Domestic Refugee Health Guidelines: Malaria

November 26, 2018

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Presumptive Treatment of *P. falciparum* Malaria in Refugees Relocating from Sub-Saharan Africa to the United States

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Key Points

- Refugees from sub-Saharan Africa who have received pre-departure treatment with a recommended antimalarial drug or drug combination do not need further evaluation or treatment for malaria unless they have signs or symptoms of disease.
- Subclinical *P. falciparum* malaria may be present in refugees from hyperendemic or holoendemic regions of sub-Saharan Africa. If a refugee has been in a non-endemic region for more than 3 months, falciparum malaria is unlikely, though possible—symptomatic patients should be tested.
- Refugees originating from sub-Saharan Africa who have not received pre-departure therapy with a recommended regimen should receive presumptive treatment at the domestic medical screening visit, if within 3 months of arrival (Table 1).
Table 1. Dosing of antimalarials that may be considered for presumptive or directed* treatment of *P. falciparum* malaria in sub-Saharan African refugees after arrival in the United States

<table>
<thead>
<tr>
<th>Presumptive Therapies</th>
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<tbody>
<tr>
<td><strong>Medication</strong></td>
<td><strong>Child Dosing</strong></td>
<td><strong>Adult Dosing</strong></td>
</tr>
<tr>
<td></td>
<td><em>Children weighing 5 kg to &lt; 35 kg</em></td>
<td><em>Persons weighing &gt; 35 kg</em></td>
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<tr>
<td>Atovaquone-proguanil</td>
<td></td>
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<tr>
<td>(adult tab = 250 mg atovaquone/100 mg proguanil)</td>
<td><strong>5-8 kg</strong>: Two pediatric tablets once a day for 3 days</td>
<td>Four adult tablets once a day for 3 days</td>
</tr>
<tr>
<td>(pediatric tab = 62.5 mg atovaquone/25 mg proguanil)</td>
<td><strong>9-10 kg</strong>: Three pediatric tablets once a day for 3 days</td>
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<tr>
<td></td>
<td><strong>11-20 kg</strong>: One adult tablet once a day for 3 days</td>
<td></td>
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<tr>
<td></td>
<td><strong>21-30 kg</strong>: Two adult tablets once a day for 3 days</td>
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<tr>
<td></td>
<td><strong>31-35 kg</strong>: Three adult tablets once a day for 3 days</td>
<td></td>
</tr>
<tr>
<td>Artemether-lumefantrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(20 mg artemether and 120 mg lumefantrine)</td>
<td>A six-dose regimen is recommended with 1 to 3 tablets per dose, depending on body weight:</td>
<td>A standard 3-day treatment schedule with a total of 6 doses (total course: 24 tablets). Initial dose consists of four tablets, after 8 hours four more tablets (dose 2). Then four tablets twice daily (morning and evening) for the following 2 days.‡</td>
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<tr>
<td></td>
<td><strong>5 to &lt; 15 kg</strong>: One tablet, then one tablet after 8 hours, then one tablet twice daily (morning and evening) on each of the following 2 days (total course: 12 tablets)</td>
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<tr>
<td></td>
<td><strong>15 to &lt; 25 kg</strong>: Two tablets as a single dose, then two tablets after 8 hours, then two tablets twice daily (morning and evening) on each of the following 2 days (total course: 18 tablets)</td>
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<tr>
<td></td>
<td><strong>25 to &lt; 35 kg</strong>: Three tablets as a single dose, then three tablets after 8 hours, then three tablets twice daily (morning and evening) on each of the following 2 days (total course: 18 tablets) ‡</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Directed Therapy* Alternatives</th>
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<tbody>
<tr>
<td><strong>Medication</strong></td>
<td><strong>Child Dosing</strong></td>
<td><strong>Adult Dosing</strong></td>
</tr>
<tr>
<td></td>
<td><em>Children weighing 5 kg to &lt; 35 kg</em></td>
<td><em>Persons weighing &gt; 35 kg</em></td>
</tr>
</tbody>
</table>

