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**CHLOROQUINE-RESISTANT PLASMODIUM VIVAX IN TRANSMIGRATION SETTLEMENTS OF WEST KALIMANTAN, INDONESIA**

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CHLOROQUINE-RESISTANT PLASMODIUM VIVAX IN TRANSMIGRATION SETTLEMENTS OF WEST KALIMANTAN, INDONESIA

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Abstract. Malarial surveys were conducted during July 1996 in native Dayak villages and predominantly Javanese transmigration settlements in Ketapang district of West Kalimantan, Indonesia. Malaria prevalence ranged from 0.9% to 2.7% in Dayak villages and from 1% to 20% in the transmigration settlements. Plasmodium falciparum accounted for 67% of the cases among Dayaks but P. vivax was dominant among transmigrants, accounting for more than 72% of the infections. Chloroquine sensitivity/resistance was assessed by 28-day in vivo testing of uncomplicated malaria infections and measurement of chloroquine blood levels in cases where parasitemias reappeared within the 28-day test period. Resistance was based on the appearance of asexual parasites against chloroquine plus desethylchloroquine levels exceeding the minimally effective whole blood concentrations proposed for sensitive parasite strains (P. vivax, 100 ng/ml; P. falciparum, 200 ng/ml). All parasitemias cleared initially within four days of beginning supervised chloroquine therapy (25 mg base/kg over a 48-hr period), but asexual parasites reappeared within 28 days in 27 of 52 P. vivax and three of 12 P. falciparum cases. Chloroquine blood levels at the time of recurrent parasitemias revealed resistance in 12 of the 27 P. vivax cases and in one of the three P. falciparum cases. Genotypes of nine of the 12 recurrent P. vivax isolates matched with their primary isolates and ruled out reinfection. These findings establish the presence of chloroquine-resistant P. vivax on the island of Borneo. The pattern of malaria and the high frequency of chloroquine resistance by P. vivax at the West Kalimantan location may relate to demographic, ecologic, agricultural, and socioeconomic changes associated with transmigration.

Chloroquine has long been the world’s standard effective drug for prevention and treatment of vivax malaria, but resistance appears to be an emerging problem in the Indopacific region that may have already spread globally. The first report of clinical resistance came from Papua New Guinea in 19891 followed by successive reports of chloroquine-resistant vivax malaria from Irian Jaya,2-5 Myanmar,6,7 India,8 Sumatra,9 and Sulawesi.10 In the New World, chloroquine-resistant Plasmodium vivax has been described in Guyana.11

Key to making a definitive pronouncement of in vivo resistance to therapeutic levels of chloroquine is strict supervision of the appropriate dose, careful follow-up to monitor parasitemia, and demonstration of chloroquine blood levels at the time of an unremitting or recurrent parasitemia in excess of the minimally effective concentrations (MECs) established for sensitive strains of the malaria parasites (> 100 ng/ml for P. vivax; > 200 ng/ml for P. falciparum). Genetic fingerprinting can also determine whether recurrent infections arise from recrudescence/relapse of the primary infection or from a separate inoculation. These stringent criteria and the methodologies they entail are not easily met and definitive reports of chloroquine-resistant P. vivax have been slowly forthcoming. A systematic effort has been underway to detect and measure the occurrence of this problem in Indonesia. This report describes studies conducted among native Pesaguan Dayaks and non-indigenous transmigrants in West Kalimantan (Borneo), Indonesia using an in vivo test format developed at this laboratory.12 Results are presented of in vivo tests for chloroquine sensitivity/resistance, drug levels, and selective parasite genotyping from among the infected subjects that were treated.

