Diagnosis and Therapy for Hospitalized Imported Malaria in Adults in Italy

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Background. The diagnosis and treatment of malaria in non-endemic countries presents a continuing challenge.  

Methods. Medical records were reviewed for 291 patients hospitalized with microscopically confirmed malaria diagnosed consecutively in two infectious diseases wards in Milano, Italy, between 1998 and 2007.  

Results. One hundred eighty-six (64%) were male; median age was 35 y (range 16–72 y). Of the 291 patients, 204 (70.1%) were non-immune travelers and 87 (29.9%) were considered semi-immune. In 228 patients (78.3%), Plasmodium falciparum was identified as the only causative malarial parasite. In 48 (16.5%), 9 (3.1%), and 1 (0.3%) cases, Plasmodium vivax, Plasmodium ovale, and Plasmodium malariae were diagnosed, respectively. Five mixed infections were observed (1.7%). Of the 233 falciparum cases (including mixed infections), 222 (95.3%) were acquired in sub-Saharan Africa. Fifty-four percent of P vivax infection were acquired in the Indian subcontinent and Southeast Asia. Chemoprophylaxis was used by 23.6% (61/258) subjects with only 32 fully compliant with the recommended regimen. At admission, fever, chills, and headache were present in 95.5, 59.5, and 55.3% of cases, respectively. Elevated serum lactate dehydrogenase levels (95%) and thrombocytopenia (82%) were the most frequently detected laboratory abnormalities. Thirty-five patients (15%) with P falciparum malaria presented with severe malaria according to the WHO criteria; in 19 patients (54.3%) more than one criteria was present. All patients recovered uneventfully. Inappropriate anti-malarial treatment occurred in 25 patients (8.6%) and were recorded more frequently among patients with a diagnosis of P vivax malaria (29.1%) as opposed to those affected by P falciparum (3.9%).  

Conclusions. In our study more than two thirds of imported malaria cases were due to P falciparum with an excess of cases diagnosed in immigrants starting from the year 2000. Despite many available guidelines inappropriate initial malaria treatment is relatively frequent even when patients are managed in an infectious diseases ward.

The number of malaria cases reported in European Union Countries each year is between 10,000 and 12,000 (crude rate 2.3/100,000 population) with France, UK, Germany, and Italy reporting the majority; approximately 1300–1500 cases per year are reported in the USA (CDC).2 Several studies have highlighted the clinical and epidemiological characteristics of imported malaria among travelers and immigrants and the problems related to delayed diagnosis, but only few data exist on the treatment of imported malaria.3–6 In fact, malaria treatment is becoming increasingly difficult due to widespread drug resistance of Plasmodium falciparum and the more recent emergence of chloroquine-resistant Plasmodium vivax7,8 together with possible drug-associated adverse events.5

There are several guidelines on the treatment of malaria that refer specifically to non-immune subjects, but recommendations are generally based on expert opinion more than on evidence arising from randomized clinical trials.9–12 The objective of this retrospective study was to describe the travel patterns, clinical characteristics, and the drug regimens used for the treatment of imported malaria in Milano, Italy and compare it with published series from Europe, North America, and Pacific regions.

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Patients and Methods

The site of our study, Luigi Sacco Hospital in Milano, Italy, is a 550-bed teaching hospital that is the reference infectious disease hospital of the metropolitan area of Milano.

All smear-positive malaria cases diagnosed between 1998 and 2007 at the II and III Division of Infectious Diseases were reviewed. Diagnosis and *Plasmodium* species identification were based on thin and thick malaria-positive smears stained with 5% Giemsa stain and examined by experienced laboratory personnel. Medical records were captured retrospectively, and data were entered into a malaria chart review form that was made in 2007 with the following items: demographic information (ie, age, sex, and nationality), travel history (ie, country of visit and length of stay, interval between date of return to Italy and diagnosis), immigration status, anti-malarial chemoprophylaxis use, interval between the date of onset of symptoms and the diagnosis, symptoms and signs, laboratory parameters, glucose-6-phosphatedehydrogenase testing in patients given primaquine, drug therapy and adverse events, fever clearance, and outcome. The immunologic status of patients relative to malaria infection was categorized as either non-immune or semi-immune; those classified as semi-immune either had reported a history of previous malaria or had been born in and recently emigrated from an endemic area. For the purpose of our analysis anemia was defined as a hemoglobin level of less than 12 g/dL; leukopenia as a white blood cell count of less than 4,000/μL; thrombocytopenia as a value of less than 150,000/μL.