*Note: *The above dosages are intended for use as a guideline and should be adjusted based on individual patient characteristics and clinical judgment. ‡ Additional details and considerations for directed therapy are provided in the original reference text.*
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Details</th>
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<tbody>
<tr>
<td>Quinine sulfate</td>
<td>30 mg salt/kg three times a day for 3 days§</td>
</tr>
<tr>
<td>plus clindamycin</td>
<td>20 mg base/kg/d divided in three doses for 7 days§</td>
</tr>
<tr>
<td>or doxycycline</td>
<td>2.2 mg/kg/d for 7 days§</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>&lt; 45 kg: 15 mg/kg then 10 mg/kg 12 hours later§</td>
</tr>
<tr>
<td></td>
<td>45 kg to 65 kg: 10 mg/kg then 10 mg/kg 12 hours later§</td>
</tr>
<tr>
<td></td>
<td>65 kg: 20 mg/kg then 10 mg/kg 12 hours later§</td>
</tr>
<tr>
<td></td>
<td>75 kg: 30 mg/kg then 10 mg/kg 12 hours later§</td>
</tr>
<tr>
<td></td>
<td>80 kg: 40 mg/kg then 10 mg/kg 12 hours later§</td>
</tr>
<tr>
<td></td>
<td>100 kg: 60 mg/kg then 10 mg/kg 12 hours later§</td>
</tr>
</tbody>
</table>

* Directed therapy refers to treatment after *P. falciparum* malaria infection is confirmed

† Should be taken with foods rich in fat, such as milk. If vomiting occurs within 1 hour after taking the medicine, another dose should be taken.

§ Do not exceed adult dosing.

¶ Not approved for use in children less than 8 years old.

‖ Should not be used with quinine or quinidine. Common adverse effects include nausea, vomiting, diarrhea, dizziness, toxic psychosis, and seizures.

NOTE: More specific guidance can be found at the CDC malaria website.

- If presumptive treatment is contraindicated, laboratory screening should be done if the patient has signs or symptoms of malaria. Presumptive treatment is contraindicated for the following groups:
  - Pregnant women
  - Women breastfeeding infants weighing < 5 kg
  - Infants weighing < 5 kg
  - Those with a known allergy to the specific malaria medication being used

  - Sensitivity of the testing modality varies in persons with asymptomatic or subclinical infections.

Table 2: Testing modalities for malaria in refugees with contraindications to presumptive treatment

<table>
<thead>
<tr>
<th>Very Sensitive</th>
<th>Moderately Sensitive</th>
<th>Least Sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria polymerase chain reaction (PCR)</td>
<td>Blood smears (three samples obtained 12–24 hours apart)</td>
<td>Malaria rapid diagnostic test (RDT)</td>
</tr>
</tbody>
</table>

- Refugees from regions endemic for malaria who present with signs or symptoms of malaria, irrespective of receipt of presumptive treatment, should be promptly evaluated and treated, as indicated.

- Refugees from areas other than sub-Saharan Africa are not routinely presumptively treated or tested, unless specifically directed.

- Special note: Infants and pregnant women are considered at high risk for rapid progression as well as significant morbidity and mortality from *P. falciparum* malaria infection.

**Background**

Each year, as many as 70,000 refugees are accepted for resettlement to the United States. The proportion of newly arriving refugees originating from Africa increased from 9% in 1998 to 39% in 2005 [1]. Since
2005, African refugee arrivals have accounted for 30%–40% of all new arrivals annually [1]. Because of its potential virulence and dynamic epidemiology, including its high prevalence, malaria has emerged as a disease of particular concern in this population.

Although global malaria incidence has declined, there were an estimated 214 million new cases of malaria worldwide in 2015, with 88% of cases occurring in Africa [2]. The acute clinical consequences of infection and disease are most severe in persons who are not immune; as a result, in highly endemic areas, young children account for most malaria deaths. Although four species of malaria infect humans, the burden and consequences of *Plasmodium falciparum* predominate. Among those with no immunity, *P. falciparum* infection may lead to death within 12 hours after the onset of symptoms. In contrast, in highly endemic (hyperendemic or holoendemic) areas, most older people individuals have acquired partial immunity and may have few or no symptoms. Areas with high endemcity are most common in West and Central Africa and in geographically discrete areas of East Africa. *P. malariae* and the relapsing species of human malaria, *P. vivax* and *P. ovale*, also occur in sub-Saharan Africa but cause severe disease or death less often than *P. falciparum*.

Other areas, such as Central Asia, South Asia, Southeast Asia, and parts of Latin America and the Caribbean, have varying levels of malaria transmission, although rarely reaching hyperendemic or holoendemic levels. These areas also have varying ratios of *P. falciparum* and non-falciparum malaria; many have a higher proportion of non-falciparum malaria (specifically *P. vivax*) than *falciparum* malaria.

