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Susceptibility of human *Plasmodium knowlesi* infections to anti-malarials

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Abstract

Background: Evidence suggests that *Plasmodium knowlesi* malaria in Sarawak, Malaysian Borneo remains zoonotic, meaning anti-malarial drug resistance is unlikely to have developed in the absence of drug selection pressure. Therefore, adequate response to available anti-malarial treatments is assumed.

Methods: Here the *ex vivo* sensitivity of human *P. knowlesi* isolates in Malaysian Borneo were studied, using a WHO schizont maturation assay modified to accommodate the quotidian life cycle of this parasite. The *in vitro* sensitivities of *P. knowlesi* H strain adapted from a primate infection to *in vitro* culture (by measuring the production of *Plasmodium* lactate dehydrogenase) were also examined together with some assays using *Plasmodium falciparum* and *Plasmodium vivax*.

Results: *Plasmodium knowlesi* is uniformly highly sensitive to artemisinins, variably and moderately sensitive to chloroquine, and less sensitive to mefloquine.

Conclusions: Taken together with reports of clinical failures when *P. knowlesi* is treated with mefloquine, the data suggest that caution is required if using mefloquine in prevention or treatment of *P. knowlesi* infections, until further studies are undertaken.

Keywords: Artemisinin, Artemether, Artesunate, Dihydroartemisinin, DHA, Chloroquine, Mefloquine, Malaria

Background

From its natural simian hosts in Southeast Asia, *Plasmodium knowlesi* has emerged as a significant human pathogen, particularly in Malaysian Borneo [1-3]. Human *P. knowlesi* infections cause febrile illnesses that can rapidly progress to severe and sometimes fatal outcomes [4]. Ominously, the incidence of *P. knowlesi* malaria is increasing in geographic areas where *Plasmodium falciparum* and *Plasmodium vivax* are coming under control, thereby threatening the aim of eliminating malaria [5]. Determining the efficacy of conventional anti-malarials against *P. knowlesi* is a priority, particularly as there are no reports of anti-malarials assessed against human isolates of *P. knowlesi ex vivo*.

Here, the drug sensitivity profiles of *P. knowlesi* isolates obtained from patients being recruited into a study of the pathophysiology of knowlesi malaria in an endemic area of Sarawak, Malaysian Borneo were investigated. Currently, the WHO recommends artemisinin-based combination therapy (ACT) as first-line treatment for malaria in most endemic areas, so artemisinin and its clinically useful derivatives artesunate, dihydroartemisinin (DHA) and artemether were tested. Mefloquine, used as a partner drug in certain artemisinin-based combinations and in prophylaxis against malaria, and chloroquine that is recommended for treatment of *Plasmodium malariae* (the species which *P. knowlesi* is often confused with when diagnosed by microscopy) were also included. In addition, results from *P. falciparum* and *P. vivax* studied contemporaneously are presented, together with those obtained with the H strain laboratory isolate of *P. knowlesi* (cultured *in vitro* in rhesus erythrocytes) to confirm the methodologies used. Insights into the drug susceptibility patterns of this important emerging parasite, may prove useful in guiding

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