47 weeks). In 22% of cases with secondary episodes occurring during the dry season, the corresponding R1 also took place during the dry season of the same year (15%) or the following (7%) year (Table 3).

There was a decreasing trend in the incidence of malaria cases with age, but while the slope of this trend flattens in adults, the frequency of cases presenting secondary episodes reverts at older ages (Figure 2A). When compared with the group of localities at more elevated altitudes, the incidence of primary cases was higher in localities found between 250 and 1,249 masl (risk ratio [RR] = 15.01, 95% confidence interval [CI]: 14.44–15.59), and in localities below 250 masl (RR = 6.72, 95% CI: 6.47–6.99). On the other hand, the

**Table 2**

<table>
<thead>
<tr>
<th>Season</th>
<th>Total cases</th>
<th>% Of total</th>
<th>Cases with secondary episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry</td>
<td>13,809</td>
<td>41.33</td>
<td>4,586</td>
</tr>
<tr>
<td>Dry-rainy</td>
<td>6,753</td>
<td>20.21</td>
<td>1,676</td>
</tr>
<tr>
<td>Rainy</td>
<td>9,509</td>
<td>28.46</td>
<td>1,417</td>
</tr>
<tr>
<td>Rainy-dry</td>
<td>3,343</td>
<td>10.00</td>
<td>138</td>
</tr>
<tr>
<td>Total</td>
<td>33,414</td>
<td></td>
<td>7,817</td>
</tr>
</tbody>
</table>
incidence of secondary episodes (using primary cases as the base population) did not show significant statistical differences among elevation categories (Figure 2B). Although the incidence of malaria infections throughout the study period was consistently higher in males than in females (0.90 and 0.70 per 1,000 people, respectively, RR = 1.29, 95% CI: 1.26–1.31), the incidence of secondary episodes was similar for females and males (233.87 and 233.99 per 1,000 malaria cases, respectively), using primary cases as the population at risk (Figure 2C).

The bivariate logistic model indicated that the risk of secondary episodes in primary cases was three times lower (RR = 0.272, 95% CI: 0.2301–0.3214) during the 2000–2004 period than in the 1994–1997 period. Based on individually recorded treatment data, the proportion of cases that presented secondary episodes was higher (RR = 4.27, 95% CI: 3.57–5.11) in primary cases that received TT compared with those that received SDRT.

The results of exploratory analysis using the bivariate logistic model indicated a greater risk of presenting secondary episodes in primary cases that occurred during the dry season and the dry-rainy transition. No significant variation in the occurrence of secondary episodes was observed among localities of different sizes and at different altitudes.

In the multivariate logistic model, after the age adjustment, the variables associated with the occurrence of secondary episodes were primary episodes occurring during the dry season (RR = 1.68, 95% CI: 1.45–1.96) or dry-rainy season (RR = 1.46, 95% CI: 1.21–1.76) were positively associated. On the other hand, a decrease in the risk of secondary episodes (RR = 3.17, 95% CI: 2.61–3.84) was associated with TT after making adjustments to the age and season of occurrence of the primary episode.

To eliminate possible effects as a result of changes in vector control strategies after the 1998–1999 outbreak, all multivariate analyses using 2000–2005 data were repeated. As previously mentioned, primary cases that occurred in 2005 were not included in the analyses because there was no follow-up and no information available about secondary episodes. Cases treated with TT had a risk of presenting secondary episodes almost four times higher (RR = 3.99 95% CI = 1.95–8.19) than those treated with SDRT.

**DISCUSSION**

Overall, since the introduction of focal control, malaria incidence has been reduced but not eliminated in all residual transmission foci of Mexico. Malaria transmission in these foci is associated to high vector mosquito abundance. In the residual transmission focus of the Oaxaca State, mosquito abundance peaks during the dry season is propitiated by meteorological disturbances, such as the hurricane Pauline in 1997; that condition increased mosquito breeding.

The focal control main interventions are the abatement of mosquito populations through management of larval breeding sites and a new anti-malaria treatment (SDRT) based on increased and repeated doses of primaquine, aimed at reducing the parasite pool and reducing secondary clinic episodes as a result of reactivation of dormant liver parasites. The impossibility to determine which proportion of the secondary episodes corresponded to reactivation (relapses) of latent hypnozoites in the liver or to reinfections resulting from the bite of infected mosquitoes makes it difficult to distinguish the effect of the new treatment from that of the abatement of malaria transmission by lowering mosquito populations.