Subjects and Methods

Study site. Kalimantan is the Indonesian name given to the island widely known as Borneo. This study was focused in West Kalimantan province, Indonesia at Ketapang (2°S, 110°E), the largest and southernmost district of the province, with an area of 35,809 km2 and an estimated population of 361,000. This district does not have abundant realized mineral and timber resources, but its climate and vast lowlands are suited to rubber and oil palm cultivation and large plantations; some in excess of one million hectares have been established. The development and production of these plantation industries have required more individuals than have been locally available and the Indonesian Ministry of Transmigration has settled thousands of landless families from crowded parts of Indonesia into Ketapang for this purpose. Government figures show that during fiscal year 1995 more transmigrants were settled into West Kalimantan than into any other province of Indonesia (33,012 of 112,069), and that the majority of these West Kalimantan transmigrants (16,081 of 33,012) were settled into Ketapang District (Indonesian Ministry of Transmigration and Resettlement, 1996, unpublished data). Most of these transmigrants (86.5%) were young, subsistence-level farmers from the relatively malaria-free provinces of Java. Families from the more malarious eastern provinces of West Nusa Tenggara and East Nusa Tenggara comprised the remaining 13.5%. Approximately half of the houses in Ketapang transmigration settlements are allocated to translocal Dayak families, but many of these indigenous people also maintain residence in their traditional villages.

Malaria is second only to respiratory infection as the most...
frequently diagnosed acute illness in West Kalimantan province, accounting for 27% of all cases of infectious illness seen in health clinics during 1995. Annual incidence of clinical malaria ranged from three (Pontianak) to 44 (Sintang) cases/1,000 residents in the seven administrative districts of the province and averaged 15 cases/1,000 in Ketapang. Malarialometric survey by active case detection during 1995 revealed that malaria point prevalence ranged from 0% (Pontianak) to 16% (Kapuas Hulu) and was 12.4% in Ketapang (West Kalimantan Department of Health, 1996, unpublished data). Entomologic surveys have identified 13 different anopheline species in West Kalimantan (Anopheles lesteri, An. lessleri, An. umbrosus, An. leucosphyrus, An. tessellatus, An. baeczi, An. nigeririnus, An. sinensis, An. barbirostris, An. balabacensis, An. kochi, An. sundaicus, and An. peditaeniatus) of which An. letteri, An. sundaicus, An. balabacensis, An. barbirostris, An. nigeririnus, and An. leucosphyrus have been incriminated or reported as vectors of malaria on the island of Borneo. Human bait collections have reportedly captured An. nigeririnus and An. sinensis from within transmigration settlements (Ketapang Department of Health, unpublished data). Recent larval collections from rice paddies, streams, and weed-choked ditches at these sites have yielded only An. nigeririnus and An. peditaeniatus (Fryauff DJ, unpublished data).

**Study subjects.** All residents of four Dayak villages (Batu Tajam I, Batu Tajam II, Marau Sinar Bulan, Sei Melayu) and five transmigrant settlements (SP-4, -5, -6, -7, and Lalan Panjang) were invited to undergo parasitologic screening for malaria by submitting a drop of blood for thick and thin film preparation. The average residence time in West Kalimantan for inhabitants of the five transmigration settlements was three months, six months, three years, four months, and five years, respectively. Individuals from these screenings who were ≥ 5 years old, had uncomplicated malaria, were able to swallow chloroquine tablets, and who had used no antimalarial drug in the previous week were invited to volunteer for the 28-day *in vivo* test. Written informed consent was obtained from the subject/parent and a description of all complaints associated with the infection was verbally elicited.

This work was conducted in accordance with U.S. Navy and Republic of Indonesia regulations governing the protection of human subjects in medical research. American and Indonesian committees for the protection of human subjects reviewed and approved the procedures followed in this research.

**Chemotherapy and follow-up.** The first-line treatment for all clinical malaria cases in Indonesia is standard chloroquine therapy combined with a 15 mg dose of primaquine on the first day. Chloroquine therapy is combined with a five-day regimen of primaquine for confirmed *P. vivax* infections. If there is no clinical improvement within the first 2–3 days, chloroquine therapy is repeated with a 14-day regimen of primaquine. Primamaquine was omitted from the malaria treatments described here to yield valid *in vivo* assessments of *P. vivax* sensitivity/resistance to chloroquine alone. Combined chloroquine and primaquine have been shown to work additively or synergistically against chloroquine-resistant strains of malaria parasites.

