Overseas Refugee Health Guidelines: Malaria

US Department of Health and Human Services
Centers for Disease Control and Prevention
National Center for Emerging and Zoonotic Infectious Diseases

Division of Global Migration and Quarantine

April 29, 2019

Accessible version: https://www.cdc.gov/immigrantrefugeehealth/guidelines/overseas/malaria-guidelines-overseas.html

Guidelines for Pre-departure Presumptive Treatment and Directed Treatment for Malaria for Refugees from Sub-Saharan Africa

In addition to the standard, legally required medical examination of refugees migrating to the United States, CDC recommends the following presumptive treatment for *Plasmodium falciparum* malaria. These recommendations apply to all refugees who are living in countries that are endemic for *P. falciparum* in sub-Saharan Africa. Currently, CDC does not recommend presumptive therapy for asymptomatic/subclinical malaria for U.S.-bound refugees relocating from lower endemic areas outside sub-Saharan Africa (e.g. Southeast Asia) unless specifically identified in subsequent, separate, documents (see Domestic Malaria Guidelines).

These guidelines are intended for presumptive pre-departure treatment of asymptomatic/subclinical malaria and for directed treatment for special populations with malaria. Any patient with clinical symptoms of malaria should be referred to a healthcare facility for evaluation and treatment.

BACKGROUND

Studies have demonstrated high rates of malaria in refugees arriving in the United States and Canada from sub-Saharan Africa.[1, 2] Despite progress in malaria control in the past decade, sub-Saharan Africa still has highly endemic areas. In some parts of Africa, prevalence rates of *P. falciparum* malaria exceed 75%. Beginning in 1999, U.S. bound refugee populations originating in sub-Saharan Africa began to receive predeparture treatment with sulfadoxine-pyrimethamine (SP, Fansidar™) to prevent *P. falciparum* malaria disease following arrival in the U.S. Worldwide, the malaria parasite, *P. falciparum*, has developed resistance to many drugs used for treatment. In many areas of Africa, *P. falciparum* resistance to SP (and chloroquine) has increased to levels where these drugs are no longer effective. Based on efficacy studies showing SP treatment failures[3] and on guidance from the World Health Organization, beginning in 2007, pre-departure SP was discontinued and replaced by artemisinin combination treatment (ACT), generally the fixed combination artemether-lumefantrine (AL).

Refugee populations relocating to the United States from countries outside sub-Saharan Africa would rarely originate in hyper- or holoendemic malaria, making asymptomatic/subclinical *P. falciparum* unlikely. Refugees from areas with lower endemic rates who are infected with *P falciparum* malaria will have clinical symptoms of infection. Therefore, refugee populations relocating to the United States from endemic areas other than sub-Saharan Africa should be tested for malaria if symptomatic. No presumptive treatment is recommended for these populations unless directed in separate guidance.

RECOMMENDATIONS

This document provides guidance for presumptive treatment for asymptomatic *P. falciparum* malaria in refugees relocating to the United States (Annex I). Artemisinin derivatives are obtained from the sweet wormwood plant (Chinese: 青蒿 or qīnghāo). The optimal regimen is the artemisinin-based combination therapy, artemether-lumefantrine Tables 1 and 2, Annex 1. However, when it is not accessible, other artemisinin-based combinations may be used until

artemether-lumefantrine can be obtained. Currently artesunate-amodiaquine (ASAQ) is currently the preferred second line therapy, Annex 1. Dosing formulations for ASAQ are less standardized. When AL is unavailable and ASAQ will be used as a second option, Centers for Disease Control and Prevention (CDC) should be contacted for specific dosing instructions based on the formulation available in country. Specific populations including infants, pregnant women in the first trimester and those with other contraindications, delineated below, require directed treatment after diagnostic testing and should not receive presumptive treatment for asymptomatic malaria.

Special instructions:

1. Pre-departure presumptive and directed malaria treatment regimens must be administered as directly observed therapy.
2. Test results and pre-departure treatment should be documented on the pre-departure medical screening form. If treatment was not administered, this should be clearly indicated along with the reason that treatment was not administered.
3. The malaria treatment should be completed no sooner than 5 days before departure.

Specific Populations and Precautions/Contraindications to Presumptive Anti-malarial Treatment

Infants who weigh less than 5 kilograms (kg), pregnant women, lactating women breastfeeding infants who weigh under 5 kg were previously considered to have a contraindication for use of AL. In 2015, the World Health Organization (WHO) revised the guidelines for the treatment of clinical malaria to include AL treatment for pregnant women during the second and third trimester, children weighing < 5 kg and for lactating women.[5] At this time, presumptive treatment with AL for asymptomatic malaria may be administered to pregnant women during their second and third trimester and to lactating women regardless of the weight of the infant. Children < 5 kg and women in their first trimester of pregnancy should not receive presumptive treatment but should receive testing and treatment if they are found to have malaria. In addition, all persons with a known allergy to AL or any component of the medication should not receive presumptive treatment with AL.

Refugees who do not receive presumptive treatment, including women during their first trimester of pregnancy and children < 5 kg, should have diagnostic testing, and if the tests show they have malaria, receive directed treatment. Diagnostic testing should be performed with blood smears or rapid diagnostic tests (RDT) with a kit agreed upon in consultation with CDC's Division of Global Migration and Quarantine (DGMQ). Both blood smear and RDT have limited sensitivity and do not rule out malaria.[4] Therefore, any refugee who develops clinical symptoms of malaria should receive further evaluation regardless of the screening test results. Treatment for clinical or laboratory confirmed malaria should be given according to national guidelines. If no national guidelines exist, consult with CDC regarding a treatment plan.

