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Chloroquine-resistant *Plasmodium malariae* in south Sumatra, Indonesia

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Oral chloroquine is the treatment of choice for uncomplicated *Plasmodium malariae* infections worldwide. We did a prospective 28-day in-vivo assessment of the efficacy of chloroquine for treatment of *P malariae* on Legundi Island in Lampung Bay, Sumatra, Indonesia. Of 28 patients, one had recurrent parasitaemia on day 28, and two had persistent parasitaemia to day 8. Whole-blood chloroquine and desethylchloroquine concentrations were at ordinarily effective levels (≥100 μg/L) on day 8 in both cases of persistent parasitaemia. These findings suggest that clinical resistance to chloroquine by *P malariae* occurs in the Indonesian archipelago of southeast Asia.

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*Plasmodium malariae* causes quartan malaria—an important re-emerging parasitic disease around the globe. Although well described in eastern Indonesia and common in Java and Sumatra during the early 20th century, we have found no recent record of *P malariae* in the western Indonesian archipelago. Oral chloroquine remains the treatment of choice for uncomplicated quartan malaria, and although chloroquine therapy for *Plasmodium falciparum* and *Plasmodium vivax* infections in Indonesia often fails, *P malariae* is presumed sensitive to chloroquine, and resistance has not been documented.

In August, 2000, we identified a focus of *P malariae* on the island of Legundi in Lampung Bay near the southernmost tip of Sumatra at the Sunda Strait. Since chloroquine use is heavy in this area, we aimed to find out whether chloroquine resistance could develop in *P malariae*. Infected individuals were identified by a cross-sectional prevalence survey for malaria, and were enrolled in a 28-day in-vivo test of resistance to chloroquine. Patients were treated with the standard chloroquine regimen, in accordance with a protocol approved by the United States Naval Medical Research Unit Institutional...
We therefore considered *P falciparum* and *P vivax*. At the two primary villages of Selesung and Keramat, prevalence was 15% (59/408) and 23% (56/247), respectively. *P malariae* was the most common species at both locations, accounting for 41% (24/59) in Selesung and 39% (22/56) of positive smears in Keramat. Spleen rates and average enlarged spleen (AES) indices among children (2–9 years) were 68% (59/87; AES 1.8) in Selesung and 81% (43/53; AES 2.7) in Keramat.

Among 47 patients with *P malariae* infection in the prevalence survey, we enrolled 28 in the test of resistance to chloroquine. 15 were male and 13 were female, and ages ranged from 6 to 65 years (mean 13). Four patients had mixed *P malariae* and *P vivax* infections. One declined further participation after day 2, which left 27 individuals who successfully completed the test. The mean asexual parasite count was 220 µL (range 40–1120) at baseline. Only one patient had detectable *P malariae* gametocytes. The blood of 18 individuals had evidence of chloroquine and its major metabolite desethyl-chloroquine before treatment (mean concentration 142.5 µg/L [SD 116.5]), which suggested that island residents practised routine self-administration of chloroquine.

All but two of the 28 enrolled patients cleared *P malariae* parasitaemia after treatment. The mean time to asexual-stage parasite clearance in 24 of 26 individuals who initially cleared parasitaemia, irrespective of eventual outcome, was 2 days (range 1–4). The times to clearance could not be determined in the other two patients. In both cases, parasitaemia was still present on day 4, but the patients did not undergo another malaria smear until day 7 in 1 case and day 13 in the other, at which time malaria smears were negative for parasites. 18 of the 27 individuals who completed the test remained parasite-free on day 28. During follow-up, six patients developed asexual-stage parasitaemia with a species other than *P malariae*: three with *P falciparum* on day 18, one with *P vivax* on day 21, and two with *P vivax* on day 28. These cases represented intercurrent infections with a different species or possibly relapse in cases of *P vivax* infection.

Of the three remaining patients, two had persistent *P malariae* parasitaemia to day 8, and one had recurrent parasitaemia on day 28. The 28-day cumulative incidence of therapeutic failure was 12% by life-table (actuarial) analysis. Thick-smear asexual parasite counts (per µL) for the two patients with persistent parasitaemia on days 0, 1, 2, 3, 4, 7, and 8 were 520, 120, not done, not done, 80, 80, 40; and 520, 240, 40, 80, 80, 80, 80, respectively. In the same two individuals, day 2 chloroquine and desethylchloroquine concentrations were 205 µg/L and 680 µg/L, respectively. Just before rescue therapy with pyrimethamine-sulfadoxine on day 8, their chloroquine and desethylchloroquine concentrations were 100 µg/L and 142·5 µg/L [SD 116·5], respectively.
natural infection, time to parasite clearance did not exceed 2 days. Collins and colleagues reported 13 chloroquine-treated experimental P malariae infections with parasite clearance times ranging from 1 to 7 days. However, these were experimental infections, many of which were managed by low-dose quinine sulphate for several months before definitive treatment with chloroquine, and in most cases, patients received only a single dose of 600 mg chloroquine base rather than a standard 3-day regimen. Those parasite clearance times cannot therefore be compared with those in naturally infected patients treated with the standard 3-day course of chloroquine. The presence of early ring-form parasites as late as day 8 (figure 1) also suggests ongoing schizogony. The persistence of healthy asexual-stage parasitaemia to day 8 after adequate chloroquine absorption and in the presence of ordinarily effective chloroquine and desethylchloroquine concentrations is highly suggestive of resistance to chloroquine by P malariae.

Health-care providers could encounter patients with uncomplicated P malariae infection that proves unresponsive to the recommended chloroquine regimen. Further assessment of chloroquine-resistant P malariae at other locations around the world is needed, particularly in areas where indiscriminate chloroquine use is common and could lead to inadequate dosing and selection for resistant organisms.

Contributors
J Maguire was the principal investigator, project coordinator, and main author, and contributed to data interpretation; I W Sumawinata was a team field physician; S Masbar was a microbiologist and field logistical coordinator; B Laksana was the high-performance liquid chromatography technologist and laboratory supervisor; P Prodjodipuro was the senior expert microbiologist; A I Susanti was the principal PCR technologist; P Sismadi was the Indonesian Ministry of Health coordinator and a team field physician; N Mahmud was the district health office project coordinator; M J Bangs was the team field supervisor; and K Baird coordinated the implementation of the technology at NAMRU-2 and contributed to data interpretation.

Conflict of interest statement
None declared.

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