Enrolled study subjects were administered 25 mg of chloroquine (Resochin®, P. T. Bayer, Jakarta, Indonesia) base/kg of body weight as 10 + 10 + 5 mg/kg doses at 24-hr intervals. Consumption of each dose was witnessed by a member of the study team and physical complaints were recorded at the time of each visit. Study subjects were advised to take no other drugs but those provided to them by the study team and to immediately report any incident of drug reaction or heightened/recurrent malaria symptoms to an on-site team member. Thick and thin blood films were made on days 0, 2, 4, 7, 11, 14, 18, 21, and 28, or on any occasion of malaria-like illness. Giemsa-stained blood films were examined by light microscopy (oil-immersion 1,000× magnification) and considered negative if no asexual parasites were detected in 300 ocular fields of the thick film. Parasite counts/200 white blood cells were multiplied by a factor of 40 to estimate the parasite count/μl of blood. Standard sulfadoxine plus pyrimethamine or quinine therapy was provided for all unremitted or recurrent symptomatic infections.

**Chloroquine levels in whole blood.** Whole blood aliquots of 100 μl were collected by a heparinized capillary from fingersticks on days 0, 2, and 28, or on the day of a recurrent asexual stage parasitemia. This blood was blotted onto a disk of Whatman No. 1 filter paper (Whatman International Ltd., Maidstone, United Kingdom) and air-dried, with care taken to prevent contamination with chloroquine residues in the air or on fingers. In our Jakarta laboratory, the parent compound chloroquine and its major active metabolite desethylchloroquine were extracted with polar solvent according to published methods. Quantitative analysis of extracts was performed by means of high-performance liquid chromatography (HPLC) using a Bio-Rad model 2700 solvent delivery system, a Bio-Sil Polycl 90-10 column (Bio-Rad Laboratories, Inc., Melville, NY), and a model 1311 fluorometer III analyzer (LDC Analytical, Riviera Beach, FL) interfaced with an IBM (Yorktown Heights, NY) compatible desktop computer via Microsoft (Redmond, WA) Windows 3.0 and version 2.3 HPLC software (Bio-Rad) software. Clean mobile phase recycling was integrated into the system via an IRS 1000 integrated recovery system for liquid chromatography (Jones Chromatography USA, Inc., Lakewood, CO), and an internal standard of isopropyl chloroquine was used for calibration. In accordance with current survey methods, resistance to chloroquine therapy was based upon the appearance of a post-therapeutic asexual stage parasitemia against whole blood levels of chloroquine/desethylchloroquine > 100 ng/ml for *P. vivax* or > 200 ng/ml for *P. falciparum.**