Malaria was endemic in most of the continental United States and much of Europe into the 20th century. Most of the continental United States has *Anopheles* mosquitoes (particularly *An. quadramaculatus* and *An. freeborni*), which are competent vectors of malaria under favorable conditions. Local US vector-borne transmission has resulted in more than 150 locally transmitted cases and more than 60 outbreaks in the United States over the past 50 years [3, 4]. In addition, more than 1,700 cases of malaria are reported annually in the United States, with most cases occurring in returned travelers [5].

Malaria has historically plagued displaced populations in endemic areas, and this situation continues in many refugee settings [6, 7]. When refugees lack access to host country national health programs, they may be at increased risk for many diseases, including malaria and other parasitic infections.

**Pre-departure presumptive malaria therapy in US-bound refugees**

Refugees may arrive in North America with asymptomatic or subclinical malaria infection [7-9]. Some refugees who have subclinical infection will develop disease after arrival, while others will clear infection without developing disease [10]. Lack of knowledge of malaria among healthcare professionals in the United States frequently leads to delay in diagnosis and inappropriate treatment [11, 12]. This lack of familiarity has been associated with fatal outcomes [12]. In addition, malaria may interfere with a refugee’s successful integration into a host community by creating issues such as physical incapacity, added financial stresses, and social stigma.

Refugees may have subclinical *P. falciparum* malaria, which could persist for months after arrival. Although rare, there is potential that circulating parasites could be a source of autochthonous transmission. To date, no transmission has been traced conclusively to a newly arrived refugee.

Data collected from 1997 to 1999 showed that 60% of Liberian refugees, arriving from four primary countries of asylum in holoendemic West Africa, were parasitemic 4 weeks after arrival [13]. Of untreated refugees arriving in Canada from an area of lower transmission in Tanzania, 18% had evidence of infection 3 months after arrival [8]. In the late 1990s, concerns about the high prevalence of
Plasmodium infection in refugees from sub-Saharan Africa led the CDC to recommend that all refugees departing for the United States from malaria-endemic areas in sub-Saharan Africa receive presumptive therapy for malaria. These recommendations were issued in May 1999 to organizations and clinicians performing pre-departure examinations and management (“panel physicians”). The treatment recommended at that time was a presumptive course of sulfadoxine-pyrimethamine (SP, Fansidar™).

Following implementation of presumptive therapy, there was a dramatic drop in imported cases in a high-risk West African cohort of refugees arriving in Minnesota, with the incidence decreasing from more than 8% to nearly zero between 1996 and 2005 [10]. An evaluation found substantial cost savings for host communities and estimated that the presumptive treatment program was cost-effective when the rate of clinical malaria in a population exceeded 1.5% in departing populations. This analysis estimated that among West African refugees, 12 refugees needed to be treated to prevent one case of clinical malaria [10].

However, by 2000, it was noted that SP treatment of malaria in Africa was becoming increasingly ineffective because of rising resistance. Among 103 newly arrived Liberian refugees who were treated with SP before resettlement in Minnesota, 8.7% were found to have subclinical P. falciparum at 4 weeks after arrival [9]. In 2006, the World Health Organization (WHO) changed its recommendation for the treatment of choice for clinical malaria in Africa from SP to artemisinin-based combination therapy (ACT) [14]. CDC subsequently revised its domestic refugee malaria guidelines to correspond with the WHO recommendations because of concerns for persistent malaria in refugees arriving in the United States.

However, for many reasons, including global artemisinin shortages, the US Refugee Admissions Program continued to use SP for pre-departure treatment. In spring 2007, additional cases of clinical malaria were reported to CDC in Burundian refugees arriving from Tanzania. In May 2007, active surveillance started, and pre-departure ACT was initiated (artemether-lumefantrine). Between May 2007 and February 2008, more than 6,100 African refugees were processed in Tanzania and resettled in the United States, some of whom were presumptively treated with SP while others received ACT. Thirty-nine malaria cases were detected among those resettled, with 82% of cases resulting in hospitalization and 10% having severe manifestations. Of those with severe manifestations, 27% had a parasitemia level exceeding 5%. Most importantly, disease incidence in the SP group was 15.5/1,000, while those who received ACT had an incidence of 1.3/1,000 [15]. Since 2008, presumptive ACT has been used to prevent P. falciparum malaria cases in sub-Saharan African refugees resettling to the United States.

