

## ORIGINAL ARTICLE

# Delayed Onset of Malaria — Implications for Chemoprophylaxis in Travelers

Eli Schwartz, M.D., Monica Parise, M.D., Phyllis Kozarsky, M.D.,  
and Martin Cetron, M.D.

## ABSTRACT

From the Center for Geographical Medicine and the Department of Medicine, C. Chaim Sheba Medical Center, Tel Hashomer, and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (E.S.); and the Malaria Epidemiology Branch, Division of Parasitic Diseases (M.P.), and the Surveillance and Epidemiology Branch, Division of Global Migration and Quarantine (M.C.), National Center for Infectious Diseases, Centers for Disease Control and Prevention; the Public Health Service, Department of Health and Human Services (M.P., M.C.); and the Department of Medicine, Emory University School of Medicine (P.K.) — all in Atlanta. Address reprint requests to Dr. Schwartz at the Center for Geographical Medicine and the Department of Medicine, C. Chaim Sheba Medical Center, Tel Hashomer 52621, Israel, or at elischwa@post.tau.ac.il.

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**BACKGROUND**

Most antimalarial agents used by travelers act on the parasite's blood stage and therefore do not prevent late-onset illness, particularly that due to species that cause relapsing malaria. We examined the magnitude of this problem among Israeli and American travelers.

**METHODS**

We examined malaria surveillance data from Israel and the United States to determine the traveler's destination, the infecting species, the type of chemoprophylaxis used, and the incubation period.

**RESULTS**

In Israel, from 1994 through 1999, there were 300 cases of malaria among returning travelers in which one species of plasmodium could be identified. In 134 of these cases (44.7 percent), the illness developed more than two months after the traveler's return; nearly all of these cases were due to infection with *Plasmodium vivax* or *P. ovale*. In 108 of the 134 cases (80.6 percent), the patient had used an antimalarial regimen according to national guidelines. In the United States, from 1992 through 1998, there were 2822 cases of malaria among travelers in which the cause could be evaluated. Late illness developed in 987 (35.0 percent) of these travelers. The infection was due to *P. vivax* in 811 travelers, *P. ovale* in 66, *P. falciparum* in 59, and *P. malariae* in 51; 614 (62.2 percent) of those with late-onset illness had appropriately taken an effective antimalarial agent.

**CONCLUSIONS**

In more than one third of malaria-infected travelers, the illness developed more than two months after their return. Most of these late-onset illnesses are not prevented by the commonly used and effective blood schizonticides. Agents that act on the liver phase of malaria parasites are needed for more effective prevention of malaria in travelers.

THE APPROPRIATE CHOICE OF DRUGS for chemoprophylaxis against malaria in travelers remains controversial and is affected by several issues, including drug efficacy, tolerance, convenience, and cost. The declining efficacy of chloroquine against *Plasmodium falciparum* in most malarious areas of the world precludes the routine use of this drug, which was the mainstay of prophylaxis and treatment for decades. Given the low risk of infection for many travelers, drug tolerance may limit use if adverse effects are too frequent or severe. For example, amodiaquine and sulfadoxine-pyrimethamine were found to have low but unacceptable rates of severe adverse effects.<sup>1-3</sup> Concern about adverse effects of mefloquine (particularly those related to the central nervous system)<sup>4,5</sup> has led to decreased use and compliance.<sup>6</sup> Doxycycline has good efficacy against both *P. falciparum* and *P. vivax*,<sup>7,8</sup> but adherence may be limited by gastrointestinal side effects.<sup>9</sup> In addition, there may be lower adherence to treatment with agents that need to be taken daily rather than weekly,<sup>10</sup> which reduces their effectiveness.<sup>11,12</sup>

An important factor in weighing the advantages and disadvantages of the various chemoprophylactic agents that are available is their site of action in the life cycle of the parasite. Most of the available chemoprophylactic agents are blood-stage schizonticides that do not affect the liver stage of the parasite and therefore will not prevent the late appearance of species that cause relapsing malaria. These late-onset illnesses due to *P. vivax* and *P. ovale* can become clinically apparent in travelers months after their return from areas of endemic malaria despite adherence to nationally recommended chemoprophylactic regimens. We examined the magnitude of the problem among Israeli and American travelers.

