



Editorial

Rational malaria chemoprophylaxis – The position of primaquine



“The scientific spirit is of more value than its products, and irrationally held truths may be more harmful than reasoned errors.”
Thomas Henry Huxley

Rational thought or actions accord with reason and logic, and, certainly in the realm of science, verifiable evidence underpins those attributes. This issue of *Travel Medicine and Infectious Diseases* offers a meta-analysis of a series of clinical trials of primaquine chemoprophylaxis reported 15–24 years ago [1]. Re-examining this evidence today serves the important purpose of considering the primacy of suppressive chemoprophylaxis strategies in the context of profoundly evolved views on the character of infection by the human malaria parasite *Plasmodium vivax*. The communities of science, medicine, and public health long regarded this species as intrinsically benign and relatively inconsequential. Strategies for chemoprophylaxis against malaria reflected this view – suppressive drugs dominated practice despite poor suitability for preventing attacks of vivax malaria following travel. Work over the past decade reveals *P. vivax* as often pernicious and threatening and prompts broad reconsideration of what have been ineffective strategies for the diagnosis, treatment, control, and chemoprophylaxis of this infection of many millions [2].

1. Historical perspective on mode of chemoprophylaxis

Suppressive prophylaxis against malaria kills asexual parasites attempting development in erythrocytes whereas causal prophylaxis kills asexual parasites attempting development in hepatocytes. Most suppressive drugs have no impact on hepatic stages, and causal drugs may not impact erythrocytic stages. The only currently available drug known to have broad good efficacy in causal prophylaxis is primaquine, but it is not recommended as chemoprophylaxis for travelers except as a last resort or under special circumstances. Authoritative advice for travelers instead uniformly offers several suppressive chemoprophylaxis options [3].

The primacy of suppressive chemoprophylaxis strategy for travelers dates back to at least the clinical availability of chloroquine in 1946, or its closely related immediate predecessor, atabrine (or mepacrine or quinacrine) widely used to prevent malaria in Allied forces during World War II. The US military developers of primaquine evaluated and understood its abilities as a causal prophylactic when administered daily at 0.5 mg/kg, or weekly at 0.75 mg/kg in conjunction with a suppressive drug. The several million US service

men and women serving in the Vietnam War of the 1960s and 1970s took a weekly “CP” pill containing 300mg chloroquine (to suppress acute attacks) and 45mg primaquine (to prevent the seeding of the liver by the hypnozoites of *P. vivax*). The war-spurred and rushed CP strategy lacked randomized controlled trials of efficacy, but it became widely perceived as a failure because many thousands of US soldiers suffered relapses of vivax malaria after repatriation. The strategy was ultimately abandoned and never saw broad civilian use. Weekly chloroquine suppressive prophylaxis followed by a regimen of presumptive anti-relapse therapy (PART) with primaquine (then called terminal prophylaxis, today called post-travel PART) dominated travel medicine practice for decades.

As chloroquine resistance by *P. falciparum* surged during the 1970s and 1980s, its use as the frontline chemoprophylaxis option waned and finally vanished. Drugs like weekly mefloquine and daily doxycycline became widely used by travelers in this era. During the early 1990s the US Navy and others began gathering old and new evidence for primaquine as primary causal prophylaxis against malaria in travelers [4]. Clinical trials in the same era validated daily atovaquone-proguanil (Malarone™, GlaxoSmithKline®, UK) as effective chemoprophylaxis and today this product dominates as an option favored by travel medicine providers. As with chloroquine in the 1940s and 1950s, a half-century later Malarone™ as chemoprophylaxis overshadowed and buried the later efforts to bring primaquine causal prophylaxis to mainstream practice.

