

## Editorial

### Drug-Free Holidays: Pre-Travel versus During Travel Malaria Chemoprophylaxis

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**Abstract.** Although efficacious forms of malaria chemoprophylaxis currently exist, many travelers to malaria-endemic areas fail to use them effectively. We suggest that taking anti-malarial medications prior to travel may prevent more malaria by improving compliance. Treatment regimens of antimalarial drugs taken prior to travel could protect persons for up to one month of exposure. We urge additional testing of pre-travel malaria chemoprophylaxis regimens.

For most Americans, Canadians, Europeans, and Austrians, personal experience with malaria is limited to travel-related exposure in tropical areas. Imported malaria is vastly under-reported in the United States; minimum figures from the U.S. Centers for Disease Control and Prevention indicate that approximately 1,000 travelers are infected with malaria in the United States each year.<sup>1</sup> Although anti-mosquito measures such as repellants are also indicated, the primary preventive measure for international travelers remains taking antimalarial drugs during exposure (chemoprophylaxis). Efficacious drugs for the chemoprophylaxis of travelers to malaria-endemic areas already exist. Their effectiveness is seriously compromised by the human propensity to resist taking medication when one is not actually ill. Most travelers developing malaria after return to their home country have been taking no medication rather than an imperfect one. The problem of travelers' malaria cannot be solved by the development of superior new antimalarial drugs alone; one has to find a better way to get travelers to actually ingest prescribed medication.

Chemotherapy of any infectious agent is based on the administration of full dosages of a drug that kills the organism and then maintaining adequate blood concentrations for sufficient time to cure the patient. Malaria chemoprophylaxis depends on maintaining inhibitory drug concentrations over an entire exposure period such that when an infection occurs, it is aborted either in the liver or blood prior to the appearance of symptomatic malaria. This works in theory much better than practice because any adherence failure by travelers leaves them unprotected.

Currently, most travelers use some variation of continuous prophylaxis in which either daily or weekly dosing is given prior to the start of travel, during travel, and for 1–4 weeks after return. The use of long-acting drugs given in treatment doses pre-travel is an alternative strategy that could be known as pre-exposure prophylaxis. In this setting, a single 1–3-day treatment regimen is given shortly prior to travel on the basis that persistent drug levels may protect travelers for up to four weeks.

Two examples suggest this alternative approach could prove superior to continuous prophylaxis. Directly observed therapy (DOT) has revolutionized the treatment of tuberculosis not by creating a new therapeutic paradigm, but by ensuring that the patients really do ingest their medications.<sup>2</sup>

Intermittent presumptive therapy of malaria either in pregnant women (IPTp) or infants (IPTi) is delivering substantial public health benefits in malaria-endemic areas not by eliminating malaria, but by ensuring that there are periods when vulnerable populations have full treatment courses of antimalarial drugs that result in periods without parasitemia.<sup>3</sup> We think it is possible that more travelers would be protected against malaria if they were able to take a full course of an efficacious antimalarial drug shortly prior to leaving their home country as pre-exposure malaria chemoprophylaxis than by failing to take conventionally prescribed prophylactic medication. Compliance would be improved because fewer drug ingestions would be required of travelers and their attention would be focused on potential disease risks before their actual departure. Issues of counterfeit or expired medication would be minimized.<sup>4</sup> Adverse drug events could be handled in the traveler's home country by his or her own physician. The traveler would be freed to get on with business or holiday activity without worrying whether the discomforts inherent in international travel were due to a medication induced adverse event.

All this crucially depends on how long such post-treatment protection persists. There are published data indicating that pre-exposure malaria chemoprophylaxis is efficacious. Chemoprophylaxis and vaccine studies in malaria-endemic areas often incorporate a course of antimalarial medication to clear any pre-existing parasitemia. When atovaquone/proguanil (Malarone®; GlaxoSmithKline, Research Triangle, Park, NC) was used in the high transmission area of western Kenya in 1997, the first asymptomatic blood infection was noted 35 days after medication and most infections did not appear until well into the second month.<sup>5</sup> This observation has been reproduced in the same area during a vaccine study in 2004 (Polhemous M, unpublished data). Blood stage parasite challenge infections in Australia have been confounded by drug-action duration by atovaquone/proguanil persisting for more than a month.<sup>6</sup> Volunteer studies have shown that atovaquone can inhibit both mosquito stages and blood stages of malaria for six weeks after drug administration.<sup>7</sup> The unusually long time that antimalarial action was observed is not easily explained by the standard understanding of the pharmacokinetics of atovaquone. We speculate that hepatic elimination of atovaquone may cause the liver to be a drug reservoir not often appreciated by blood concentration measurements.

Even if efficacious, pre-exposure chemoprophylaxis would not apply to long-term travelers and would be best adopted

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by those traveling for one month or less. Because this time limitation includes > 95% of international tourists, pre-exposure malaria chemoprophylaxis could potentially prevent most travel-related malaria infections. Those whose travel plans extended beyond their originally anticipated schedule could take an additional course of medication after leaving the malaria-endemic area. Because atovaquone/proguanil may not be an optimal agent to prevent *Plasmodium vivax* infection, travelers to areas with substantial exposure to relapsing malaria such as Asia or Oceania could use an 8-aminoquinoline such as the long-acting primaquine analog tafenoquine, which is currently in advanced development.<sup>8</sup> Monthly prophylaxis administration has been shown to be efficacious with tafenoquine.<sup>9</sup> An additional future alternative may be another very long-acting drug under development known as piperazine.<sup>10</sup>

This approach needs further evidence that could be generated by deliberate trials to determine the efficacy of post treatment protection in non-immunes and its duration. Use of pre-exposure and post-exposure malaria chemoprophylaxis would not necessarily require the development of new drug regimens. Existing treatment schedules that already have large bodies of safety and tolerance data would be used. We submit that our proposed reversal of indications, using malaria treatment regimens for chemoprophylaxis, would require additional studies in defined traveler populations but could be adopted without extensive regulatory changes. More travelers using effective antimalarial drugs to prevent more infections is in everyone's interest, especially because most international travelers to malaria-endemic areas do not take any chemoprophylaxis. We intend this editorial to promote exploration of the issues raised herein and as a means of promoting discussion between tropical medicine and travel physicians, drug regulatory authorities, pharmaceutical companies, and the traveling public to change antimalarial drug efficacy (which is already high) into effectiveness (which is clearly suboptimal).

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