## METHODS

Malaria is a notifiable disease in both Israel and the United States; malaria surveillance is conducted by the Epidemiology Department of the Ministry of Health in Israel and by the Malaria Epidemiology Branch of the Division of Parasitic Diseases at the Centers for Disease Control and Prevention (CDC) in the United States. In both countries, cases are defined by parasitemia confirmed by blood smear. In Israel, a nurse-epidemiologist interviews each patient with malaria and records the purpose of the travel, the travel itinerary, and the use or nonuse of chemoprophylaxis against malaria. In the United

States, similar data are sent from local and state health departments to the CDC. We analyzed surveillance data from Israel and the United States for the periods from 1994 through 1999 and from 1992 through 1998, respectively. Only civilian residents of these countries were included in the analyses.

## RESULTS

During the years 1994 through 1999, there were 307 reported cases of malaria among returning Israeli travelers. The most frequently reported species was *P. vivax*, with 156 cases (50.8 percent), followed by *P. falciparum*, with 135 cases (44.0 percent), *P. ovale*, with 5 cases (1.6 percent), and *P. malariae*, with 4 cases (1.3 percent). In seven cases (2.3 percent), the species was undetermined (six cases) or the illness was due to a mixed infection (one case); these were excluded from the analysis.

All cases of *P. falciparum* malaria in Israel were detected within two months after the traveler's return (Table 1). Ninety-seven of the 135 persons who acquired *P. falciparum* infection (71.9 percent) had not used any chemoprophylaxis. Twenty-four (17.8 percent) admitted noncompliance or had used chloroquine alone or the combination of chloroquine and chloroguanide in areas with chloroquine-resistant *P. falciparum*; only 14 (10.4 percent) had used effective agents (e.g., mefloquine or doxycycline) for travel to areas with chloroquine-resistant *P. falciparum*.

In contrast, in 133 of 161 persons with *P. vivax* or *P. ovale* malaria (82.6 percent), the onset of illness occurred more than two months after the traveler's return. One hundred eight (81.2 percent) of these travelers had used what was presumed to be an ef-

**Table 1. Characteristics of Imported Cases of Malaria among 300 Israeli Travelers from 1994 through 1999.**

| Plasmodium Species   | No. of Cases | Early Onset (≤2 mo after Return) |   | Late Onset (>2 mo after Return) |                              |
|----------------------|--------------|----------------------------------|---|---------------------------------|------------------------------|
|                      |              | Total                            | Use of Effective Prophylaxis number (percent) | Total                           | Use of Effective Prophylaxis |
| <i>P. falciparum</i> | 135          | 135 (100)                        | 14 (10.4)                                     | 0                               | 0                            |
| <i>P. vivax</i>      | 156          | 27 (17.3)                        | 3 (11.1)                                      | 129 (82.7)                      | 104 (80.6)                   |
| <i>P. ovale</i>      | 5            | 1 (20)                           | 0   | 4 (80)                          | 4 (100)                      |
| <i>P. malariae</i>   | 4            | 3 (75)                           | 0   | 1 (25)                          | Unknown                      |
| Total                | 300          | 166 (55.3)                       | 17 (10.2)                                     | 134 (44.7)                      | 108 (80.6)                   |

fective prophylactic regimen; 70 percent had taken mefloquine. These 108 cases represent 36 percent of the 300 cases of malaria whose cause could be attributed to a single species.

In the United States, from 1992 through 1998, epidemiologic information was available for 2964 of 5185 reported cases of malaria. *P. vivax* and *P. falciparum* accounted for 1321 (44.6 percent) and 1290 (43.5 percent) of these cases, respectively; 124 (4.2 percent) were due to *P. malariae*, 87 (2.9 percent) were due to *P. ovale*, and 2 (0.07 percent) were mixed infections. The species was undetermined in 140 cases (4.7 percent). After mixed infections and infections by undetermined species had been excluded, 2822 cases remained for analysis (Table 2).

More than 95 percent of patients with *P. falciparum* malaria presented within two months after their return. Eight hundred sixty-three of 1231 patients (70.1 percent) had used no chemoprophylaxis, and 201 (16.3 percent) had taken a drug that was not considered effective for the prevention of malaria in the area to which they traveled (most commonly chloroquine in areas of chloroquine-resistant *P. falciparum*). Only 167 patients (13.6 percent) had taken an agent that was effective for the prevention of malaria in the area to which they traveled. Among those who took an effective drug but still acquired *P. falciparum* malaria, mefloquine was used most frequently (by 73.3 percent of the patients). Information was not available on adherence to the chemoprophylactic regimen, nor were samples available for determination of the blood levels of the antimalarial drugs; therefore, possible mefloquine resistance could not be properly evaluated in these patients.