Severe malaria was defined according to the last published World Health Organization (WHO) criteria.13

 Appropriateness of anti-malarial treatment was assessed using as references published guidelines from the Centers for Disease Control and Prevention referred to the period of observation of the patients and taking into account the drugs available in our country.9

Comparison of categorical variables were performed using the chi-squared test or Fisher’s exact test (two-tailed), depending on which was appropriate. Numerical variables were compared using t-test or the Mann–Whitney rank-sum test based on the distribution. All analyses were performed by using statistical software (SPSS version 15.0, SPSS Inc., Chicago, IL, USA). The limit of significance was p < 0.05.

Results

During the study period, 291 cases of malaria were diagnosed in non-immune (204, 70.1%) or semi-immune individuals (87, 29.9%). There were 186 male (63.9%) and 105 female (36.1%) patients with a median age of 35 years (range 16–72 y); 156 (53.6%) were Italian citizens, 5 (1.7%) were European citizens, and 130 (44.7%) were extra-European citizens. Of the latter, 35 (27%) were recent immigrants from malaria-endemic areas and 95 (73%) settled immigrants traveling to their country of origin (ie, visiting friends and relatives—VFRs). Extra-European patients originated from Africa (98, 75.3%), Asia (14, 10.7%), the Indian subcontinent (10, 7.7%), South-America (6, 4.6%), and the Middle-East (2, 1.5%). In more detail, African patients originated from 18 countries with Senegal (43, 43.8%), Nigeria (12, 12.2%), and Ivory Coast (7, 7.1%) being the most represented. All patients acquired malaria while traveling or living in malaria-endemic areas. The median duration of travel for tourism was 21 days (range 6–61 d) for Italian or European citizens and was significantly shorter than the period spent in malaria-endemic areas by VFRs (35 d, range 15–189 d) (p < 0.001). Overall, 61 of 258 (23.6%) subjects reported using chemoprophylaxis, but only 32 had taken an appropriate and well-followed chemoprophylaxis. Use of chemoprophylaxis was much more frequent among Italian travelers (53/146, 36%) than among extra-European immigrant subjects (8/112, 7.1%; p < 0.001). Of those fully compliant with chemoprophylaxis use, the regimens consisted of mefloquine (18/36, 56.2%), chloroquine plus proguanil (7/32, 21.8%), and chloroquine alone (7/32, 21.9%). Thirteen patients taking mefloquine chemoprophylaxis suffered from malaria caused by *P. vivax* (8 cases) or *Plasmodium ovale* (5 cases), and five by *P. falciparum* malaria (acquired in Kenya, Ivory Coast, Cameroon, Benin, and Senegal).

Malaria was caused by *P. falciparum* in 228 (78.3%) patients, *P. vivax* in 48 (16.5%) patients, *P. ovale* in 9 (3.1%) patients, *P. malariae* in 1 (0.3%) patient; 5 (1.7%) patients had mixed infections (four *P. falciparum* + *P. malariae*; one *P. falciparum* + *P. vivax*). In our series, patients with *P. falciparum* infections were much more likely to have been exposed in Africa than were patients with non-*falciparum* infections (222, 96.5% vs 26, 44.8%; p < 0.0001). All cases of *P. ovale* malaria were acquired in sub-Saharan Africa. Fifty-four percent of *P. vivax* infections were acquired in the Indian subcontinent and Southeast Asia; twenty-three percent each were acquired in sub-Saharan Africa (3 in west Africa, 7 in east Africa) or Central–South America.