Recommendations for Pre-departure Presumptive and Directed Treatment for P. falciparum Infection for Refugees From sub-Saharan Africa

The currently recommended ACT regimen is artemether-lumefantrine because it is widely available as a fixed combination tablet, is available in most refugee camps, has a wide therapeutic window and a minimal adverse event profile, and is consistent with most national guidelines for treating clinical malaria. Pre-departure presumptive malaria therapy must be administered and documented as directly observed therapy, and the refugee must carry this documentation. To be considered valid, the presumptive therapy must be completed no sooner than 5 days before departure.

Special populations, including pregnant women, infants weighing less than 5 kilograms (kg), and lactating women who are breastfeeding infants under 5 kg, should not receive presumptive pre-departure treatment. These individuals should receive only directed treatment after diagnostic testing identifies
malaria parasitemia. The most common treatment regimens for these populations include a combination of oral quinine and clindamycin (preferred), or a longer course of oral quinine, although the treatment of clinical malaria is beyond the scope of this document.

Refugees who have signs or symptoms of clinical malaria before departure should be evaluated and treated according to the host country’s national guidelines.

**Recommendations for Post-arrival Presumptive and Directed Treatment for Malaria for Refugees From sub-Saharan Africa**

- Refugees who have received pre-departure treatment with a recommended antimalarial drug or drug combination do not need further evaluation or treatment for malaria unless they have signs or symptoms of disease. Subclinical *P. falciparum* malaria may be present in infants and children from hyperendemic and holoendemic regions of sub-Saharan Africa. Clinical disease, when it occurs, generally manifests within 3 months of arrival. If a refugee has been living in a non-endemic region for more than 3 months, falciparum malaria is unlikely, although any symptomatic refugee should be tested.

- It is recommended that refugees (including children) originating in sub-Saharan Africa who have not received pre-departure therapy with a recommended regimen either receive presumptive treatment on arrival (preferred) or have laboratory screening to detect *Plasmodium* infection within 3 months of arrival.

- Refugees from regions endemic for malaria, and who present with signs or symptoms of malaria, should be promptly evaluated and treated, as indicated.

- Refugees from areas other than sub-Saharan Africa who are asymptomatic do not need routine presumptive treatment or testing, unless under specific instructions by CDC.

- For refugees with contraindications to presumptive treatment, testing should be performed if seen within 3 months of arrival (e.g., pregnant women, infants weighing < 5 kg).

**Post-arrival Presumptive Antimalarial Treatment**

When presumptive treatment for malaria is deemed necessary, atovaquone-proguanil (trade name Malarone™) and artemether-lumefantrine (Coartem™) are the medications of choice in the United States. Atovaquone-proguanil and artemether-lumefantrine are effective treatments for *P. falciparum* malaria as well as *P. malariae* and the blood stages of *P. vivax* and *P. ovale* (Table 1). In addition, there is little parasite resistance to these medications, the treatment regimens are short, and they are well tolerated with few adverse effects. All other available oral medications have higher rates of adverse effects (e.g., mefloquine) or more complex dosing regimens of combination medications (e.g., quinine plus a second agent) and are therefore of limited use for presumptive treatment. Additional information on the treatment of malaria can be found on the CDC malaria website.

**Medical and Laboratory Screening After Arrival**

An alternative to presumptive treatment is to test newly arriving sub-Saharan African refugees for malaria infection. However, the limitations to available testing in those with asymptomatic or subclinical infection should be considered. Although microscopic examination of a properly stained blood smear remains the standard for diagnosis of *Plasmodium* infection in symptomatic individuals presenting in the United States, studies have demonstrated that a single malaria thick and thin blood smear has low
sensitivity for detecting asymptomatic or subclinical malaria [8, 9]. Three separate blood films taken at 12- to 24-hour intervals (standard recommendation for diagnosis of clinical malaria) have a greater sensitivity than a single blood smear. However, this approach may not be feasible for screening newly arriving refugees because of cost constraints and the need for multiple visits.

A rapid diagnostic test (RDT) is approved for use in the diagnosis of symptomatic malaria in the United States. Although this test has excellent sensitivity for *P. falciparum* in symptomatic patients, it is less than 30% sensitive in the diagnosis of asymptomatic or subclinical infection for *P. falciparum* in newly arrived refugees [9]. Because of this, a blood smear should also be done to validate RDT results. Polymerase chain reaction (PCR) is the most sensitive test and is the preferred method to test for asymptomatic or subclinical malaria [16]. Challenges with PCR include limited availability (it is available in larger referral laboratories), cost, and time to receive results.

