Short Report: Prevalence and Chloroquine Sensitivity of *Plasmodium malariae* in Madagascar

Céline Barnadas, Arsène Ratsimbasoa, Hanitra Ranaivosoa, Didier Ralaizandry, Diamondra Raveloisèheno, Vony Rabekotonorina, Stephane Picot, and Didier Ménard*

Parasitology and Tropical Medicine, University Lyon 1, Lyon, France; Epidemiology Unit, and Malaria Unit Research, Institut Pasteur de Madagascar, Antananarivo, Madagascar

**Abstract.** We report the results of clinical studies carried out at six sites in Madagascar, between January and October 2006. The aims were (i) to update our knowledge of the burden of *Plasmodium malariae* infection and (ii) to assess the therapeutic efficacy of chloroquine for uncomplicated quartan malaria. Our findings confirm that *P. malariae* is the third leading cause of malaria, accounting for 1.1% of all malarial infections. They also demonstrate that chloroquine—currently recommended for the home management of presumed malaria in children under the age of five years and commonly used by adults—remains highly effective in patients with uncomplicated *P. malariae* infection.

*Plasmodium malariae*, one of the four species of *Plasmodium* affecting humans, is found in tropical and subtropical regions, often in sympatry with other *Plasmodium* species, as in Madagascar. Its reported prevalence varies from less than 4% to more than 20% in endemic regions.1–4 No accurate estimate of the prevalence of *P. malariae* infection worldwide is currently available, but it has been calculated that there are probably at least 60 million infections per year, based on the prevalence of *P. falciparum*5–8 and known underestimation of the prevalence of *P. malariae*.7,8 The clinical features associated with febrile bouts of *P. malariae* are generally milder than those caused by other species.6 Fever displays quartan (4-day) periodicity, parasite density is usually considerably below 1000 parasites per ml of blood, and infection is rarely life-threatening in the absence of complications, such as nephrotic syndrome.10–12

All four of the main malaria parasites affecting humans are present in Madagascar, a crossroads of African, Indo-Asian, Middle Eastern, and European civilizations. Malaria remains a serious public health problem (e.g., official data reported 1,227,632 cases of suspected malaria in 2005) and the leading cause of morbidity and mortality, especially in children under 5 years of age.13–15

No recent data concerning the prevalence and chloroquine (CQ) sensitivity of *P. malariae* have been published. CQ is the antimalarial treatment recommended by the National Malaria Control Program (NMCP) for the home management of presumed malaria (HMM) in children under 5 years of age. *P. malariae* clearance from the blood is known to take longer than that of other species after chloroquine treatment16 and two cases of resistance have been documented in south Sumatra, Indonesia.17

Recent WHO guidelines for the testing of therapeutic efficacy have not yet been applied to *P. malariae* infection. We therefore report here the results of a clinical study carried out at six sites in 2006. The aims of this study were to: (i) update our knowledge of the burden of *Plasmodium malariae* infections and (ii) assess the therapeutic efficacy of CQ for uncomplicated quartan malaria.

This clinical study, approved by the National Ethics Com-
were six male and 10 female patients (62.5%), aged from 1 to 25 years (median 4.5), with a median weight of 10.5 kg (range 5–63). All patients had had fever during the past 48 hours and none declared having taken antimalarial drugs. Neither microscopy nor real-time PCR showed mixed infections (*P. malariae* with other species). The geometric mean of asexual parasite count was 947 parasites/μL (range 250–14,000) at baseline.

None of the patients had detectable gametocytes on microscopy at day 0 or during the time of follow-up. Mean hemoglobin concentration was 9.1 g/dL on day 0, and the mean increase in hemoglobin concentration observed on day 28 (mean of individual increases in Hb) was 1.0 g/dL.

Fifteen patients successfully cleared *P. malariae* parasitemia after CQ treatment. One case was excluded on day 28 because *P. falciparum* parasites were detected on a blood smear (confirmed by real-time PCR). Microscopy showed parasite clearance before day 7 in all patients. However, real-time PCR showed parasites to be present in the blood, as described for diagnosis in one patient, and this patient displayed clearance between days 7 and 14 (Figure 2).