Clinical Manifestations

The median time from arrival in Italy to the onset of symptoms was significantly longer for non-*falciparum* malaria as opposed to *P. falciparum* malaria (73 d vs 6 d; p < 0.001). The median time from symptoms’ onset to diagnosis was 3 days (range 0–47 d), with a statistically significant difference between *P. falciparum* (3 d, range 0–10 d) and non-*falciparum* (5 d, range 0–47 d) malaria (p = 0.001). The most common symptoms reported at the time of the initial positive smear were fever (278, 95.5%), chills (173, 59.5%), headache (161, 55.3%), and arthralgias/myalgias (137, 47.1%), whereas among signs the most frequent was hepatomegaly (121, 41.6%) with splenomegaly observed in 96 patients (33%) and jaundice in 17 (5.8%).

Laboratory Findings

The most common laboratory abnormalities observed in our case series were thrombocytopenia (239, 82%), elevated serum lactate dehydrogenase levels (276, 95%), elevations of liver transaminases (96, 33%), and anemia (89, 30%); only five patients (1.7%) had a hemoglobin level below 80 g/L. Plasmodium vivax-infected patients had lower mean platelet counts than P falciparum-infected subjects (86 × 10^9/L vs 97.9 × 10^9/L; p = 0.02). Quantification of parasites by direct microscopy was available on admission for 145 patients (49.8%) of whom 117 with P falciparum malaria (50%) and 28 (49.1%) with P vivax/P ovale; in more detail, for the former, parasite counts ranged from 68/μL to 1,652,000/μL (median value 60,600/μL) with 26 patients showing a parasite count of more than 5% (median 338,000/μL, range 253,460–1,652,000/μL). For the latter, parasitemia ranged from 210/μL to 57,600/μL (median 1,340/μL).

Clinical Course and Outcome

Of the 233 patients with P falciparum malaria, 35 (15%) fulfilled the WHO criteria for severe malaria; 19 patients (54.3%) had more than one WHO criteria; 6 patients (2.6%) were initially admitted to the intensive care unit (ICU) and 5 more patients were subsequently referred to the ICU (11 total patients requiring intensive care). Four patients received exchange transfusion as adjunctive therapy; all patients recovered uneventfully, but those treated in ICU had longer hospital stay (median 16 d vs 4 d; p < 0.001).

Management and Therapy

All patients, irrespective of the infecting Plasmodium species were admitted to the hospital; drug regimens employed are reported in Table 1. In our case file, mefloquine, either alone (173, 59.4%) or in combination with other drugs (27, 9.3%), was the most frequently used drug. It was employed in the treatment of all four Plasmodium species: in 177 patients infected by P falciparum (77.6%), 14 with P vivax (29.2%), 1 with P malariae (100%), 1 with P ovale (11.1%), and 3 mixed infections. The analysis of tolerance included 254 patients, thus excluding those who where treated with more than one drug: 34 (19.5%) adverse events were reported in those treated with mefloquine, 29 (76%) in the quinine-treated patients, and 2 (4.7%) in those receiving chloroquine (Figure 1). Cinchonism was registered exclusively in patients treated with quinine; only one patient treated with mefloquine discontinued treatment due to intractable vomiting.

Incorrect use of anti-malarial drugs occurred overall in 25 patients (8.6%) in our case file (Table 2); anti-malarial errors were recorded more frequently in patients infected by P vivax malaria (14/48, 29.1%) than in those with P falciparum malaria (9/229, 3.9%; p = 0.0001).

Table 1  Anti-malarial therapy by Plasmodium species in patients hospitalized in Milano, Italy

