IMPORTED NON–PLASMODIUM FALCIPARUM MALARIA: A FIVE-YEAR PROSPECTIVE STUDY IN A EUROPEAN REFERRAL CENTER

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Abstract. From 2000 to 2005, we investigated prospectively 98 cases of imported non–Plasmodium falciparum malaria (48 Plasmodium vivax, 34 P. ovale, and 16 P. malariae). Latency period between return and clinical attack exceeded three months in 40% of the patients. It was longer in travelers who had taken chemoprophylaxis. Time to diagnosis was longer in patients with P. malariae infection and in those with late-onset first attack. Parasite density was often lower than 500/µL, especially in P. ovale malaria. Relapses were diagnosed in 18% of all malaria episodes. Eight (17%) P. vivax and 2 (6%) P. ovale malaria episodes were due to relapse despite standard primaquine therapy. Diagnosis of imported non-falciparum malaria is often challenged by long latency period and low parasite density. In addition, the substantial relapse rate despite standard primaquine therapy supports the use of a higher dose of primaquine to eradicate P. vivax and P. ovale malaria effectively.

INTRODUCTION

In studies conducted in reference centers, malaria is the most common cause of fever in travelers and migrants arriving from the tropics. Nowadays, it is estimated that roughly 30,000 cases of travel-associated malaria occur worldwide annually, and figures are on the increase.1 The four Plasmodium species (P. falciparum, P. vivax, P. ovale, and P. malariae) which are responsible for almost all human cases present with different epidemiologic and clinical features. Their relative prevalence varies according to travelers’ destination, with P. falciparum being the leading cause in European and North American settings,2,3 and P. ovale the predominant pathogen in Australasian studies.4 Since imported non-falciparum malaria is globally less prevalent5 and usually has a benign course, information is rather limited, especially for P. ovale and P. malariae.6,7 However, some specific features challenge its management. Latency period between infection and first clinical attack may be very long, obscuring the link with travel. Correct microscopic diagnosis may be impaired by low parasite density. Finally, the picture may be also complicated by relapses emerging from liver hypnozoites (for P. vivax and P. ovale) or by recrudescence from latent erythrocytic stages (for P. malariae) if previous attacks have not been adequately treated.

Non-falciparum infection represents approximately 25% of all malaria cases in our referral center. We report on all patients microscopically diagnosed with a single P. vivax, P. ovale or P. malariae infection during a five-year prospective study, with a focus on the frequency and clinical impact of these three specific problems.

METHODS

Study setting. Between April 2000 and March 2005, we included prospectively all travelers, expatriates, and foreign visitors presenting with fever at the Institute of Tropical Medicine of Antwerp (outpatient clinic) or at the University Hospital of Antwerp (inpatient department) and with positive microscopy of non-falciparum malaria.

Definitions. Fever was defined by a documented axillary temperature ≥ 38°C, or by the combination of chills/rigor and sweats within three days prior to consultation. Travelers were defined as western patients having stayed in a malarious area for a period less than six months, or natives from malaria-endemic countries residing for more than one year in Europe and returning to their country for a visit of less than six months. Expatriates were western patients residing for more than six months in a malarious area. Foreign visitors were natives from malaria-endemic countries arriving in Europe for the first time.

Latency period was defined as the time lapse between return/arrival from the last visited malaria-endemic country and onset of fever. Adherence to chemoprophylaxis or malaria treatment referred to full compliance (thoroughly investigated) with recommended dose and duration of malaria prophylaxis or treatment.

Diagnosis. Only the cases in whom a single malaria species (P. vivax, P. ovale, or P. malariae) could be accurately identified in a thick and/or thin blood film were further studied. Low parasitemia was defined as a parasite density < 500/µL, or < 0.01% of parasitized red blood cells (RBCs) because accurate diagnosis becomes problematic below this threshold in most routine laboratories.8,9

Three-band rapid diagnostic tests (RDTs) have been used routinely in our center since 2003, including tests based on detection of histidine-rich protein 2 (HRP-2) aldolase (NOW® ICT Malaria Test for Whole Blood; Binax, Scarborough, ME), and parasite lactate dehydrogenase (pLDH) (OptiMAL®, DiaMed AG, Cressier-sur-Morat, Switzerland). Molecular techniques were not available for daily practice during the study period.

