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Real-World Therapies and the Problem of Vivax Malaria

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Wellems and Miller[1] wrote of two worlds of malaria: one, of the residents of rural tropical areas in which the disease is endemic, and the other, of travelers to those areas, who typically have greater resources. The distinction is sharp, valid, and important in considering the development of tools to combat the global burden of malaria. Drugs considered safe and effective in one world may not be so in the other.[2] The majority of the hundreds of millions of people in whom malaria will develop over the next year will obtain and consume antimalarial medication without medical supervision. Although the licensing of complex or poorly tolerated therapeutic regimens requiring clinical screening for contraindications may be perfectly suitable for populations with access to close clinical supervision, distributing the same regimen in the rural tropics is reckless.

Two other worlds of malaria are those with and without endemic *Plasmodium vivax*. Vivax malaria was known as "benign tertian malaria" for more than a century and is still viewed as rarely dangerous; evidence suggests a historical underestimation of both the burden of disease and the potential for death with *P. vivax* infection.[3-7] Endemic vivax malaria occurs throughout the tropics, except where there is a natural absence of anopheline mosquitoes (east of Vanuatu in the South Pacific) or among populations lacking the Duffy receptor on red cells (in much of Africa). Vivax malaria stands alone among the plasmodia infecting humans in its capacity to reach well into the temperate latitudes, as it does today — up to the Korean peninsula and across the southern temperate latitudes of Asia to the Mediterranean Sea. Approximately 2.6 billion people are at risk, and estimates of annual infections range from 70 to 390 million,[3,4] with about 80% occurring in South and Southeast Asia. Vivax malaria accounts for at least 70% of the malaria burden in the Americas.

Objective examination of the clinical evidence underpinning available therapies for *P. vivax* infection reveals a conspicuous neglect of this parasite.[5] More importantly, the analytical tools for critically assessing experimental or standard therapies may be considered insufficient, at best, for the task of identifying the treatments that are safe and effective and capable of reducing the disease burden of vivax malaria.

The distinction between the worlds of malaria with and without *P. vivax* finds expression in the study by Karunajeewa et al.[8] (Australian New Zealand Clinical Trials Registry number, ACTRN12605000550606) reported in this issue of the *Journal*. This state-of-the-art clinical trial evaluates the safety, tolerability, and efficacy of therapeutic options among young children exposed to endemic falciparum and vivax malaria in Papua New Guinea. By virtue of the analytical tools applied, the findings with regard to *P. falciparum* provide useful insights. The estimated 88% efficacy of dihydroartemisinin–piperaquine falls well below other estimates of efficacy for this combination against this parasite. The authors point to both suboptimal absorption of piperaquine and to cross-resistance between chloroquine and piperaquine by local parasites in vitro as a possible basis for the relatively poor performance of the drug combination. Their carefully assembled evidence makes a compelling case for the selection of artemether–lumefantrine for treatment of uncomplicated falciparum malaria in northwestern Papua New Guinea.

The authors have much less analytical leverage with regard to the data on *P. vivax*, however. The liver stage of *P. vivax* responsible for relapse (the hypnozoite) casts a nearly opaque shadow of ambiguity across the data. The curve showing occurrences of recrudescent infection provides almost no useful information for discerning the advantage of one therapeutic option over another:

all appear highly effective in the week after treatment and uniformly poor thereafter. Dihydroartemisinin–piperaquine appears to be the least inadequate of the four, but this may be an illusion created by successfully suppressed relapse. The authors did not correct the data for post-therapy reinfection or relapse using a polymerase-chain-reaction (PCR) assay, because no existing assay can achieve such a correction. Nor did they examine parasite responses to these drugs in vitro, because no standardized protocol for doing so exists, and experimental protocols yield findings that are notoriously difficult to interpret.[9,10] The authors cannot assign an attributable risk of reinfection as compared with relapse among their subjects, because there are no baseline data for doing so. Even if the authors had applied primaquine against hypnozoites, the only drug currently approved and available for this use, they could not have assumed its good efficacy, because there are no data to support that contention.

The data presented by Karunajeewa et al. should nonetheless alert public health and health care providers alike to the substantial health burden imposed by hypnozoites. One third of the children with *P. falciparum* infection in this study had recurrent *P. falciparum* parasitemia within 42 days after the start of treatment. Almost two thirds of those cases proved to be reinfections, suggesting a 6-week cumulative incidence of new infections of about 20%. Incidence-density studies in nearby Western New Guinea consistently found new *P. falciparum* infections to outnumber new *P. vivax* infections by about 2:1.[11,12] The 6-week cumulative incidence of new *P. vivax* infections in the study by Karunajeewa et al. may be thus crudely estimated at less than 10%, whereas the realized cumulative incidence of recurrent *P. vivax* parasitemia was about 65%. During the follow-up period, *P. vivax* parasitemia developed in almost half of the subjects treated for acute falciparum malaria. The hypnozoite appears to be the overwhelmingly dominant source of new parasitemia and the consequent opportunities for disease and further transmission.

For operational malarial control, attacking the hypnozoite may be more effective in relieving disease burdens than measures minimizing human contact with anopheline mosquitoes. What can be said of primaquine, the only drug available for eliminating this source of vivax malaria? Primaquine has been in continuous use for more than 50 years. Standard therapy is implemented over 14 days. Good tolerability requires that a snack or meal be taken with the drug. Safe administration requires that pregnancy and glucose-6-phosphate dehydrogenase deficiency are ruled out, by means of clinical and laboratory screening. Mechanisms of the drug's toxicity and activity are not known. There is no standardized means of gauging its efficacy against hypnozoites. No body of current clinical data show that it has good efficacy in the field, and it may have no efficacy against hypnozoites unless administered with an appropriate companion drug.[13-15]

The inadequacy of primaquine and its critical importance in attacking vivax malaria symbolizes the technical poverty of the malaria world that includes *P. vivax*. If we are to remove the barriers separating the two worlds of malaria identified by Wellems and Miller, we must deal with the control of vivax malaria, and perhaps its eradication. It seems likely that this will prove unmanageable without a safe, practical, and effective therapy aimed at the hypnozoite.

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