# Malaria Screening

## Recommendations for Pre-departure Presumptive and Directed Treatment for *P. falciparum* Infection for Refugees from Sub-Saharan Africa

The recommendations in this document provide revised guidance for presumptive treatment of asymptomatic *Plasmodium* infection in refugees relocating to the United States and should replace those issued in 1999. The revised regimen for pre-departure presumptive treatment is artemisinin-based combination therapy (ACT)—see overseas presumptive treatment guidelines for details. The currently recommended ACT regimen is artemether-lumefantrine because it is available as a fixed combination tablet, is available in most refugee camp settings, has a wide therapeutic window, minimal adverse event profile, and is consistent with most national guidelines for treating clinical malaria. (Table 1) Malaria pre-departure presumptive therapy must be administered and documented as directly-observed therapy, and this documentation must be carried by the refugee. To be considered valid the presumptive therapy must be completed no sooner than 3 days prior to departure. All suspected and confirmed medication adverse effects must be documented and reported to the CDC by the organization or panel physician providing pre-departure care (Division of Global Migration and Quarantine, (404) 498-1600).

Special populations including pregnant or lactating women and children <5 kilograms require directed treatment after diagnostic testing and thus should not receive presumptive therapy. Individuals in these groups who lack signs and symptoms of malaria but have laboratory-diagnosed *Plasmodium falciparum* infection should be treated with either a combination of oral quinine and clindamycin (preferred) or a longer course of oral quinine.

Prior to departure, refugees who have signs or symptoms of clinical malaria 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 recommended pre-departure presumptive or directed therapy
- 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 clinical symptoms.
- Refugees who have not received the recommended presumptive or directed pre-departure treatment
- It is recommended that refugees 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.

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### Post-arrival presumptive anti-malarial treatment

The medication of choice for presumptive post-arrival treatment of malaria is atovaquone-proguanil (Malarone®, AP). This antimalarial is recommended because it is highly effective for treatment of *P. falciparum* malaria (as well as *P. malariae* and the blood stages of *P. vivax* and *P. ovale*), there is little parasite resistance to the drug, the treatment regimen is short and simple, and it is generally well tolerated with few adverse effects. All other available medications have higher rates of adverse effects (e.g. mefloquine) or more complex dosing regimens of combination medications (e.g., quinine/quinidine plus a second agent) and are of limited use for presumptive treatment. ACT therapy is not yet available in the United States, when available it will be a reasonable alternative. Therefore, newly arriving sub-Saharan refugees should receive presumptive therapy with AP (Table 2) on arrival or during their new arrival refugee medical visit.

### Medical and laboratory screening after arrival

A sub-optimal alternative to presumptive therapy is to test newly arriving sub-Saharan refugees for malaria infection. Although microscopic examination of a properly stained blood smear remains the standard for diagnosis of *Plasmodium* infection in symptomatic individuals presenting in the U.S., studies have demonstrated that a single malaria thick-and-thin blood smear lacks sensitivity (<40%) for detecting asymptomatic or sub-clinical malaria in these populations. [1] [2] Three separate blood films taken at 12 to 24 hour intervals, the standard recommendation for diagnosis of clinical malaria, has a greater sensitivity. However, this approach is rarely feasible for screening newly arriving refugee populations because of cost constraints and the need for multiple visits. A rapid diagnostic test (RDT) was recently approved by the U.S. Food and Drug Administration (NOW-MalariaÔ) for use in diagnosis of symptomatic malaria in the United States. Although this test has excellent sensitivity for *P. falciparum* in symptomatic patients preliminary data suggests it is less than 30% sensitive in the diagnosis of asymptomatic *P. falciparum* in newly arrived refugees. [2] When a refugee does not receive presumptive therapy they should be monitored for signs or symptoms of disease, particularly during the initial 3 months after arrival, regardless of the post-arrival testing results.

Although this document addresses individuals with no signs or symptoms of malaria, it is worth noting hematologic and physical examination findings that may be noted on screening in asymptomatic individuals and which have a high positive predictive value for malaria. Two studies have demonstrated that no parameters, including anemia and/or thrombocytopenia, consistently predict persons with infection (poor sensitivity and negative predictive value). [1] [3] However, when thrombocytopenia or splenomegaly are present among individuals in these populations, they frequently indicate malaria (high specificity and positive predictive value). [3] Refugees with these clinical signs, even when not symptomatic, should receive appropriate evaluation for clinical malaria.

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## Precautions and Contraindications to Presumptive Treatment

Certain populations are excluded from all presumptive regimens; these groups include pregnant women, lactating women, and persons with other contraindications such as allergy or hypersensitivity to medications. In addition, children <5 kilograms should not receive pre-departure ACT or post-arrival AP.