Treatment and follow-up. Treatment was considered adequate when chloroquine (total dose = 1.5 g over a three-day period) was administered at diagnosis, but also when another treatment targeting P. falciparum was given in case of uncertain initial Plasmodium identification. As until recently widely accepted,10 all patients with P. vivax or P. ovale infections were systematically given a standard course of primaquine therapy (15 mg of primaquine base daily over a 14-day period, total dose = 210 mg), except in case of preg-
nancy or glucose-6-phosphate dehydrogenase (G6PD) deficiency. In overweight patients (no precise cut-off), clinicians could administer at discretion primaquine (22.5 mg/day for a 14-day period, total dose = 315 mg) to reach the recommended therapeutic dose of 3.5–4.2 mg/kg. In case of relapse despite standard primaquine regimen, patients were given a high primaquine dosage treatment (0.5 mg/kg for a 14-day period, total dose = 7 mg/kg). Treatment adherence and short-term outcome were assessed by a follow-up consultation or a phone call within three months after the initial contact. All patients were carefully informed of the risk of relapse/recrudescence, and were told to contact a specialized center immediately in case of fever recurrence even months or years after the first episode. Relapse of malaria was defined as a subsequent and microscopically documented attack in a person who did not travel to an malaria-endemic region since the previous diagnosed episode. From March to June 2005, all enrolled patients were re-contacted by phone and files were re-examined to assess long-term outcome.

Statistical analysis. Analyses were done with the SPSS software version 13.0 (SPSS Inc., Chicago, IL). The Pearson chi-square test, one-way analysis of variance, and Kruskal-Wallis test were used, when appropriate, to make comparisons between the three species. The chi-square test, Student’s t-test, and Mann-Whitney U test were used when two groups of patients were compared.

RESULTS

Epidemiology and latency period. During the five-year study period, 102 episodes of non-falciparum malaria were microscopically diagnosed. Concomitant P. falciparum infection was observed in four of them, which were excluded from this study (P. vivax = 1, P. ovale = 2, P. malariae = 1). The remaining 98 non-falciparum single infections occurred in 90 patients and were split up into 48 (49%) P. vivax, 34 (35%) P. ovale, and 16 (16%) P. malariae episodes. During the study period, 10 additional cases were found with plasmodia on thick blood films, but since low parasitemia precluded precise species identification by microscopy, they were not included.

Patients were mainly male (66, 67%) and travelers (61, 62%). Median age was 35 years (range = 11–77 years). Almost all foreign visitors and expatriates had been exposed in Africa, and nearly 50% of travelers were returning from Asia. Probable areas of disease acquisition are shown in Table 1. However, nearly 20% of the patients had traveled to several malaria-endemic areas during the previous year, and more than 60% during the five previous years, which made it sometimes virtually impossible to ascertain where infection was contracted. All patients diagnosed with P. ovale and P. malariae malaria had been infected in Africa, most of them in western and central Africa. Asia was the likely continent of acquisition for two-thirds of the P. vivax infections, almost exclusively in southeast Asia, Indonesia, and India.

Of the 37 patients who reported use of malaria prophylaxis, 25 had been adherent (Table 2), had taken mefloquine (n = 17), chloroquine/proguanil (n = 7), or atovaquone/proguanil (n = 1). No patient had received primaquine treatment prophylaxis. Noteworthy, P. malariae infection developed in two adherent travelers (25 and 44 days upon return, respectively; one who took chloroquine/proguanil and the second who took atovaquone/proguanil). Median latency period between return/arrival from a malarious region and onset of fever was approximately two months. As shown in Figure 1, nearly 40% of the cases occurred after three months, nearly 20% after six months, and 5% after one year. One foreign visitor diagnosed with P. malariae infection had not traveled to any malaria-endemic area for seven years. Latency period did not differ significantly between species. When considering only patients diagnosed with a first non-falciparum malaria attack (n = 80), onset of symptoms was delayed in those 21 who had been adherent to their chemoprophylaxis (median latency period = 91 days versus 40 days for the others; P = 0.002).