Several characteristics of the frequency and distribution of the recorded secondary episodes support the assumption that a significant proportion of them correspond to relapses. There was a differential seasonal distribution of primary cases (that peaked during the dry and dry-rainy seasons) and secondary episodes, which peaked during the period of lowest mosquito vector abundance (rainy season). Similarly, although the incidence of primary episodes was higher in localities situated in the areas of high vector abundance, secondary episodes did not follow this distribution. Moreover, the incidence of primary episodes was higher in men than in women (indicating different risks of infection), but the incidence of secondary episodes was similar in both genders. Additionally, the distribution of the primary cases had a tendency to diminish with age, but the secondary episodes tended to increase in the oldest age groups.
population, probably because of a decrease in the capacity to set up an immune response to block the sanguineous development of reactivated parasites. Furthermore, the analysis of cases occurring after year 2000, when the larval control was being implemented but TT and SDRT treatments coincided, indicated a higher risk of secondary episode in those patients treated with TT, further supporting an abating effect on secondary episodes incidence of the new treatment.

Several studies have documented the participation of secondary episodes in maintaining *P. vivax* transmission in endemic areas\(^18\) and in reestablishing transmission in areas with propitious conditions.\(^19,20\) Other studies have documented the inefficacy of the World Health Organization’s (WHO) 14-day primaquine treatment to achieve radical cure of vivax malaria, and higher doses have been recommend with variable results.\(^21–25\) In Mexico, since the 1960s the anti-malaria treatment scheme with 0.25 mg/kg of weight with primaquine during 14 days was shortened to 5 days, on the basis of costs and difficulties to maintain a supervised treatment during 2 weeks; this despite previous studies\(^7,26–29\) indicating the possibility of an increase in relapses with the shortened scheme. The new SDRT scheme is based on recommendations\(^12–14\) to increase its dose (from 0.50 to 0.75 mg/kg), and introduces a repeated dose strategy with the purpose of eliminating long-term relapsing.\(^10\) Primaquine affects in various degrees malaria parasites developing in the hepatic parenchyma.\(^13,14,30–32\) Its mechanism of action is not well defined, but it has been suggested that it induces the generation of free oxygen radicals or that it interferes with the parasite electron transport.\(^33\) This pharmacologic activity may be reduced as liver parasites diminish their metabolism and become hypnozoites. In our study, the decreased risk of secondary episodes associated with SDRT compared with TT may be a result of the increased dose of primaquine\(^14\) or to the timeliness of its administration (administered on the day of blood sampling in SDRT and after microscopy diagnosis in TT).

On the other hand, the highest incidence of secondary cases occurred during the outbreak of 2008, indicating that, at least in that period, localized higher transmission could produce repeated infections in a portion of the population, and we face severe limitations to distinguish reinfections from relapses. Nevertheless, our observations on secondary clinical episodes in the Oaxaca focus are indicative of the importance of repeated clinical episodes in the resilience of malaria transmission in the area, as they represent a particular portion of the population at high risk and/or that contribute to maintain the
parasite pool. In previous studies in the area, we documented that the individual risk for malaria infection was related to mosquito bites exposure, but most importantly, to the history of previous malaria cases in the same household (RM = 5.84). The results of the present study contribute more evidence for domiciliary transmission whose parasite source could be provided by subjects presenting relapses.

Besides the limitations in establishing the origin of secondary episodes, the results of this study document a decrease in their incidence after the implementation of focal control. Mosquito vector abundance seems to be under control using larval breeding management by active community participation, and insecticide (other than DDT) indoor spraying is very limited. However, vector abatement seems to be insufficient to stop malaria transmission. Our results highlight the need for better tools to identify relapses and new therapeutic schemes to radical cure Plasmodium vivax infections, as well as operational research aimed at parasite pool elimination as part of integrated malaria control interventions.

Further research is underway to assess the efficacy of SDRT as compared with TT. Concerns on a single chloroquine dose to treat malaria have been raised; preliminary results of a current prospective study in southern Mexico indicate a complete clearance of the parasitemia after the first dose of combined chloroquine and primaquine. In this study, molecular markers have been included in an attempt to document relapses, and although no hemolysis has been observed in the area or in other parts where the doses of primaquine were increased, special attention is taken to document this in treated patients. We are also evaluating the need for the repeated dose, given the difficulties to operate this scheme.

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