In contrast, in 877 of the 1408 persons who acquired *P. vivax* or *P. ovale* malaria (62.3 percent), the

onset of symptoms occurred more than two months after their return. The median time from exposure (with the end of the trip arbitrarily chosen as the time of exposure) to the onset of symptoms among those with late-onset illness was 181 days (range, 61 to 1712). Of these 877 patients, 322 (36.7 percent) had used no chemoprophylaxis, whereas 555 (63.3 percent) had taken an antimalarial regimen that should have eliminated the blood stages of *P. vivax* or *P. ovale*. Mefloquine was the most commonly used drug, taken by 293 patients (52.8 percent), followed by chloroquine, which was taken by 184 patients (33.2 percent). In 555 of the 2822 U.S. cases (19.7 percent), late illness due to *P. vivax* or *P. ovale* developed despite the use of an effective antimalarial regimen.

DISCUSSION

A 50 percent infection rate with *P. vivax* among Israeli travelers (who had adhered to mefloquine prophylaxis) three months after their return from Ethiopia called attention to the gap in coverage with currently available drugs.<sup>13</sup> This led to the current review of this problem in Israel and the United States. We found that up to one third of all reported cases of malaria in both Israel and the United States were late-onset illnesses caused by *P. vivax* or *P. ovale* that occurred despite adequate blood-stage prophylaxis.

Although malaria typically occurs in travelers because of lack of pretravel health information, poor compliance resulting in inadequate drug levels, or drug resistance, these factors do not appear to account for the late onset of illness in the patients in this study. In fact, the acquisition of malaria by travelers despite their adherence to medical recommendations may result in reduced compliance and decreased trust in the advice given by health care providers. Moreover, the diagnosis of late-onset illness in travelers who have used a nationally recommended antimalarial regimen is more challenging for physicians and may be more difficult for patients to associate with previous travel. The phenomenon of late-onset illness is not well understood, and many physicians and travelers believe that the use of prophylaxis against malaria should prevent all cases of infection.

The life cycle of the parasite in humans consists of two stages. In the initial stage, known as the liver or exoerythrocytic stage, the parasites multiply in the hepatocytes and eventually cause them to rup-

**Table 2. Characteristics of Imported Cases of Malaria among 2822 U.S. Travelers from 1992 through 1998.**

| Plasmodium Species   | No. of Cases | Early Onset (≤2 mo after Return) |  | Late Onset (>2 mo after Return) |                              |
|----------------------|--------------|----------------------------------|--|---------------------------------|------------------------------|
|                      |              | Total                            | Use of Effective Prophylaxis<br>number (percent) | Total                           | Use of Effective Prophylaxis |
| <i>P. falciparum</i> | 1290         | 1231 (95.4)                      | 167 (13.6)                                       | 59 (4.6)                        | 20 (33.9)                    |
| <i>P. vivax</i>      | 1321         | 510 (38.6)                       | 148 (29.0)                                       | 811 (61.4)                      | 501 (61.8)                   |
| <i>P. ovale</i>      | 87           | 21 (24.1)                        | 9 (42.9)   | 66 (75.9)                       | 54 (81.8)                    |
| <i>P. malariae</i>   | 124          | 73 (58.9)                        | 23 (31.5)  | 51 (41.1)                       | 39 (76.5)                    |
| Total                | 2822         | 1835 (65.0)                      | 347 (18.9)                                       | 987 (35.0)                      | 614 (62.2)                   |

ture. Two species, *P. vivax* and *P. ovale*, have persistent liver stages, which can emerge and cause a relapse months to years later. The use of blood-stage schizonticides will not prevent these relapses. In addition, their use can mask symptoms of the first infection with *P. vivax* or *P. ovale*. The first apparent symptoms of infection may then occur months later.

The second stage, the blood or erythrocytic stage, occurs when the parasites are released into the bloodstream, invade the erythrocytes, and cause clinical illness. We defined an early-onset illness as one in which the first clinical presentation was within two months after exposure to the parasite (taking into account the fact that patients may have followed a chemoprophylactic regimen for up to four weeks after travel); such infections may be due to any of the malaria species. An early-onset illness is usually prevented if a traveler adheres to one of the nationally recommended antimalarial chemoprophylactic regimens just before, during, and after travel.

The current model for chemoprophylaxis divides the areas of the world in which malaria is endemic into two zones: one with chloroquine-sensitive *P. falciparum* and one with chloroquine-resistant *P. falciparum*. The resistance of *P. falciparum* to chloroquine has been confirmed in all areas with *P. falciparum* malaria except the Dominican Republic, Haiti, Central America west of the former Panama Canal Zone, Egypt, and some countries in the Middle East.<sup>14,15</sup> Although this model has been serviceable for decades for the primary purpose of preventing lethal malaria due to *P. falciparum*, it clearly ignores a substantial portion of the burden of malaria acquired through travel — infections due to *P. vivax* (and, to a much lesser extent, *P. ovale*).