<table>
<thead>
<tr>
<th>Plasmodium species</th>
<th>Drug therapy</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P falciparum (228)</td>
<td>Mefloquine</td>
<td>164 (71.9)</td>
</tr>
<tr>
<td></td>
<td>Quinine + doxycycline</td>
<td>21 (9.2)</td>
</tr>
<tr>
<td></td>
<td>Quinine</td>
<td>15 (6.6)</td>
</tr>
<tr>
<td></td>
<td>Mefloquine + doxycycline</td>
<td>6 (2.6)</td>
</tr>
<tr>
<td></td>
<td>Mefloquine + quinine + doxycycline</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td></td>
<td>Mefloquine + quinine</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Atovaquone/primaquine</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Artether-lumefantrine</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Dihydroartemisinin-piperaquine</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Chloroquine</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>P vivax (48)</td>
<td>Chloroquine + primaquine</td>
<td>25 (52.1)</td>
</tr>
<tr>
<td></td>
<td>Mefloquine + primaquine</td>
<td>9 (18.7)</td>
</tr>
<tr>
<td></td>
<td>Chloroquine</td>
<td>6 (12.5)</td>
</tr>
<tr>
<td></td>
<td>Mefloquine</td>
<td>5 (10.4)</td>
</tr>
<tr>
<td></td>
<td>Halofantrine + primaquine</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td></td>
<td>Quinine + doxycycline + primaquine</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>P ovale (9)</td>
<td>Chloroquine + primaquine</td>
<td>7 (77.8)</td>
</tr>
<tr>
<td></td>
<td>Chloroquine</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td></td>
<td>Mefloquine</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>P malariae (1)</td>
<td>Mefloquine</td>
<td>1 (100)</td>
</tr>
<tr>
<td>P falciparum +</td>
<td>Mefloquine</td>
<td>3 (75)</td>
</tr>
<tr>
<td>P malariae (4)</td>
<td>Quinine + doxycycline</td>
<td>1 (25)</td>
</tr>
<tr>
<td>P falciparum +</td>
<td>Chloroquine + primaquine</td>
<td>1 (100)</td>
</tr>
</tbody>
</table>

Discussion

The epidemiological distribution in our cases was consistent with recent national malaria surveillance statistics, showing a preponderance of infections due to P falciparum (with near two thirds of cases attributable to this species) and with an excess of cases observed in immigrants beginning from the year 2000.14 In our series, patients coming from Africa were more likely to be infected with P falciparum (96.5%), whereas those coming from the Indian subcontinent or Southeast

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<table>
<thead>
<tr>
<th>Country</th>
<th>Reference, year</th>
<th>No. of cases/species identified</th>
<th>Treatment (most frequently used)</th>
<th>Percentage of inappropriate drug use (%)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>PR, 2011</td>
<td>291 ($P. falciparum$ 228; $P. vivax$ 48; $P. ovale$ 9; $P. malariae$ 1; mixed 5)</td>
<td>$P. falciparum$: mefloquine (71.9%); quinine + doxycycline (9.2%); others (19.9%)</td>
<td>8.6</td>
<td>All recovered</td>
</tr>
<tr>
<td>Canada</td>
<td>22, 1995</td>
<td>482 ($P. vivax$ 246; $P. falciparum$ 182; $P. ovale$ 24; $P. malariae$ 12)</td>
<td>$P. falciparum$: quinine-Py-S (30%); quinine + tetracycline (29%); others (41%)</td>
<td>11.2</td>
<td>1 death ($P. vivax$)</td>
</tr>
<tr>
<td>Canada</td>
<td>3, 1998</td>
<td>100 ($P. vivax$ 51; $P. falciparum$ 40; $P. ovale$ 5; mixed 4)</td>
<td>$P. falciparum$: quinine-Py-S (60.6%); chloroquine ± primaquine (18.2%); others (21.2%)</td>
<td>27</td>
<td>Failure of first therapy 11 patients; all recovered</td>
</tr>
<tr>
<td>USA</td>
<td>21, 2003</td>
<td>83 ($P. vivax$ 46; $P. falciparum$ 35; $P. ovale$ 11; mixed 10)</td>
<td>$P. falciparum$: (35): quinine + doxycycline (42.8%); quinine + clindamycin (20%); others (37.2%)</td>
<td>26.5</td>
<td>All recovered</td>
</tr>
<tr>
<td>France</td>
<td>5, 2005</td>
<td>474 ($P. falciparum$ 402; $P. vivax$ 37; $P. ovale$ 30; $P. malariae$ 11; mixed 10)</td>
<td>$P. falciparum$: quinine (53.2%); mefloquine (16.2%); others (29.6%); no treatment (1%)</td>
<td>6.2</td>
<td>Recovery 92%; the remainder lost to follow-up</td>
</tr>
</tbody>
</table>