For information regarding domestic management of malaria (screening and presumptive treatment) for refugees after arrival in the United States, please see Domestic Refugee Guidelines.

Table 1: Summary malaria treatment and testing recommendations for asymptomatic refugees in sub-Saharan Africa relocating to the United States

Population	Presumptive treatment without testing	Test by blood smear or rapid diagnostic test[1]	Test result[2]	Treat	Medication
All adults and children (except pregnant women during their first trimester, children who weigh less than 5 kg, and persons with known contraindication to recommended regimen. Lactating women can receive treatment regardless of infant weight.)	Yes	No	N/A	N/A	Option 1: artemether-lumefantrine; Option 2 (only if Option 1 is not available): artesunate-amodiaquine (consult CDC)
Pregnant women during the first trimester	No	Yes	Positive	Yes	National guidelines
			Negative	No	None
Infants weighing less than 5 kg	No	Yes	Positive	Yes	National guidelines
			Negative	No	None
Persons with other contraindications to recommended regimen (e.g. known allergy)	No	Yes	Positive	Yes	Discuss with CDC
			Negative	No	None

[1] Test with blood smear or rapid diagnostic test using a test kit agreed upon in consultation with DGMQ

[2] Malaria thick and thin smear or RDT

Table 2: Dosing of artemether-lumefantrine for asymptomatic *P. falciparum* malaria

Weight (kg)	Artemether-lumefantrine Number of tablets per dose Given at 0 hours, 8 hours, 24 hours, 36 hours, 48 hours, and 60 hours
< 5	Not recommended
5–14	1 tablet
15–24	2 tablets
25–34	3 tablets
> 35	4 tablets

ANNEX I:

Specific information about acceptable pre-departure presumptive anti-malarial therapy regimens for sub-Saharan refugees relocating to the United States

A. **OPTION 1**

- Formulation of artemether-lumefantrine: tablets containing 20 mg of artemether plus 120 mg of lumefantrine.
- Dose: artemether-lumefantrine (AL). Treat with the 6-dose schedule as described below in Table 2.
- Other instructions: Administer with food.
- Metabolism of drug: Maximum blood levels occur 6–12 hours after administration. The half-life is 88 hours in healthy persons and twice as long in persons with malaria. The drug is excreted via the liver and feces.
- Adverse effects: dizziness, fatigue, anorexia, nausea, vomiting, abdominal pain, palpitations, myalgia, sleep disorders, arthralgia, headache, rash.
- Exceptions for the use of artemether-lumefantrine:
  - Children weighing less than 5 kg
  - Pregnant women in the first trimester
  - Persons with known hypersensitivity to either component
- Alternatives approaches for persons who cannot receive artemether-lumefantrine:
  - Children weighing less than 5 kg: Test with blood smear or rapid diagnostic test using a test kit agreed upon in consultation with DGMQ. Children who test positive for malaria should be treated according to national guidelines or consult CDC, if no national guidelines exist.
  - Pregnant women: Test with blood smear or rapid diagnostic test using a test kit agreed upon in consultation with DGMQ. Pregnant or lactating women who test positive for malaria should be treated according to national guidelines or consult CDC, if no national guidelines exist.
  - Persons with known hypersensitivity to either artemether or lumefantrine may receive alternative treatment. If allergic to both artemether component, discuss with CDC.
  - Persons with symptomatic malaria should be treated according to national guidelines or consult CDC if no national guidelines exist.

B. **OPTION 2**

- Dosage and Formulation of Artesunate-amodiaquine (ASAQ) combination therapy. Various formulations are available and CDC should be contacted prior to using for guidance based on available formulations in the country of departure.
- Metabolism
    - Artesunate as in Option #1
    - AQ is metabolized primarily in the liver, with plasma half-life of ~5 hours.
- Adverse effects. Nausea, vomiting, abdominal pain, diarrhea, itching, bradycardia (less common). Prolonged QT (avoid with other medications that prolong QT). Can induce toxic hepatitis and fatal agranulocytosis (with prolonged use). Overdosage can cause syncope, spasticity, convulsions and involuntary movements.
- Exceptions of use for artesunate (AS) and amodiaquine (AQ)
    - Children weighing less than 5 kg (AS)
    - First term of pregnancy (AS)
    - Known hypersensitivity to either AS or AQ
    - Known abnormal white blood count, kidney disease or severe hepatic disorder/disease (AQ)
    - Caution should be exercised in patients on treatment drugs for HIV/AIDS (AQ), cases should be discussed with CDC prior to presumptive treatment.
    - Known prolonged QTc or another medication known to lengthen QTc

REFERENCES

1. Maroushek SR, Aguilar EF, Stauffer W, Abd-Alla MD. Malaria among refugee children at arrival in the United States. Ped Infect Dis J 2005;24(5):450-2, 2005.
2. 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.
3. Phares CR, Kapella BK, Doney AC, et al. Presumptive treatment to reduce imported malaria among refugees from East Africa resettling in the United States. Amer J Trop Med Hyg 2011;85(4):612-615.
4. Stauffer WM, Newberry A, Cartwright C, Rosenblatt J, et al. Evaluation of malaria screening in newly arriving refugees to the United States by microscopy and rapid antigen capture assay. *Ped Infect Dis J*. 2006 Oct;25(10):948-50.
5. The World Health Organization. Guidelines for the treatment of malaria. Third Edition. Available online (accessed March 22, 2019)