**Genetic fingerprinting of primary and failure isolates of *P. vivax*.** The DNA was extracted from whole blood samples of paired primary and failure infections. Portions of the genes coding for the merozoite surface protein-1 and the circumsporozoite protein were amplified by polymerase chain reaction (PCR) using oligonucleotide primers synthesized to conserved sequences flanking the variable regions. The paired primary and failure PCR products were analyzed by single-stranded conformational polymorphism (SSCP) according to published methodology. Isolates from treatment failures were considered to be clones of the primary infection if the SSCP pattern of the failure isolate was the same as or contained within the SSCP pattern of the primary isolate.
Malaria prevalence. A total of 758 ethnic Dayaks and 1,450 predominantly Javanese transmigrants were screened for malaria infection. Screening prevalence ranged from 0.9% to 2.7% in the four Dayak villages (Sei Melayu, 0.9%; Batu Tajam II, 1.2%; Marau Sinar Bulan, 2.0%; and Batu Tajam I, 2.7%) and falciparum malaria accounted for 10 of the 15 cases identified in this population (67%). Malaria prevalence ranged from 1.0% to 20.0% in the five transmigrant settlements (SP-7, 1.0%; SP-5, 1.2%; SP-4, 1.7%; SP-6, 5.8%; and Lalang Panjang, 20.0%), and vivax malaria accounted for 72.2% of the 72 cases identified. The highest prevalence occurred in the oldest transmigrant settlement where numerous rice paddies and fish ponds had been established. Table 1 shows the proportions of malaria infection by species and age group in the two populations. In both populations, the majority of infections were found in children 2–15 years old (Dayaks, 10 of 290 cases; transmigrants, 16 of 25 cases). The prevalence of malaria in transmigrant children 2–15 years old (37 of 567 cases) was significantly greater (P = 0.03) than that of Dayak adults >15 years old (4 of 433 = 0.9%). Overall, malaria prevalence in transmigrants (72 of 1,450 = 5.0%) was significantly greater (P < 0.001) than in Dayaks (15 of 758 = 2.0%).

**RESULTS**

**Table 1**

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
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<tr>
<td>&lt;2</td>
<td>124</td>
<td>0</td>
<td>0</td>
<td>35</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2–5</td>
<td>270</td>
<td>3 (1g)†</td>
<td>6 (1g)</td>
<td>114</td>
<td>3 (2g)</td>
<td>1</td>
</tr>
<tr>
<td>6–10</td>
<td>212</td>
<td>5 (3g)</td>
<td>13 (1g)</td>
<td>109</td>
<td>2 (2g)</td>
<td>1</td>
</tr>
<tr>
<td>11–15</td>
<td>85</td>
<td>1</td>
<td>9 (4g)</td>
<td>67</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>16–25</td>
<td>314</td>
<td>6 (4g)</td>
<td>8 (3g)</td>
<td>113</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25–40</td>
<td>405</td>
<td>5 (3g)</td>
<td>13 (5g)</td>
<td>186</td>
<td>2 (1g)</td>
<td>0</td>
</tr>
<tr>
<td>&gt;40</td>
<td>40</td>
<td>0</td>
<td>3 (3g)</td>
<td>134</td>
<td>1</td>
<td>2‡ (1g)</td>
</tr>
<tr>
<td>Total</td>
<td>1,450</td>
<td>20 (1.4%)</td>
<td>52 (3.6%)</td>
<td>758</td>
<td>10 (1.3%)</td>
<td>6 (0.8%)</td>
</tr>
</tbody>
</table>

* P.f. = Plasmodium falciparum; P.v. = P. vivax.
† (g) denotes number of cases with gametocytes.
‡ One mixed P. falciparum + P. vivax infection.

**Table 2**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Plasmodium falciparum</th>
<th>Plasmodium vivax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number tested</td>
<td>12</td>
<td>52</td>
</tr>
<tr>
<td>Age (years)</td>
<td>25.2 (18.3–32.2)</td>
<td>24.7 (21.1–28.3)</td>
</tr>
<tr>
<td>Hemoglobin (mg/dL of blood)</td>
<td>10.4 (9.2–11.5)</td>
<td>9.6 (9.3–10.0)</td>
</tr>
<tr>
<td>GM* parasitemia (/μL of blood)</td>
<td>440 (139–1,390)</td>
<td>803 (525–1,228)</td>
</tr>
<tr>
<td>Cf† of therapeutic failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>0</td>
<td>1.9% (+1)</td>
</tr>
<tr>
<td>Day 14</td>
<td>8.3% (+1)</td>
<td>5.8% (+2)</td>
</tr>
<tr>
<td>Day 21</td>
<td>16.5% (+1)</td>
<td>34.6% (+15)</td>
</tr>
<tr>
<td>Day 28</td>
<td>25% (+1)</td>
<td>51.9% (+9)</td>
</tr>
<tr>
<td>Drug‡ levels (ng/ml of blood)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>24§</td>
<td>17§</td>
</tr>
<tr>
<td>Day 2</td>
<td>911 (687–1,133)</td>
<td>940 (807–1,073)</td>
</tr>
<tr>
<td>Day of recurrence</td>
<td>205</td>
<td>203 (156–251)</td>
</tr>
</tbody>
</table>