PR = present report; Py-S = pyrimethamine-sulphamethoxypyrazine; NR = not reported.
Asia were infected with *P. vivax* in more than half of cases. A study of imported malaria performed in France regarding over 2,000 cases showed similar results with 94% of infections acquired in Africa and 80% of cases due to *P. falciparum*.12

It is well known that marked regional difference exists in the species of *Plasmodium* identified among different published series with *P. falciparum* accounting for over 80% in Europe,4,5,14–19 whereas in North America5,20–22 and the Pacific region *P. vivax* is diagnosed in 54% to 59% of imported cases.23,24 In this regard, travel history can provide useful clues in determining the responsible *Plasmodium* spp. when the microscopical diagnosis is uncertain. In our investigation the majority of patients who acquired malaria were not taking drugs for chemophrophylaxis or were non-compliant with the prescribed regimens—a data consistent with the 11% to 51% prevalence reported in previous studies.1,18,20–22 However, among those taking malaria chemophrophylaxis the highest rates of use were observed among tourists while the lowest among immigrants, thus corroborating previously reported figures.20,25 Worth noting, 72.2% of the 18 patients who developed malaria despite mefloquine prophylaxis, had *P. vivax* or *P. ovale* infections suggesting that even with effective chemophrophylaxis patients remain at risk for relapsing infections caused by hypnozoites. The absence of pharmacokinetic/pharmacodynamic data about mefloquine in the five patients with *P. falciparum* malaria makes elusive any conclusion about resistance. Clinical symptoms of imported malaria are not specific and thus their value is high only in the context of a carefully taken travel history. Moreover, case-control studies demonstrated that the only strong predictors of imported malaria were an enlarged spleen, hyperbilirubinemia, and thrombocytopenia,17,18,26 but splenomegaly (28.7%) and jaundice (11.5%) are only rarely observed. On the contrary, a platelet count below 50,000/µL was observed in 82% of our patients that is slightly higher than the 62.9% figure (range 50%–82%) reported in several studies.16,20,22,24 Although a recent study demonstrated that no single clinical or biological feature had both good sensitivity and specificity to predict malaria in febrile travelers, thrombocytopenia was the single most sensitive criterion (98.1%) and with a relatively high specificity (82.6%).26

A first problem about management of malaria emerging from our study concerns the fact that in about 50% of patients, levels of parasitemia were not established at the time of initial diagnosis. However, this unacceptable high inaccurate laboratory diagnosis was observed mainly in cases diagnosed before 2002 (data not shown).

Where incorrect prescription of anti-malarial drugs is concerned, in our series it occurred in 8.6% of cases, a figure that is consistent with estimates of 6 to 11% reported in three previous studies from France, the United States, and Canada,5,20,22 but better than the 26 to 27% observed in two other studies from Canada3 and the United States21 (Table 2). We observed statistically significantly fewer incorrect uses of anti-malarials in the treatment of patients with diagnosis of *P. falciparum* infection (3.9%) than in the treatment of *P. vivax* (29.1%), a data consistent with the results of the studies of Kain, Singh, and Ranque.3,5,21 However, in a study from the United States, incorrect use in anti-malarial therapy was much more frequent in the treatment of *P. falciparum* infection.20 Inappropriate initial anti-malarial therapy is of great concern especially in the case of *P. falciparum* malaria as this infection may run a life-threatening course. In our study, all the errors made in the treatment of *P. falciparum* infection should be considered serious errors as they regarded the selection of the wrong drug relative to the travel history (ie, chloroquine for patients coming from areas of chloroquine-resistance) or to the inappropriate consideration of the clinical presentation (ie, the use of mefloquine in patients with signs, or laboratory evidence of, severe malaria). In the three series reporting errors in anti-malarial therapy, we have calculated that serious treatment errors occurred, respectively, in 5.4%,21 17.2%,20 and 18%3 of *P. falciparum* infections. Even though two studies have clearly demonstrated that receiving inappropriate initial anti-malarial treatment was significantly associated with treatment employed at community hospital3 or to the absence of infectious disease specialist consultation,21 our present experience highlights that these errors occur also in a highly specialized setting. Moreover, our study shows that although almost 76% (222/291) of patients received four appropriate regimens (ie, mefloquine, quinine, quinine + doxycycline, and chloroquine + primaquine) the remaining patients were treated with nine different regimens; however, similar results are observed reviewing the published papers on malaria in travelers when treatment is detailed.1,13,20–22 In our experience, this unacceptable high variability of the drug regimen chosen is probably the consequence of the high number of physicians in charge, together with the absence of in-house “user-friendly” treatment guidelines.