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 Assurance Program for Panel Physicians. Pregnant and lactating women as well as children weighing <5 kilograms who test positive at overseas sites should have directed therapy with quinine/clindamycin or a prolonged quinine course. (Table 3)

Testing in the U.S. by malaria blood film is acceptable since the specificity is high, but any patient that tests negative must be followed clinically for occurrence of disease because of the poor sensitivity of these tests in individuals without symptoms. The FDA approved rapid test in the U.S. has been shown to be neither sensitive nor specific.[9] Testing by RDT may be performed but is neither sensitive nor specific. If the RDT is negative the patient must still be monitored for clinical disease; if positive, a confirmation test should be performed such as blood film or polymerase chain reaction (PCR). Given that *P. falciparum* malaria is known to be particularly severe in pregnant women and infants, and given the poor sensitivity and negative predictive value of blood film and RDT, PCR should be considered for screening in these selected populations when it is available. PCR is commercially available and may also be accessed through some State Health Departments and the CDC. Pregnant and lactating women who test positive for *Plasmodium* infection on screening in the U.S. should be treated according to U.S. standards and may need to be referred to a specialist for therapy. (Table 4)

## 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 absent levels of malaria transmission. In contrast to the situation among refugees from sub-Saharan Africa it is rare for persons from these areas to have asymptomatic or sub-clinical *P. falciparum* malaria infection. In these refugee populations, the risk and cost of post-arrival presumptive treatment currently outweighs the potential benefits. Furthermore, laboratory screening, especially given the issues with sensitivity, specificity and availability of the testing, is not indicated. Therefore, currently, CDC does not recommend presumptive treatment or routine laboratory screening for malaria in refugees from areas other than sub-Saharan Africa. However, any refugee from an endemic area with signs or symptoms of malaria should be receiving diagnostic testing for *Plasmodium* and subsequent treatment for confirmed infections.

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## Table 1a. Pre-departure Treatments for U.S.-bound Refugees

| >This table describes the current status of presumptive pre-departure treatments for refugees from various regions. | | | | |
|---|---|---|---|---|
| **Region** | **Presumptive Pre-departure Treatment** | | | **Malaria Regimen [ACT] ◊** |
| | **MMR Vaccine *** | **Intestinal Parasites†** | **Malaria†** | **Date of Implementation** |
| **Sub-Saharan Africa** | | | | |
| **Kenya** | | | | |
| Nairobi | √ | √ | √ | 10/1/2007 |
| Kakuma | √ | √ | √ | 7/11/2007 |
| Dadaab | √ | √ | √ | 8/21/2007 |
| **Tanzania** | | | | |
| Kibondo | | √ | √ | 7/4/2007 |
| *-Kanembwa* | | √ | √ | 7/4/2007 |
| *-Nduta* | | √ | √ | 7/4/2007 |
| Kasulu | | √ | √ | 7/4/2007 |
| *-Mtabila I* | | √ | √ | 7/4/2007 |
| *-Mtabilia II* | | √ | √ | 7/4/2007 |
| *-Mabanda* | | √ | √ | 7/4/2007 |
| *-Muyovosi* | | √ | √ | 7/4/2007 |
| *-Lugufu I* | | √ | √ | 7/4/2007 |
| *-Lugufu II* | | √ | √ | 7/4/2007 |
| *-Nyarugusu* | | √ | √ | 7/4/2007 |
| Ngara | | √ | √ | 7/4/2007 |
| *-Lukole A* | | √ | √ | 7/4/2007 |
| *-Lukole B* | | √ | √ | 7/4/2007 |
| **Ethiopia** | | | | |

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| | **MMR Vaccine *** | **Intestinal Parasites†** | **Malaria†** | **Date of Implementation** |
| **Sub-Saharan Africa** | | | | |
| Addis Ababa | | √ | √ | 10/1/2007 |
| Shimelba | | √ | √ | 10/1/2007 |
| **Southeast Asia** | | | | |
| **Thailand** | √ | √ | | |

* Given according to ACIP recommendations. All refugees born after 1957 or later receive at least 1 dose of vaccine.

† IOM does an excellent job of providing U.S.-bound refugees with pre-departure antimalaria and deworming treatment. Please assume all eligible U.S.-bound refugees have received this treatment, even if they arrive without documentation.

◊ The majority of arrivals will have received ACT (Artemisinin-based Combination Therapy), with the exception of certain refugees. See the Overseas Refugee Health Guidelines for details.

**Table 1b. Presumptive Pre-departure Treatment Regimens for Intestinal Parasites**

| **Condition** | **Regimen** | |
|---|---|---|
| | **Adults** | **Children** |
| **Intestinal Parasites** | | |
| **Albendazole (Albenza) (Albuzol)** | • 400 mg in one dose<br>• Except pregnant women in 1st trimester | • 400 mg in one dose<br>• Except children <2 years of age |