Our data confirm that *P. malariae* is the third leading cause of malaria in Madagascar after *P. falciparum* and *P. vivax*. No *P. ovale* parasites were observed due to the very low prevalence of this species in Madagascar.

The prevalence of *P. malariae*, estimated at 1.1% of all malaria infections, was higher in the Western and the Central Highlands areas. This prevalence was most probably underestimated by using RDT based on pLDH detection for malaria diagnosis. According to our previous study, its sensibility was estimated at 88.9–100% for parasitemias between 500 to 5000 non-*P. falciparum* parasites/μL and at 50.0% when the number of parasites detected with microscopy falls below 100 parasites/μL. Previous studies also reported a heterogeneous distribution of this species according to season, transmission rate, and location: 1% of malaria infections in Analamiranga (western foothill area of the Highlands) to 8.5% in Andasibe (eastern foothill area of the Highlands) and 12.3% at Sainte Marie (island east of the main island of Madagascar).

Our study provides the first demonstration that CQ is highly effective against uncomplicated *P. malariae* infection in Madagascar. Three days of CQ treatment gave a clinical and parasitological cure rate of 100% by day 28 and a mean increase in hemoglobin concentration of 1 g/dL over the study period, whereas CQ is only effective in 55.6% of cases of uncomplicated *P. falciparum* malaria and in 89.7% of *P. vivax* malaria cases. The NMCP has revised its treatment policy since December 2005, replacing CQ with artemisinin-based combination therapy (AQ+AS, artesunate plus amodiaquine), with the support of the Global Fund. However, ACT treatment is used in only 31 of the 111 health districts in Madagascar.
Eastern Madagascar, CQ remains the drug most widely available (distribution and financial criteria) and is the first drug used in most of areas in Madagascar, particularly in the prepackaged PaluStop® form, sold at an affordable price (US $0.025), or as Ody Tazomoka®, distributed free at primary public health facilities.²⁷ Obviously, with the progressive implementation of the artemisinin-based combination therapy, which is effective in treating malaria infections,²⁷ an approach that does not consider Plasmodium species seems to be the most suitable policy treatment at the primary health-care facilities level in a country where material and human resources to perform a species-specific diagnosis are lacking.

In conclusion, our findings demonstrate that oral CQ, which is commonly used, remains highly effective in patients with uncomplicated P. malariae infection, the third leading cause of malaria in Madagascar.

Received April 30, 2007. Accepted for publication July 2, 2007.

Acknowledgments: We thank the patients and healthcare workers involved in the national network for the surveillance of malaria resistance in Madagascar (Réseau d’Etude de la Résistance, RER) from which these samples were derived, and the staff of the Ministry of Health of Madagascar for their collaboration.

Financial support: This work was supported by a grant from the French Ministry of Foreign Affairs, FSP/RAI 2001-168 project. The collection of samples was supported by funding from the Global Fund project for Madagascar round 3 (Community Action to Roll Back Malaria, Grant number: MDG-304-G05-M).

Disclosure: C. Barnadas is a graduate PhD student supported by the Fondation Jeunesse Internationale (Fondation de France), bioMérieux “Prix bioMérieux infectiologie 2006” and Association des Internes et Anciens Internes en Pharmacie des Hôpitaux de Lyon “Prix R. Rizard.”

Authors’ addresses: Céline Barnadas and Stephen Picot, Parasitology and Tropical Medicine, University Lyon 1, Lyon, France. Arsène Ratsimbaoa, Epidemiology Unit, Institut Pasteur de Madagascar, Antananarivo, Madagascar. Hanitra Ranavisoa, Didier Ralazandry, Diamandra Ravelosiochein, Vony Rabekotonorina, and Didier Ménard, Malaria Unit Research, Institut Pasteur de Madagascar, Antananarivo, Madagascar.

Reprint requests: Didier Ménard, Malaria Research Unit, Institut Pasteur de Madagascar, BP 1274-Antananarivo 101. E-mail: dmenard@pasteur.mg

REFERENCES

24. Menard D, Nina Harimanana Andrianina N, Ramindrasoa Z, Randriamantana A, Rasoirialao N, Jahevitra M, Tusco L,