The current strategy for prevention of *P. vivax* and *P. ovale* relapses includes the addition of two weeks of terminal prophylaxis with primaquine for travelers who have had prolonged exposure to areas where those species are endemic.<sup>14</sup> Unfortunately, this approach has a number of inherent problems. The recommendations are confusing and are not well communicated to health care providers. The geographic distribution of the areas where travelers are exposed to the species causing relapsing malaria is not defined in national guidelines for chemoprophylaxis, and the requirement of two antimalarial medications increases the likelihood of adverse events, increases the cost, and decreases compliance (which is often lower after a return from travel).<sup>16,17</sup>

The types of chemoprophylaxis against malaria are summarized in Table 3. Liver-stage (causal) pro-

**Table 3. Types of Chemoprophylaxis against Malaria.**

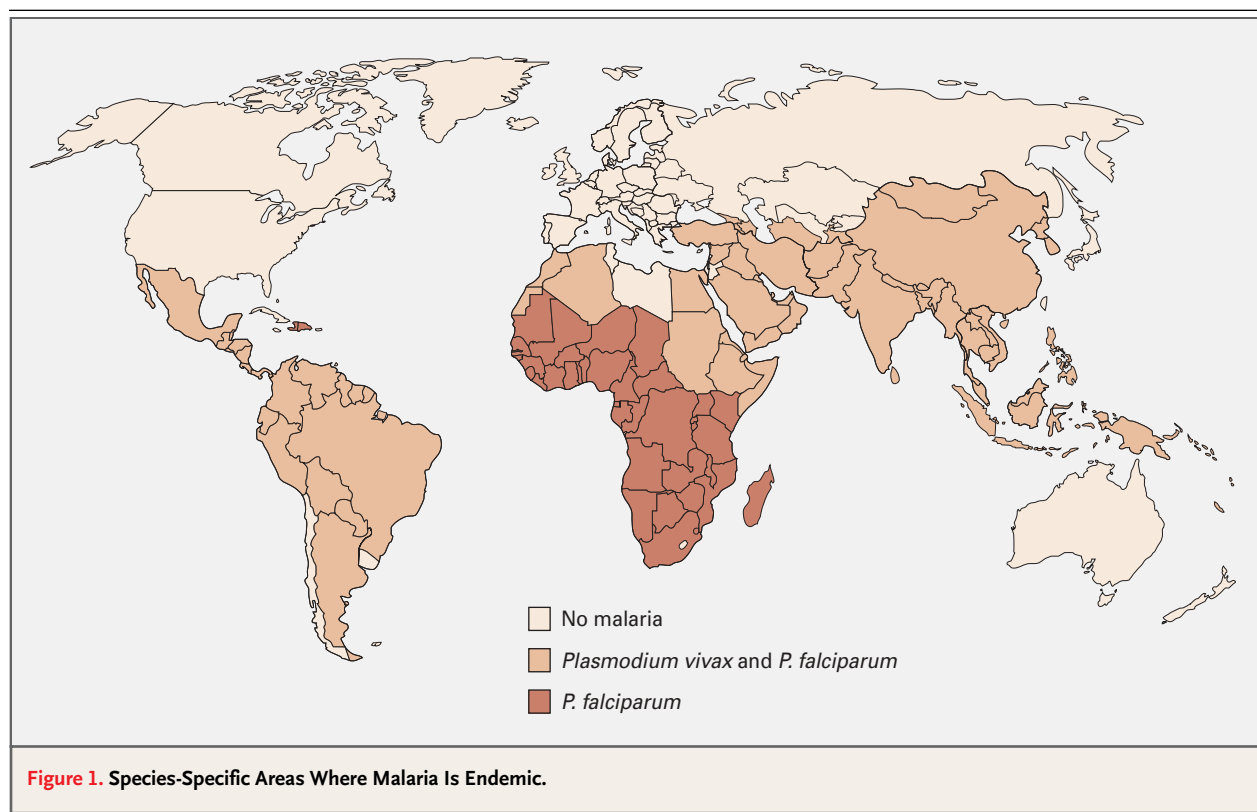
| Type and Agent*   | Characteristics  |
|---|--|
| Blood-stage (suppressive) prophylaxis<br>Mefloquine<br>Doxycycline<br>Chloroquine | Prevents primary infection; completely prevents only <i>P. falciparum</i> and <i>P. malariae</i> infection; should be continued for 4 wk after the traveler has left the area of endemic disease |
| Liver-stage (causal) prophylaxis<br>Primaquine                                    | Prevents primary infection and late-onset illness; completely prevents all types of malaria; can be discontinued after the traveler has left the area of endemic disease                         |