In our study, mefloquine was the most frequently employed drug for the treatment of uncomplicated *P. falciparum* malaria with an overall frequency of adverse effects documented in 19.5% of patients. Although our study was retrospective and not specifically addressed to evaluate tolerance, mefloquine was generally well-tolerated, with only one case of drug discontinuation. This is in contrast with the results of a French multicenter study showing a 4.9 RR of discontinuation of treatment with mefloquine due to adverse effects when compared with another anti-malarial drugs.5 It is worth noting that in the four more recent and authoritative guidelines for the treatment of malaria, mefloquine was excluded for the treatment of acute uncomplicated malaria in two cases (ie, WHO and UK guidelines)11,13 and in the others the drug was ranked as second (French guidelines)12 or fourth line treatment (CDC).10 In the light of a widespread availability of

**Table 2.** Number and percentage of treatment errors reported in previous studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Errors in Treatment</th>
<th>Number of Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kain</td>
<td>200</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>Singh</td>
<td>100</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Ranque</td>
<td>190</td>
<td>15</td>
<td>28</td>
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In conclusion, it is necessary to provide an updated and accurate knowledge in order to successfully treat imported malaria and to provide easily accessible guidelines that can be well comprehended by physicians, travelers, and public health officials. In our study, we confirmed that an essential role in the management of imported malaria is represented by an accurate and careful evaluation of travel history and clinical presentation. Moreover, the present evidence suggests that the way in which the responsible physician chooses the anti-malarial treatment is of major importance in determining the therapeutic outcome. This is particularly relevant in a context of high variability of treatment regimens and frequent and inappropriate prescribing practices. Accordingly, this calls for the development of user-friendly guidelines as those published in the United States CDC.10
artemisinin compounds also in Europe it is plausible that mefloquine will be progressively abandoned to avoid the infrequent, but sometimes severe psychiatric side effects. As far as the rate of imported Plasmodium falciparum malaria is concerned in our case file it was slightly higher (15%) in comparison with the pooled frequency obtained from series of imported malaria considered here (102/1,465, 6.9%),1–3,6,21,23,24 but the outcome was favorable with no death from malaria. Although the retrospective nature of our study is subject to several biases we can speculate that the rapid and high level collaboration with our intensivists might have played an important role in achieving this result. It is worth noting that the average case fatality rate registered in Italy between the years 2000 and 2006 was 0.5%; that is substantially similar to the 0.4% observed in France in a study performed over 8 years regarding about 22,000 patients with P falciparum malaria27,28 and better than those reported in other European countries.29 In the management of severe Plasmodium falciparum malaria the universally recognized issue is the immediate start of the appropriate par- enteral treatment. The recently published results of AQUAMAT study definitively demonstrated, together with those obtained in the SEQUAMAT, that in the treatment of severe falciparum malaria, intravenous artesunate (not available in Europe and investigational in treatment of severe Plasmodium falciparum malaria imported from the tropics. Antimicrob Agents Chemother 2001; 45:932–935.


In conclusion, our study and the analysis of the literature concerning treatment of imported malaria show that incorrect prescription of anti-malarial therapy occurs also in highly specialized infectious diseases wards. Retrospective surveys of case files are helpful to identify inappropriate management and to introduce corrective measures to ensure high standards of care.

Declaration of Interests
The authors state that they have no conflict of interests.

References