Therefore, screening with laboratory testing can present challenges to clinics, and local determination of feasible testing modalities must be considered. If PCR is not available, examination of blood smears should be conducted, as it is the next most sensitive option. A single blood smear has limited sensitivity, and ideally multiple blood smears (up to three) should be performed over 2 or 3 days. If RDT is the only test available, note that it has an even lower sensitivity in detecting asymptomatic infections than a single smear, and that a smear should also be done as soon as possible to validate RDT results. Regardless of testing modality or presumptive treatment, all refugees should be advised to report any signs or symptoms of disease, as no presumptive treatment or diagnostic test is 100% effective.

Some hematologic or physical examination findings in screening of asymptomatic individuals, such as thrombocytopenia or splenomegaly, are associated with malaria in individuals from highly endemic areas [13]. Malaria should be considered in the differential diagnosis of refugees with these clinical signs, even when not symptomatic. High rates of splenomegaly have been observed in Congolese refugees, and CDC has issued specific guidance for this population [17, 18].

**Precautions and Contraindications to Presumptive Treatment**

Certain populations are excluded from malaria presumptive regimens; these groups include pregnant women, and persons with other contraindications such as allergy or hypersensitivity to malaria medications. In addition, infants weighing less than 5 kilograms, and women breastfeeding infants under 5 kg, should not receive pre-departure or post-arrival ACT, or atovaquone-proguanil.

Before departure, individuals in these groups should all undergo diagnostic laboratory testing and receive directed treatment if they are found to have *Plasmodium* infection. Overseas diagnostic testing should be performed with blood films or rapid diagnostic tests with a kit approved for use by CDC’s Division of Global Migration and Quarantine in accordance with the Quality Assessment Program for Panel Physicians. Pregnant women, children weighing < 5 kilograms, and lactating women breastfeeding children who weigh < 5 kg who test positive at overseas sites should have directed therapy according to the national guidelines in their host country.

**Refugees from Other Regions**

Refugees arriving from Southeast Asia, South Asia, Central Asia, and all areas in the Western Hemisphere generally come from areas with low or no malaria transmission. In contrast to refugees from sub-Saharan Africa, it is rare for persons from these areas to have asymptomatic or subclinical *P.*
falciparum malaria infection. In these refugee populations, the risks and cost of post-arrival presumptive treatment outweigh the potential benefits. Furthermore, routine laboratory screening (given challenges with sensitivity and predictive value in low prevalence populations, cost, and test availability) is not indicated unless signs or symptoms of disease are present. Therefore, CDC recommends presumptive treatment or routine laboratory screening for malaria only in specific groups of refugees from areas outside sub-Saharan Africa. However, any refugee from an endemic area with signs or symptoms of malaria should receive diagnostic testing for Plasmodium and treatment for confirmed infections.

Strategies to Prevent Non-falciparum Malaria in Newly Arriving Refugees

Non-falciparum malaria (caused by P. ovale, P. vivax, or P. malariae) is less often associated with severe illness or death. Two species, P. ovale and P. vivax, may form a parasite life stage (hypnozoite) that lies dormant in the liver for months to years before re-emerging to cause blood stage infection and subsequent clinical disease. Primaquine is the only Food and Drug Administration-approved medication in the United States to treat hypnozoites and must be administered for 14 days. Presumptive therapy is complicated by the need to test glucose-6-phosphate dehydrogenase (G6PD) enzyme level before treating with primaquine, because of the potential risk of life-threatening hemolytic anemia in G6PD-deficient individuals. P. vivax has many variants, and the efficacy of primaquine can vary depending on the variant—14 days of primaquine dosed at 15 mg/day (the traditional regimen) may cure only 30% to 80% of hypnozoite infections [19]. A higher dose (30 mg/day) is now recommended for better efficacy in both radical cure and presumptive antirelapse therapy. Laboratory testing by blood film and rapid testing for non-falciparum malaria has even lower sensitivity than for P. falciparum malaria and is of no value in screening asymptomatic individuals.

Plasmodium malariae may cause persistent infections, although it has no dormant liver stage. Infected individuals are frequently asymptomatic, although they may develop clinical malaria leading to other complications, including nephrotic syndrome. P. malariae is the most common malaria species associated with blood transfusion-acquired infection in the United States. Since this organism is not common and is thought to respond to currently recommended presumptive therapy for P. falciparum, there are no additional recommendations for P. malariae infection.

References