\* The agents listed are examples of those that may be used for chemoprophylaxis.

phylaxis, by acting on the hepatic phase, theoretically offers the most complete protection, since it may actually prevent primary infections by all malaria species, as well as late relapses. Liver-stage prophylaxis (provided that an effective agent was taken and the regimen was adhered to) might have prevented infection in the persons in our study who had late-onset illness from *P. falciparum* or *P. malariae*. Liver-stage prophylaxis should also enable travelers to discontinue prophylaxis at the time of or soon after departure from malarious areas, thus increasing adherence. In areas where there is transmission of only *P. vivax* or of *P. vivax* and other species (Fig. 1), liver-stage prophylaxis offers definite advantages. In areas where *P. falciparum* is overwhelmingly dominant, protection is similar with liver- and blood-stage prophylaxis (although liver-stage prophylaxis still offers the advantage that it can be discontinued when the traveler leaves the malarious area).

In sub-Saharan Africa, where *P. falciparum* accounts for more than 90 percent of infections in most areas, blood-stage prophylaxis is sufficient. However, in the Horn of Africa (Ethiopia and Somalia), a large proportion of infections are caused by *P. vivax*, and thus prophylaxis against blood-stage parasites alone would lead to gaps in coverage. In most malarious areas outside sub-Saharan Africa, where both *P. falciparum* and *P. vivax* are transmitted, liver-stage prophylaxis would also provide the most complete protection.

Unfortunately, the number of available agents for liver-stage prophylaxis and our experience with these agents are limited. The agents are primaquine and atovaquone–chloroguanide (Malarone).<sup>18–20</sup> Although primaquine has been used primarily for terminal prophylaxis (presumptive eradication of hypnozoites) or radical cure of relapsing malaria, it has



been evaluated as a chemoprophylactic agent and has been effective in several studies, with protective efficacy of more than 90 percent for *P. falciparum* malaria and from 85 to 90 percent for *P. vivax* malaria.<sup>21-23</sup> It has been well tolerated, even during long-term use.<sup>21</sup> To date, the only study that has evaluated the prophylactic efficacy of primaquine among travelers without immunity to malaria involved Israeli tourists taking rafting trips in areas of Ethiopia where malaria is highly endemic.<sup>24</sup> In this study, the overall rate of malaria infection during a two-week trip was 52 percent among travelers who took mefloquine (13 of 25 persons became infected), as compared with 6 percent among those who took primaquine (6 of 106 persons). During a mean follow-up of 16 months, there were no cases of late-onset illness among the primaquine users. The main disadvantage of primaquine is the risk of hemolysis in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The time required to test the blood for G6PD deficiency before using primaquine and the cost of the test remain problems.

The combination of atovaquone and chloroguanide has blood-stage and liver-stage activity.<sup>19,20,25</sup> The combination has proved effective for the treat-

ment of *P. falciparum* malaria,<sup>26-34</sup> has been shown to be effective for chemoprophylaxis against *P. falciparum* malaria in both semi-immune<sup>35-37</sup> and non-immune persons,<sup>38</sup> and has been well tolerated by nonimmune persons.<sup>39,40</sup> However, data on the efficacy of the combination for the treatment of and prophylaxis against *P. vivax* malaria are more limited.<sup>27,38,41</sup>

Tafenoquine, an 8-aminoquinolone thought to provide complete prophylaxis, is undergoing clinical trials. A major advantage of tafenoquine is its long elimination half-life of 14 days,<sup>42</sup> which would allow for either weekly dosing or possibly a short course of medication before a trip lasting less than 1 or 2 months. Studies in Kenya and Gabon have shown that tafenoquine has excellent prophylactic efficacy against *P. falciparum*.<sup>43</sup>

The development of new agents for the prevention of malaria that act against the liver stage could provide attractive chemoprophylactic alternatives. In addition to efficacy, factors that should be weighed in considering the appropriateness of chemoprophylaxis against malaria include tolerability, pharmacokinetic properties that determine dosing frequency, and cost.

Dr. Kozarsky reports having received consulting fees from Glaxo-SmithKline.

The use of trade names is for identification only and does not imply endorsement by the Public Health Service or the Department of Health and Human Services.

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Rick Crootof, M.D.