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Real-World Therapies and the Problem of Vivax Malaria

J. Kevin Baird, Ph.D.

Wellems and Miller 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. 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. Enzyme 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, 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. 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. (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. Dihydro- 
artemisinin–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 ex-
amine 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 re-
infection as compared with relapse among their 
subjects, because there are no baseline data for 
doing so. Even if the authors had applied pri-
maquine against hypnozoites, the only drug cur-
rently 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 bur-
den 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 two cases proved to be reinfections, 
suggesting a 6-week cumulative incidence of new 
infections of about 20%. Incidence-density stud-
ies 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 in-
fecions in the study by Karunajeewa et al. may be 
thus crudely estimated at less than 10%, where-
as 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 hu-
man contact with anopheline mosquitoes. What 
can be said of primaquine, the only drug avail-
able for eliminating this source of vivax malaria? 
Primaquine has been in continuous use for more 
than 50 years. Standard therapy is implemented 
on 14 days. Good tolerability requires that a 
meal be taken with the drug. Safe ad-
ministration requires that pregnancy and glucose-
6-phosphate dehydrogenase deficiency are ruled 
out, by means of clinical and laboratory screen-
ing. 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 ef-
ficacy 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 eradica-
tion. It seems likely that this will prove unman-
ageable without a safe, practical, and effective 
therapy aimed at the hypnozoite.

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