Median delay between fever onset and consultation at our center was five days, but was longer for patients with P. malariae infection (7 days; P = 0.014). Thirty-nine (40%) patients had seen previously another practitioner, and 28% of them (11 of 39) were directly referred with a diagnosis of malaria (often without precise identification). A total of 20 (20%) patients were already receiving anti-malarial therapy before consulting us, including 10 using self-medication (emergency self-treatment prescribed before travel for 6). Another 12 (12%) malaria cases had been previously given presumptive antibiotics. Referral pattern and previous treatment were similar for the three species. Of the 80 patients diagnosed with a first malaria attack, those in whom fever developed more than three months after return were diagnosed later (seven days versus five days; P = 0.013), and had previously consulted another practitioner more often (P = 0.043).

Clinical features, laboratory findings, and diagnosis. Table 3 summarizes prevalence of main symptoms, signs, and laboratory findings for all patients with non-falciparum malaria. Besides fever, most patients (84, 86%) complained of headache and/or myalgia, and 25 (26%) had digestive symptoms (vomiting and/or diarrhea and/or abdominal pain). A typical fever pattern (tertian or quartan) was reported by 33 (34%) patients. Splenomegaly was the only major clinical sign observed (24, 24%). Elevated lactate dehydrogenase (LDH ≥ 650 IU/L), thrombocytopenia (platelet count < 150,000 µL),

<table>
<thead>
<tr>
<th>Probable area of infection</th>
<th>P. vivax (n = 46)</th>
<th>P. ovale (n = 34)</th>
<th>P. malariae (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>13</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Western Africa†</td>
<td>3</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Central Africa‡</td>
<td>6</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Eastern Africa§</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Southern Africa¶</td>
<td>1</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Asia</td>
<td>33</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Middle East#</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Indian subcontinent**</td>
<td>8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Southeast Asia††</td>
<td>6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Indonesia/Pacific††</td>
<td>17</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* Two Plasmodium vivax infections were acquired in Surinam.
† Including the following probable countries of disease acquisition: Ghana (n = 6), Senegal (n = 4), Côte d’Ivoire (n = 3), Mali (n = 3), Benin (n = 3), Sierra Leone (n = 2), Liberia (n = 2), Mauritania (n = 2), Burkina Faso (n = 1), Gambia (n = 1), Gabon (n = 1), and Chad (n = 1).
‡ Including Democratic Republic of Congo (n = 14), Cameroon (n = 4), Burundi (n = 3), Rwanda (n = 2), and Central African Republic (n = 2).
§ Including Uganda (n = 3), Sudan (n = 1), and Kenya (n = 1).
¶ Including Madagascar (n = 2) and Zimbabwe (n = 2).
†† Including Afghanistan (n = 1) and Jordan (n = 1).
** Including India (n = 8).
†† Including Myanmar (n = 2), Malaysia (n = 2), Cambodia (n = 1) and Laos Republic (n = 1).
†† Including Indonesia (n = 17).
and total hyperbilirubinemia (≥ 1.3 mg/dL) were observed in 63%, 62%, and 40%, respectively, of the cases. Mean platelet count was 132,000/μL (range 27,000–353,000/μL). Pronounced anemia (hemoglobin level < 10 g/dL) and thrombocytopenia (< 50,000 platelets/μL) were infrequent (< 10%).

No patients had clinical or laboratory criteria of severe malaria, except one with a total bilirubin concentration of 6 mg/dL. Clinical and laboratory presentations were indistinguishable between the three malaria species.