2. Pernicious vivax malaria

Contemporary malariology of the 1990s and early 2000s espoused distinctly trivializing views on the malaria caused by *P. vivax* (along with *Plasmodium ovale* and *Plasmodium malariae*, the so-called non-falciparum malarias). Vivax malaria was then widely viewed as an intrinsically self-limiting, mild, and very rarely fatal infection. Chloroquine and primaquine radical cure was believed to be widely available, affordable, efficacious, and relatively safe even without screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency. The malaria caused by *P. falciparum*, the malignant one, commanded our attention, energies and strategies. Clinical medicine, science, and public health narrowly focused on that species to the almost complete neglect of the others [5]. Clinical, laboratory, and epidemiological evidence gathered since have either challenged or upended the entrenched dogma of vivax malaria as a benign infection, depending upon how one views the thoroughness of that evidence [6]. A diagnosis of *P. vivax* comes

with risk of severe anemia or thrombocytopenia, acute respiratory distress, renal or hepatic dysfunction, seizures or coma, and shock. Although the frequency, rapidity, and circumstances under which *P. vivax* deteriorates to severe malaria syndromes associated with fatal outcomes remain poorly defined, that it sometimes does so is confirmed and beyond rational refutation. The notion of malignant and benign species of plasmodia should be considered a dangerous fallacy. All of them seriously threaten the non-immune patient.

3. Reasoned chemoprophylaxis strategy

The ability of *P. vivax* to cause attacks in the months following exposure despite successful suppressive chemoprophylaxis is widely known and grounded in reason and firm evidence [7]. Likewise, as the evidence analyzed in the current report in this journal affirms [1], daily primaquine causal prophylaxis during exposure effectively prevents those attacks. The task for experts and the practitioners they advise is to weigh the risks and benefits of any given malaria prevention strategy for individual travelers. The view of *P. falciparum* as the utmost threat to travelers against a backdrop of seemingly inconsequential *P. vivax* or *P. ovale* malarias tilted the scales of risk and benefit in favor of suppressive prevention strategies. The many distinct advantages of daily primaquine causal prophylaxis nonetheless come with the necessity of daily dosing, contraindication in pregnancy and early infancy, the absolute requirement for screening against G6PD deficiency, risk of failure with naturally occurring human cytochrome P-450 2D6 isozyme polymorphisms, and the necessity of off-label prescribing [3]. These disadvantages have historically outweighed the risk of post-travel attacks by the relapsing malarias.

The G6PD screening obstacle to safe access has been eased by the recent availability of point-of-care diagnostics of relatively modest commercial cost (about USD 15 per test) [3]. Those evaluate whole blood G6PD enzyme activity phenotype independently of the great variability in deficient genotypes, reliably (100% sensitivity) detecting male hemizygotes and female homozygotes and heterozygotes with <30% of normal activity. Female heterozygotes having >30% activity may be classified as G6PD normal and caution or quantitative testing is warranted for them (>70% of normal activity probably relatively safe). While failure of primaquine due to poor metabolizer CYP2D6 polymorphisms must be considered, none of the trials evaluated [1] screened against those and the reported measures of prophylactic efficacy included this factor. Population frequencies of disabling alleles have not been widely measured, but 1%–10% may be a reasoned forecast [3]. Daily primaquine for prophylaxis ranging from 12 to 50 weeks was safe, remarkably well tolerated, and highly effective against *P. falciparum* and *P. vivax* in non-pregnant, G6PD-normal children and adults exposed in endemic areas of Asia, South America, and Africa [1].

The key issue today is a practical, scientific, and clinical weighing of evidence that includes the reality of post-travel clinical attacks unless actively prevented by applying primaquine as primary or terminal prophylaxis following suppressive chemoprophylaxis. Although Malarone exerts causal activity against liver stages of *P. falciparum*, this activity against *P. vivax* is not known and merits much more investigative attention than it has received.

Both *P. vivax* and *P. ovale* occur wherever there is *P. falciparum* malaria (with only rare exceptions, e.g., Haiti), and, like *P. falciparum*, sometime deteriorate to life-threatening severe malaria syndromes associated with death [8–10]. Experts and providers of travel medicine services may rationally exclude the reasoned error of benign *vivax* and *ovale* malarias in weighing the complex factors guiding recommendations for prescribing drugs that protect travelers from the malarias. As with all chemoprophylaxis options, daily primaquine is imperfect in most and prohibited in some, but unlike others, it effectively solves the difficult problem of post-travel *P. vivax* and *P. ovale* attacks.

Conflict of interest

The author conducted several of the trials summarized in reference #1 but holds no financial interest in any relevant diagnostic device or antimalarial drug, or any companies that produce these products. The author receives research support funding from GlaxoSmithKline in the United Kingdom for clinical trials of the experimental 8-aminoquinoline drug tafenoquine for radical cure of *P. vivax* malaria.

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