* Geometric mean parasitemia.
† Cumulative incidence of recurrent parasitemias.
‡ Mean mg/ml of chloroquine (CQ) + desethylchloroquine (DCQ).
§ CQ only detected in 15 of 52 subjects; CQ + DCQ detected in 3 of 52 subjects at enrollment.

**Summary of 28-day in vivo test results for chloroquine sensitive/resistant malaria in transmigration settlements of Ketapang, West Kalimantan, Indonesia, July–August 1996** (95% confidence intervals are given in parentheses)
clearance was achieved by day 2 in 72% of the cases and by day 4 in 98%. Trophozoites in steadily reducing numbers remained through day 4 in one case but cleared by day 7 and remained absent through the remaining three weeks of follow-up. Trophozoites reappeared between seven and 28 days post-therapy in 52% (27) of the *P. vivax* cases (Table 1). Gametocytes, present at the start of treatment in 31.4% of the *P. vivax* cases, disappeared with treatment and did not reappear within the 28 days of follow-up in any subject. Whole blood levels of chloroquine measured at the time of each recurrence (reinfection/recrudescence/relapse) ranged from 0 to 411 ng/ml. Fifteen parasitemias appeared between test days 18 and 28 against whole blood levels of chloroquine plus desethylchloroquine less than 100 ng/ml. Drug levels in 12 cases that recurred from seven to 21 days post-treatment (mean = 17 days) were above this MEC. Genotypic fingerprints of primary and failure isolates, which matched in eight of these cases, ruled out reinfection and indicated true treatment failure. The other four pairs were mismatches as a result of either insufficient DNA from the drug-resistant clone in the primary infection or reinfection. Whole blood chloroquine plus desethylchloroquine levels in vivax malaria subjects measured on day 2, after the first two doses of chloroquine, ranged from 187 to 2,095 ng/ml (mean = 940 ng/ml), with a 95% confidence interval around this mean of 807–1,072 ng/ml. There was no significant correlation between low day 2 drug levels and early recurrence of parasitemia (r = 0.16, P = 0.22). Low drug absorption, indicated by day 2 levels of chloroquine plus desethylchloroquine less than 500 ng/ml, was seen in seven subjects and parasitemias appeared within the 28-day follow-up period (days 14, 18, 18, 18, and 28) in five of these cases.

**DISCUSSION**

These survey results revealed distinct demographic patterns of malaria occurring in Ketapang District of West Kalimantan, Indonesia, and an unexpectedly high frequency of chloroquine resistance in *P. vivax*. The overall higher prevalence rate of malaria among transmigrants was not surprising. Most of these people came from the crowded provinces of Java where the incidence of malaria has been estimated to be less than two cases per 10,000 person-years since 1965, and were thus highly vulnerable to infection and clinical symptoms. Indonesia’s transmigration settlements are sited by design in the underpopulated and underdeveloped frontier provinces of the nation, and plans for each location allocate up to half of the new houses for members of the local ethnic population. This cross-cultural mixing is intended to introduce transmigrants to appropriate cultural practices and agricultural techniques, while benefiting the indigenous people with jobs, schools, places of worship, and a variety of government services that were previously beyond their reach. This blending inadvertently brings gametocyte carriers into proximity with the malaria naïve newcomers and may be partly responsible for explosive outbreaks that occur each year. However, this scenario was not evident in Ketapang. Although half of the houses in each Ketapang transmigration settlement were allocated to local Dayak families, many of these houses were vacant and Dayaks, if present, did not participate in our open malaria screenings. Moreover, survey within Dayak communities showed low malaria prevalence. It seems possible that the nuclei of infection in Ketapang transmigration settlements may have arisen from among the transmigrants themselves; possibly from among the hundreds of families that immigrated from the more malarious provinces of eastern Indonesia. Recent screening of 260 apparently healthy school-children from a populous district in East Nusa Tenggara (Sikka, Flores Island) showed the malaria prevalence to be 40% (Fryauff DJ, unpublished data). While chloroquine resistance characterizes more than 70% of *P. vivax* cases among transmigration settlements in Irian Jaya, it is not yet known whether there are also significant pools of chloroquine-resistant *P. vivax* circulating in the nearby provinces of East Nusa Tenggara and West Nusa Tenggara.