Parasite density was lower in patients who were taking antimalarial therapy (n = 20) than in those who were not (geometric mean = 309/μL versus 1148/μL; P = 0.022). In antimalarial treatment-naive patients (n = 78), 28 (36%) had a parasite density lower than 500/μL at presentation at our center (Table 3). Cases with low parasitemia had a clinical presentation similar to those with high parasitemia. As shown in Table 3, mean parasite density was lower for *P. ovale* malaria (P = 0.004); half of them (14 of 27) had a low parasitemia at presentation.

Table 4 summarizes the performances of the rapid diagnostic tests that were used. The pLDH-based RDT showed positive results in 65% (13 of 20) and the HRP-2/aldolase-based RDT showed positive results in 38% (5 of 13) of the cases confirmed by microscopy. Sensitivities were 33% and 0%, respectively, for parasitemia < 500 plasmodia/μL, but samples were small. During the study period, none of these tests showed positive results in patients with negative blood smears.

**Evolution and relapse.** Diagnosis of non-falciparum malaria could not be made at the first contact for five patients, and at least a second blood smear was required to detect the causative pathogen after a mean delay of three days. Hospitalization was required for 23 (23%) of all malaria episodes. None of the patients developed any complications.

Long-term follow up data could be obtained for 74 cases (median duration = 38 months, range = 6–61 months) including all but 1 traveler. Patients lost to follow-up were expatriates (n = 8) and foreign visitors (n = 15) who had moved permanently abroad.

![Figure 1](image_url)  
**Figure 1.** Distribution of non-*Plasmodium falciparum* malaria according to latency period between date of return/arrival from last visited endemic country and onset of fever (n = 98).
Nearly 20% (18 of 98) of all malaria episodes were due to relapses. None of the 16 P. malariae episodes was considered a recrudescence, and none of the patients reported fever recurrence after chloroquine treatment. Three (9%) of the 34 P. ovale episodes were diagnosed as relapses: one in a patient non-adherent to the primaquine regimen, and two in two patients who received adequate treatment (quinine/doxycycline and a standard primaquine regimen). The latter two patients then received a high primaquine dosage without further relapse. The other 31 patients were given a standard primaquine course, except for four patients lost to follow-up, and no one reported any recurrence of symptoms.

Of the 48 included P. vivax episodes, 15 (29%) were due to relapses, but six of them (40%) occurred in patients who had not taken any primaquine therapy after their previous malaria attack (not proposed by their physician = 4, non-adherence = 1, pregnancy = 1). Eight of the 9 remaining relapses occurred despite a standard primaquine treatment after a mean delay of 16 weeks, corresponding to a relapse rate of 17% (8 of 48). None of them could be related to the patients being overweight. All received a high primaquine dosage, without further relapse. In one patient infected in Indonesia, P. vivax relapsed a third time despite treatment with standard primaquine therapy and once with a high dose of primaquine (total dose = 7 mg/kg). Although he refused another course of primaquine at that time, he experienced no more relapses (follow-up = 57 months).

Relapses of P. vivax malaria despite primaquine therapy occurred in patients infected in Indonesia (n = 3), India (n = 2), Surinam (n = 2), Myanmar (n = 1) and Rwanda (n = 1). No predictive factors for relapse (location of disease acquisition, duration of initial episode of fever, initial parasitaemia, use of primaquine therapy) could be identified.

**DISCUSSION**

To date, the largest series on imported malaria have focused on P. falciparum and to a lesser extent on P. vivax malaria. Little is known about the two other species of *Plasmodium* in imported pathology because of their low frequency and limited morbidity. Data presented here reflect epidemiology as observed in a European referral center for tropical diseases, but are somewhat limited by the lack of molecular analysis of some unidentified malaria cases.

Approximately 40% of the patients developed symptoms more than three months after return, and some much later. Late-onset malaria was associated with a longer diagnostic delay because the perceived link between a tropical travel and the etiology of a febrile episode wanes with time in patients’ and physicians’ minds. However, this had no major clinical consequence. As already observed at least for *P. vivax* infection, latency period was much longer (median difference of nearly two months) when chemoprophylaxis was correctly taken. This might have prevented the initial non-falciparum blood stage episode.

