More than 40% of the world population is at risk for malaria caused by *Plasmodium vivax* [1]. Because this parasite rarely causes severe disease in travelers or populations in temperate climates, it has been regarded as a relatively benign infection. We now know that this is not the case; in the tropics, vivax malaria can be severe and fatal [2]. Moreover, *P. vivax* has a persistent liver stage that can cause relapses many months or even years after the initial infection, and these hypnozoites can only be eliminated by additional treatment with primaquine. Treatment to accomplish radical cure of these hypnozoites is complicated by several factors that continue to elude scientific resolution. Most important, the 14-day primaquine treatment for relapse is unreliable, and patients with G6PD-deficiency are susceptible to primaquine toxicity and the additional risk of hemolysis [3]. The complexity of the biology and treatment of *P. vivax* have discouraged research, and this relative paucity of studies means that the public health impact of vivax malaria has been seriously underappreciated.

Until recently, chloroquine was generally effective as treatment for clinical episodes of vivax, but chloroquine resistance is prevalent and increasing in Oceania, Indonesia, and Peru [4]. Sulfadoxine-pyrimethamine (Fansidar) has not been the recommended treatment for vivax, but outside of Africa, patients are frequently infected with both *P. vivax* and *P. falciparum*, so extensive use of this agent to treat falciparum malaria has also selected resistance to both sulfadoxine and pyrimethamine, at least in Southeast Asia [5, 6].

Clearly, drug-resistant vivax malaria has become a pressing issue in the control of this disease. Given the urgent need for new vivax treatments, the report in this issue of the *Journal* by Mallika Imwong and her colleagues [7] presents some encouraging news. This group has shown that the antifolate drug methotrexate (MTX), an inhibitor of the enzyme dihydrofolate reductase (DHFR), is also a potent inhibitor of *P. vivax* DHFR. MTX has long been used at high doses in anticancer therapy, but it is also used at much lower doses as long-term treatment for rheumatoid arthritis. At these lower doses, the drug is well tolerated even over very long periods [8]. Dr. Imwong and her colleagues have used a novel in vitro system [9] to show that *P. vivax* growth is inhibited by MTX in the low nanomolar range, well within the concentrations that are known to be nontoxic in rheumatoid arthritis patients. This very high level of efficacy was observed even in the presence of physiological concentrations of folate cofactors that one might expect to compete with MTX activity. In addition, the group studied parasites from Thai patients who carried alleles of *P. vivax dhfr* that have been shown to confer extremely high resistance to pyrimethamine, another DHFR inhibitor [5]. Therefore, these findings strongly suggest that methotrexate would be highly efficacious against the vivax parasite in the human host.

In the tropics outside Africa, many patients are infected with both *vivax* and *falciparum* species. There is a growing awareness of the need for a unified treatment strategy: drug combinations that would be effective against both species. Artesunate-mefloquine and dihydroartemisinin-piperaquine are the best current candidates for such a unified treatment, a strategy that is currently being studied [10, 11]. It has already been shown that MTX is extremely effective against *P. falciparum* in vitro [12, 13], so MTX in combination with artesunate, dihydroartemisinin, or a novel partner can now be added to the short list of drugs that might be useful for such a unified treatment. The study by Imwong and her colleagues [7] is the first very positive step in that direction.
References