Imported Chloroquine-Resistant *Plasmodium vivax* in Singapore: Case Report and Literature Review

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DOI: 10.1111/j.1708-8305.2009.00376.x

Chloroquine-resistant *Plasmodium vivax* (CRPV) infection is emerging as a clinically significant problem. Detailed travel history is crucial to the management of imported malarial cases. We report a 58-year-old business traveler who returned from Indonesia and experienced relapse due to CRPV. The epidemiology and diagnostic challenges of CRPV for travel medicine clinicians are reviewed.

Malaria is a clinically important cause of febrile illness in local populations as well as in travelers in areas with endemic transmission. Among ill travelers seen at GeoSentinel sites who had returned from all destinations and had fever, malaria accounted for 21% of specific causes identified.1 Although *Plasmodium falciparum* remains the major clinical concern due to severity of illness and widespread drug resistance, there is growing awareness of the serious morbidity and emerging drug resistance associated with *Plasmodium vivax* infection.2 Chloroquine-resistant *P. vivax* (CRPV) was not reported until 1989,3 and it remains relatively uncommon except in Papua New Guinea and Indonesia. Unless a detailed travel exposure history is obtained, the risk of CRPV may not be recognized among travelers, especially those who are present in countries that are non-endemic for malaria.4,5 We report here a Singaporean permanent resident who acquired CRPV malaria while traveling on business in Indonesia.

**Case Report**

A 58-year-old Indonesian man developed fever while traveling in Jakarta, Indonesia, during April 17 to 29, 2008. He had resided in Singapore for 10 years and was otherwise healthy. He reported hospitalization in Jakarta with the diagnoses of *P. falciparum* and dengue fever, and was treated with artesunate and sulfadoxine-pyrimethamine. He had made frequent business trips to Indonesia during the previous year without antimalarial prophylaxis and had no prior episodes of malaria.

His fever recurred 30 days later on July 5, 2008. He was re-admitted on July 7, 2008 when a malaria blood film showed *P. vivax* with 0.2% parasitemia. He had been compliant with primaquine treatment and there was no travel between his June and July admissions in Singapore. He was initially re-treated with chloroquine. However, further questioning revealed that he worked as a timber merchant and his travel included trips to Kalimantan and Indonesian Papua. Given concern about his clinical relapse and CRPV, he was treated with mefloquine instead (750 mg followed by 500 mg, 12 h later). His fever resolved in 2 days and malaria blood films cleared in 3 days (Figure 1). He was discharged with instructions to complete a second course of primaquine at 30 mg per day.

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Journal of Travel Medicine 2010; Volume 17 (Issue 1): 69–71
Discussion

For many years after its introduction in 1946, chloroquine was considered first-line treatment for *P. falciparum* and *P. vivax*. As *P. falciparum* resistance to chloroquine became widespread, the use of chloroquine for treatment and prophylaxis has declined except in defined geographic areas such as Central America and the Middle East. In contrast, CRPV had been relatively rare but is increasingly reported from the Americas, Asia, and Oceania. Epidemiological data on the geographic extent of CRPV is probably not exhaustive due to technical limitations in confirming chloroquine resistance.

Although autochthonous malaria does not currently occur in Jakarta, Indonesia, data on imported malaria cases seen in Jakarta indicate that Indonesian Papua was among the most frequent destinations cited by civilian cases seen in Jakarta. Awareness of the patient’s travel to Kalimantan and Indonesian Papua for his timber business was critical in recognizing possible CRPV.

Definitive proof of CRPV would require demonstration of *P. vivax* parasitemia in the presence of plasma chloroquine levels above 10 ng/mL. This assay is not widely available or commonly used in clinical care. We have used the in vivo diagnosis proposed by Baird, defining clinical resistance as any parasitemia occurring within 35 days of standard chloroquine therapy. The rationale for this in vivo diagnosis is plasma chloroquine levels taken 35 days to fall below 10 ng/mL, the minimum effective concentration of chloroquine against *P. vivax*. At present, no genetic markers for CRPV have been identified. Recent work by Suwanarusk demonstrated two polymorphisms: the pvmdr1 Y976F mutation and an insertion in the first exon of pvcr1-o, associated with a significantly higher chloroquine inhibitory concentration. However, research is still going on to define the role of these genetic polymorphisms in CRPV.

Any diagnosis of CRPV is further complicated by the role of hypnozoites in *P. vivax* relapses. Relapse with *P. vivax* may represent failure to treat with primaquine, failure of primaquine therapy against hypnozoites, or recrudescence of blood-stage parasites resistant to chloroquine, assuming there has been no intervening exposure causing re-infection.

In this patient’s case, we were unable to confirm if the patient did have falciparum malaria while hospitalized in Jakarta. The possibilities include initial misdiagnosis of *P. vivax* as *P. falciparum*, unrecognized mixed infection with both species, or subsequent re-infection with *P. vivax*. But between his second and third hospital admissions in Singapore, these three possibilities were ruled out. The very slow clearance of his parasitemia on chloroquine (Figure 1) strongly suggests CRPV because chloroquine-sensitive *P. vivax* should become undetectable within 48 to 72 hours of initiating therapy. His relapse within 24 days of directly observed inpatient therapy consisting of chloroquine followed by primaquine eradication would confirm an in vivo diagnosis of biological resistance to chloroquine.

Given the difficulties in diagnosing CRPV prior to clinical relapse, treatment decisions rely upon careful travel exposure history and epidemiological data on emerging resistance in malarial species. The Centers for Disease Control and Prevention (CDC) currently recommends quinine sulfate plus doxycycline or mefloquine instead of chloroquine for initial treatment for *P. vivax* acquired in Indonesia or Papua New Guinea, followed by a 14-day course of primaquine for hypnozoite eradication.

There are to date relatively few clinical trials supporting recommendations for CRPV treatment regimens. In an open label trial involving 243 Javanese adults and children with falciparum and vivax malaria acquired in Indonesian Papua, mefloquine had a cumulative 28-day efficacy of 99.6% compared to 82%
for chloroquine against *P. vivax* infection, albeit with primaquine included in both arms of the study. Atovaquone/proguanil for 3 days was used to treat 16 patients with *P. vivax* and 3 patients with mixed *P. vivax* and *P. falciparum* infection with 100% response at 28 days. Artesunate combination therapy looked promising in a small trial in Indonesian Papua with 19 patients demonstrating 89.5% clinical and parasitologic response at 28 days. However, a larger recent trial in Papua New Guinea of 195 children with vivax malaria treated with different artemisinin-based combination therapies compared with conventional chloroquine-sulfadoxine-pyrimethamine (CQ-SP) demonstrated adequate clinical and parasitologic response of only 69% in the dihydroartemisinin-piperazine group compared to 13% in the CQ-SP group. In summary, CRPV is emerging as a clinically significant issue among travelers with imported malaria. Awareness of epidemiology and a detailed travel exposure are critically important to the recognition of CRPV. Mefloquine is an effective treatment for patients potentially infected with CRPV, and treatment strategies for *P. vivax* may eventually need to be reconsidered if CRPV becomes more widespread. Further research is needed to elucidate the mechanisms of resistance and to validate better prospective assays for chloroquine resistance.

Malaria prophylaxis for travel to destinations with CRPV may not require change if *P. falciparum* is the predominant clinical concern, but an expanded role for primaquine in prevention could be considered. Pre-travel advice to travelers going to such destinations should include discussion of CRPV and the risk of resistance and/or relapse.

**Declaration of Interests**

The authors state they have no conflicts of interest to declare.

**References**