Diagnosis of non-falciparum malaria is not always easy to confirm, particularly when parasite density is low. It sometimes requires repeated blood smear examinations even in specialized settings. Sensitivity of detection generally achieved in most routine laboratories is approximately 500 parasites/μL (0.01% of the RBCs), and experienced microscopists are expected to reach a sensitivity of 50 parasites/μL (0.001% of the RBCs). A parasitemia less than 500/μL is a common occurrence in *P. ovale* infection and in partially treated patients. Self treatment should therefore be systematically asked for, in particular with the increasing popularity of pocket anti-malarial emergency treatment. At the present time, microscopy is still the gold standard for malaria diagnosis and species identification. As illustrated here, the sensitivity of commercial rapid diagnostic tests is unsatisfactory for all three non-falciparum species and more so when parasitemia is low. This confirms that current antigenic tests cannot compensate the imperfections of microscopy. Hopes

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**Table 3**

Prevalence of symptoms, signs and laboratory findings in patients diagnosed with non-*Plasmodium falciparum* malaria (n = 98)

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>All non-falciparum malaria (n = 98)</th>
<th>P. vivax (n = 48)</th>
<th>P. ovale (n = 34)</th>
<th>P. malariae (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>positive</td>
<td>tested</td>
<td>positive</td>
<td>tested</td>
</tr>
<tr>
<td>Headache and/or myalgia, n (%)</td>
<td>84 (86)</td>
<td>100</td>
<td>40 (83)</td>
<td>48</td>
</tr>
<tr>
<td>Fever ≥ 39°C, n (%)</td>
<td>44 (45)</td>
<td>100</td>
<td>24 (50)</td>
<td>48</td>
</tr>
<tr>
<td>Tertian or quartan fever pattern, n (%)</td>
<td>33 (34)</td>
<td>100</td>
<td>15 (31)</td>
<td>48</td>
</tr>
<tr>
<td>Any digestive symptom*, n (%)</td>
<td>25 (26)</td>
<td>100</td>
<td>13 (27)</td>
<td>48</td>
</tr>
<tr>
<td>Splenomegaly, n (%)</td>
<td>24 (25)</td>
<td>100</td>
<td>11 (23)</td>
<td>48</td>
</tr>
<tr>
<td>Jaundice, n (%)</td>
<td>15 (15)</td>
<td>100</td>
<td>8 (17)</td>
<td>48</td>
</tr>
</tbody>
</table>

**Laboratory findings**

<table>
<thead>
<tr>
<th></th>
<th>positive</th>
<th>tested</th>
<th>positive</th>
<th>tested</th>
<th>positive</th>
<th>tested</th>
<th>positive</th>
<th>tested</th>
<th>positive</th>
<th>tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia &lt; 50,000/μL, n (%)</td>
<td>8 (6)</td>
<td>100</td>
<td>5 (10)</td>
<td>48</td>
<td>2 (6)</td>
<td>34</td>
<td>1 (6)</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin &lt; 10 g/dL, n (%)</td>
<td>6 (6)</td>
<td>100</td>
<td>1 (2)</td>
<td>48</td>
<td>3 (9)</td>
<td>34</td>
<td>2 (12)</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasitemia &lt; 500/μL, n/n in 78 anti-malarial treatment–naïve patients (%)</td>
<td>28/78 (36)</td>
<td>100</td>
<td>9/36 (25)</td>
<td>48</td>
<td>14/27 (52)</td>
<td>34</td>
<td>5/15 (33)</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric mean parasitemia/μL (± SD) in 78 anti-malarial treatment–naïve patients</td>
<td>1148</td>
<td>2991</td>
<td>2291</td>
<td>479</td>
<td>1023</td>
<td>135–7,762</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Including vomiting and/or diarrhea and/or abdominal pain.