Environmental and cultural factors are believed to have also strongly determined the different patterns of malaria transmission at our survey sites. Dayak communities were long-established, traditional villages situated within or at the fringe of secondary forest. Their houses were more densely clustered than those of the transmigrant settlement, domestic animals were abundant, and their villages were well-shaded by diverse species of mature trees. Dayak villages also appeared to be well drained, due to their placement along swiftly flowing streams and rivers. A highly conspicuous, and perhaps critical difference between transmigrant and native communities was the Dayak’s tendency to distance their rice paddies from their homes and to grow rice by shifting cultivation in naturally occurring swamp areas. In contrast, the radically altered environment of the young palm plantation and its new settlements eliminated the original diverse populations of flora and fauna and opened the land to almost unchecked colonization by a relative few mosquito species. In the absence of either wild or domestic animals, humans are virtually the only source of blood feeding by mosquitoes in the new settlements. *Anopheles nigerimus*, which was collected as larvae from rice paddies and irrigation ditches within the Lalang Panjang settlement, has been responsible for localized malaria outbreaks when it proliferates in close proximity to large human populations and when domestic animal blood sources are scarce. The vectorial status of *An. peditaeniatus*, found in the same breeding habitats as *A. nigerimus*, is unknown, but both of these species are considered predominantly zoophilic and breed preferentially in rice paddies and open freshwater habitats exposed to the sun. Bed nets, chloroquine prophylaxis for the first 90 days, and insecticide (bendiocarb) spraying of the interior walls of each house are important government efforts that are routinely made to protect the new transmigrants. While these measures were insufficient to prevent the early and explosive malaria outbreaks seen in transmigration settlements of Irian Jaya, they may be effective during the first year in Ketapang where different transmission dynamics prevail and are only overcome in subsequent years when extensive rice cultivation and irrigation systems increase and stabilize the anopheline vector populations. This phenomenon of delayed malaria outbreak has also been observed and reported for the Satai transmigration settlement of West Kalimantan. In the more established transmigration settlements (SP-4, 3 years; Lalang Panjang, 5 years), night time elec-
Chloroquine-resistant \textit{P. vivax} in Indonesia

In summary, the results indicate that important differences characterize malaria in native Dayak and transmigrant communities of Ketapang District in West Kalimantan. Geographic, ecologic, agricultural, and socioeconomic factors may be responsible for the patterns observed. Insufficient cases of \textit{P. falciparum} were found to enable a useful or conclusive analysis of chloroquine sensitivity or resistance for this location. However, \textit{P. vivax} cases were abundant within transmigration settlements and our unexpected \textit{in vivo} test results confirmed chloroquine resistance in 23\% of the cases treated. Within Indonesia, this \textit{in vivo} testing methodology has only identified sites in Irian Jaya with higher frequencies of chloroquine resistance by \textit{P. vivax}. It is an interesting coincidence that in both Irian Jaya and Kalimantan, where high frequencies of \textit{P. vivax} resistance to chloroquine have been documented, the \textit{in vivo} test subjects at each site have been predominantly Javanese transmigrants. These results encourage additional surveys for chloroquine-resistant vivax malaria among transmigrant communities in other provinces of Indonesia.

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