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**Table 2. Dosing of anti-malarials that may be considered for presumptive or directed* treatment of *P. falciparum* malaria in sub-Saharan refugees after arrival in the U.S.**

| Medication | Child dosing | Adult dosing |
|---|---|---|
| **Presumptive therapy**<br>**Atovaquine-Proguanil**<br>(adult tab = 250 mg atovaquone/100 mg proguanil<br>Pediatric tab = 62.5 mg atovaquone/25 mg proquanil) | **5-8 kg:** two pediatric tabs po once a day for 3 days<br>**9-10 kg:** three pediatric tabs po once a day for 3 days<br>**11-20 kg:** One adult tablet once a day [1] for 3 days<br>**21-30 kg:** two adult tablets once a day [1] for 3 days<br>**31-40 kg:** three adult tablets once a day [1] for 3 days<br>**>40 Kg:** four adult tablets once a day [1] 3 d days | Four adult tablets once a day [1] for 3 days |
| **Alternatives that may be used as directed therapy *** <br>Quinine sulfate | 30 mg/kg/d divided in 3 doses x 3 days | 650 mg q 8 hours x 3 days [2] |
| **plus** clindamycin | 20-40 mg/kg/d in 3 doses x 7d | 900 mg. tid x 7 days [2] |
| **or** doxycycline [3] | 2 mg/kg/d x 7 d | 100 mg bid x 7 d [2] |
| **Other Alternatives**<br>Mefloquine [4] | **<45 kg:** 15 mg/kg then 10 mg/kg 12 hours later | 750 mg then 500 mg 12 hours later [2] |

* Directed therapy refers to treating after *P. falciparum* malaria has been detected by diagnostic examination in an asymptomatic individual.
NOTE: more specific guidance can be found at:
www.cdc.gov/malaria/diagnosis_treatment/tx_clinicians.htm

[1] May divide dose bid for better gastrointestinal tolerance.

[2] Do not exceed adult dosing.

[3] Not approved for use in children less than 8 years.

[4] Should not be given together with quinine or quinidine. Common adverse effects include nausea, vomiting, diarrhea, dizziness, toxic psychosis and seizures.

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**Table 3.** **Summary of guidelines for pre-departure presumptive treatment, diagnosis, and directed treatment of malaria for refugees resettling to the U.S. from sub-Saharan Africa**

| Population | PRESUMPTIVE TREATMENT WITHOUT TESTING | TEST BY BLOOD SMEAR OR RAPID DIAGNOSTIC TEST APPROVED BY CDC | TEST RESULT | TREAT | MEDICATION |
|---|---|---|---|---|---|
| **All adults and children weighing more than 5 kilograms (except pregnant and lactating women or known medication contraindication as listed in protocol)** | Yes | No | | | Artemether-lumefantrine |
| **Pregnant women, Lactating women, children weighing < 5 kgs and those with other known contraindications** | No | Yes | Positive | Yes | Quinine/clindamycin or quinine, see overseas guidance for dosing. |
| | | | Negative | No | None, monitor for clinical disease |
| **Persons with other contraindications to recommended regimen** | No | Yes | Positive | Yes | Discuss with CDC |
| | | | Negative | No | None, monitor for clinical disease |

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**Table 4. Summary of guidelines for post-arrival presumptive treatment, diagnosis, and directed treatment of malaria for refugees resettling to the U.S. from sub-Saharan Africa who have not received recommended pre-departure therapy**

| Population | PRESUMPTIVE TREATMENT WITHOUT TESTING | TESTING | TEST RESULT | TREAT | MEDICATION |
|---|---|---|---|---|---|
| **All adults and children weighing ≥ 5 kilograms (except pregnant or lactating women or if known contraindication as listed in protocol)** | Preferred | Malaria Smear [1] | | | Atovaquone-proguanil: see Annex II |
| **Pregnant women, lactating women, and children < 5 kgs, and those with other known contraindications.** | No | Yes. PCR preferred. Malaria smear. [1] | Positive | Yes | Consult malaria guidelines, consider consultation with an expert [2] |
| | | | Negative | No | None, monitor for clinical disease |

RDT Rapid diagnostic test, PCR polymerase chain reaction

[1] Blood smear has high specificity. Both blood smear and RDT have poor sensitivity and those with a negative test must still be monitored for clinical disease.

[2] Treatment information available at: www.cdc.gov/malaria/diagnosis_treatment/tx_clinicians.htm. In addition, health care providers needing assistance with diagnosis or management of suspected cases of malaria may call the CDC Malaria Hotline: 770-488-7788 (M-F, 8am-4:30pm, eastern time). Emergency consultation after hours, call: 770-488-7100 and request to speak with a CDC Malaria Branch clinician.

[1] Ndao M , Bandyayera E, Kokosin E, et al. Comparison of blood smear, antigen detection, and nested-PCR methods for screening from regions where malaria is endemic after a malaria outbreak in Quebec, Canada. J Clin Microbiol 2004;42(6):2694-700.

[2] Stauffer WM, Newberry AM, Cartwright CP, Rosenblatt JE, Hanson K, Sloan L, et al. Evaluation of malaria screening in newly arrived refugees to the United States by microscopy and rapid antigen capture enzyme assay (Binax-NowÔ). Pediatr Infect Dis J. 2006;25(10).

[3] Maroushek SR, Aguilar EF, Stauffer W, Abd-Alla MD. Malaria among refugee children at arrival in the United States. Pediatr Infect Dis J 2005; 24(5):450-2, 2005.