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**Table 4**

Performances of two three-band rapid diagnostic tests for non-falciparum malaria according to parasite density*

<table>
<thead>
<tr>
<th>Parasite LDH-based RDT</th>
<th>HRP-2/aldolase-based RDT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) positive</td>
</tr>
<tr>
<td>Total</td>
<td>13 (65)</td>
</tr>
<tr>
<td>&lt; 500 plasmodia/μL</td>
<td>3 (33)</td>
</tr>
<tr>
<td>≥ 500 plasmodia/μL</td>
<td>10 (91)</td>
</tr>
</tbody>
</table>

* LDH = lactate dehydrogenase; RDT = rapid diagnostic test; HRP-2 = histidine-rich protein 2.
are set on new molecular techniques that detect all four plasmodia.\textsuperscript{17} Serologic analysis for all four species simultaneously is used as a retrospective diagnostic test in our center but its performance has never been properly validated. Recurrent clinical attack may occur in all three species if not adequately treated. Recrudescence of \textit{P. malariae} malaria was not observed because chloroquine treatment is straightforward and chloroquine resistance is anecdotal at most.\textsuperscript{18} In contrast, a relapse was diagnosed in 29\% of \textit{P. vivax} and 9\% of \textit{P. ovale} malaria cases. Primaquine is the only available anti-relapsing drug. Presumptive eradication of liver hypnozoites by using terminal (post-travel) prophylaxis with primaquine has been proposed for preventing relapse, but unclear recommendations and practical problems make it difficult to implement.\textsuperscript{5,7} Even for radical cure of documented \textit{P. vivax} and \textit{P. ovale} malaria, failure to initiate primaquine is frequently observed.\textsuperscript{19} Non-adherence, drug unavailability, return to malaria-endemic areas, fear of toxicity, and specific contraindications related to pregnancy and G6PD deficiency may all contribute to this low rate of primaquine use. However, we found that most \textit{P. vivax} relapses occurred despite a correctly taken standard primaquine regimen, irrespective of the geographic origin of the cases. Rate of relapse despite standard regimen (17\%) was similar to what has been reported in other studies on imported vivax malaria.\textsuperscript{1,3-20,21} In some series, relapses were more frequently reported in Indonesian vivax strains,\textsuperscript{3,21} but this was not observed in this study. Resistance of \textit{P. vivax} to the standard primaquine regimen is probably more widespread than previously thought. A higher dosage regimen of primaquine for \textit{P. vivax} infection (0.5 mg/kg/day for 14 days) has led to better cure rates without increase of adverse events,\textsuperscript{10} and this recommendation has been recently officially endorsed.\textsuperscript{22} In this series, a high-dosage primaquine failure was seen in only one patient infected in Indonesia, suggesting a true primaquine resistance.

Relapse of \textit{P. ovale} after standard primaquine therapy is extremely unusual and only two cases have been reported, but compliance with primaquine treatment was doubtful.\textsuperscript{23,24} Re-infection and non-adherence had been thoroughly excluded in the two cases from this series. Another recent observation in a Belgian center suggests that a standard primaquine regimen may also be insufficient for \textit{P. ovale}.\textsuperscript{25} Therefore, a high-dosage primaquine regimen may be recommended for \textit{P. ovale} and \textit{P. vivax} infections, regardless of the region where the infection was acquired.\textsuperscript{22} Imported \textit{P. vivax}, \textit{P. ovale}, and \textit{P. malariae} infections cause significant morbidity even if complications are less severe than those with \textit{P. falciparum} malaria. In addition, some specific features need attention. First, the long latency period may weaken clinical suspicion. Our observations stress the need for the attending physician not only to obtain a travel history that extends back beyond the most immediate past, but also a prophylaxis and self-treatment history when malaria is considered. Second, parasite density is often low, thus rendering species identification by microscopy difficult. The current rapid diagnostic tests do not offset these limitations, and better techniques are needed. Finally, relapse after a standard primaquine therapy is widespread for \textit{P. vivax} regardless of its geographic origin and also occurs occasionally with \textit{P. ovale} infection. This is most likely due to underdosing, especially in heavier patients, rather than true resistance. Increasing the primaquine dosage regimen as recently recommended is therefore probably the best answer to these problems.

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REFERENCES


IMPOR TED NON-FALC IPARUM MALAR IA

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