

contacts with clandestine gold panners, mainly Brazilian illegal residents. This population, in which malaria incidence is almost impossible to evaluate, comes from Amapa State, where the incidence of malaria is increasing (5). In 2003, 60.9% of patients with malaria cases at Cayenne Hospital had a Brazilian name compared with 35.4% in 2000 (6). Also, the gold panners diverted the river and built basins where vectors could easily multiply (7).

Initial malaria attacks were treated with chloroquine or quinine. Five patients experienced ≥ 1 relapses (maximum 3 relapses). The relapses were treated with 50-mg daily doses of primaquine for 4 patients and by chloroquine for the fifth patient. Two patients had relapses after receiving primaquine. Primaquine resistance information was not available. However, resistance to primaquine has emerged in *P. vivax* strains (8).

We recommended that pre-impregnated battlefield uniforms be available for French policemen and chemoprophylaxis adherence be reinforced by directly observed intake by supervisory staff. Relapses of *P. vivax* malaria are a major therapeutic problem, particularly after primaquine therapy.

Acknowledgment

We thank G. Debrabander for assistance with the preparation of this article.

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Plasmodium vivax Malaria Relapses after Primaquine Prophylaxis

To the Editor: Standard treatment of patients with *Plasmodium vivax* malaria includes chloroquine, followed by primaquine terminal prophylaxis. Reports of true primaquine failure and subsequent *P. vivax* relapse are unusual; most suspected cases can be ascribed to poor patient adherence, recrudescence of a chloroquine-resistant strain, or *P. vivax* reinfection. We report a case of *P. vivax* malaria relapse after therapy with quinine, doxycycline, and primaquine, and again after treatment with chloroquine and primaquine. *P. vivax* relapses after primaquine treatment are exceedingly rare in travelers to South America and are a serious therapeutic challenge. Our patient was subsequently treated with weekly, single-dose chloroquine without recurrence of symptoms.

A 77-year-old man had fever and chills 2 weeks after returning from Brazil. These symptoms were accompanied by sweating, fatigue, and a mild, productive cough. Review of systems was notable for dark, concentrated urine and a 10-lb weight loss. The patient's 25-day journey included Salvador, Manaus, and a 2-day stay in the Amazon River basin. He did not take malaria prophylaxis during his trip.

On physical examination, the patient was afebrile with blood pressure of 90/53 mm Hg. Cardiovascular, pulmonary, and abdominal examination results were unremarkable. Several petechiae were noted on both lower extremities. Laboratory tests showed the following: leukocyte count 6,300 cells/ μ L, hemoglobin level 13.7 g/dL, platelet count 40,000 cells/ μ L, serum creatinine level 1.2 mg/dL, serum alanine aminotransferase level 63 IU/L, and serum

aspartate aminotransferase level 56 IU/L. Thick and thin peripheral blood smears revealed *P. vivax* with a parasitemia level of 0.67%. Although the existence of chloroquine-resistant *P. vivax* in Brazil is debatable, the patient was conservatively treated with quinine, 650 mg, 3×/day and doxycycline, 100 mg, 2×/day for 7 days, followed by primaquine terminal prophylaxis, 30 mg/day for 30 days with complete resolution of symptoms.

In the absence of travel abroad, the patient experienced similar symptoms 5 months later. On the basis of thick and thin peripheral blood smear examination, a relapse of *P. vivax* malaria was diagnosed. He was given chloroquine, 2.5 g over 3 days, followed by primaquine, 30 mg/day for 30 days. Again, the patient's symptoms resolved.

Four months after treatment (9 months after the initial episode), the patient experienced the abrupt onset of fever, chills, and dark urine. He had a leukocyte count of 5,900 cells/μL, a hemoglobin level of 14.0 g/dL, and a platelet count of 117,000 cells/μL. Repeat thick and thin blood smears showed *P. vivax* with a parasitemia level of 0.993%. Therapy with chloroquine was initiated (2.5 g over 3 days), and symptoms resolved. Repeat blood smears 4 days later were negative for *P. vivax*. In lieu of yet another course of terminal prophylaxis with primaquine, the patient was given chloroquine, 300 mg/week for 4 months; he has been asymptomatic for an additional 2 months.

Even before Food and Drug Administration approval of primaquine in 1951, primaquine failure was documented in experimental cases of the Chesson (tropical) *P. vivax* strain (1). Additional reports soon followed, citing dosing differences as the likely reason for *P. vivax* relapse. Baird and Hoffman summarized cases of primaquine failure over nearly 3 decades, noting that 26

(25%) of 103 patients given primaquine, 15 mg/day for 14 days, relapsed, while infection returned in only 1 (3.9%) of 26 patients given 22.5–30 mg/day (2). Among 50 patients treated for *P. vivax* malaria in Brazil, total primaquine dose per patient was the only variable in relapse; 7 relapses occurred in patients who received 2.76 mg/kg, while those who received 3.35 mg/kg remained free of infection (3). As a consequence, patients weighing >70–80 kg should receive 0.5 mg/kg/day (2).

The issue of primaquine resistance in *P. vivax* remains unresolved for several reasons. First, the organism cannot be propagated in vitro, and injection of *P. vivax* into nonhuman primates is required for analysis (4). Second, the pharmacokinetics of primaquine are poorly understood. Despite standard dose administration, 1 study suggested substantial interethnic differences in peak plasma concentrations of primaquine and its major metabolite, carboxypimaquine (5). Finally, confounding factors such as drug dosing and patient compliance have complicated most failure reports.

Our patient initially received quinine and doxycycline, which excluded a chloroquine-resistant infection. In addition, he completed a primaquine regimen of 10.8 mg/kg, which is twice the current recommended dose. In the absence of reexposure, the patient had a relapse 5 months later. His condition was treated with chloroquine and again with high-dose primaquine. He reported strict adherence to the treatment regimen, citing the fastidious use of a weekly pill box as evidence. Despite these measures, another relapse occurred 4 months later. This patient's course suggests *P. vivax* primaquine failure and possible resistance. When high-dose regimens of primaquine (total 5–6 mg/kg) fail, suppressive doses of chloroquine, 300 mg/week for several months to years may be considered. Our patient

received chloroquine therapy, 300 mg/week for the past 4 months without evidence of recurrence.

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