
OVERSEAS REFUGEE HEALTH GUIDELINES: MALARIA

**U.S. 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

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

In addition to the standard, legally required medical examination of refugees migrating to the United States and previous CDC recommendations, CDC recommends the following presumptive treatment for *P. falciparum* malaria. These recommendations apply to all refugees who are currently living in countries that are endemic for *P. falciparum* in sub-Saharan Africa. Currently, refugees living in lower endemic areas outside sub-Saharan Africa (i.e. Southeast Asia) should not receive empirical therapy for asymptomatic malaria (see domestic malaria guidelines for details). This document provides background information, rationale for the recommendations, and technical information for physicians.

These guidelines are intended for presumptive pre-departure treatment of asymptomatic malaria and directed treatment for special populations with asymptomatic malaria. Any patient with clinical symptoms of malaria should be referred to the camp health care facility for evaluation and treatment.

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Special Instructions:

1. Malaria pre-departure presumptive and directed treatment regimens must be administered as directly-observed therapy.
2. Oral quinine should only be administered for persons who test positive by blood smear or rapid diagnostic testing.
3. Test results and pre-departure treatment should be documented on forms carried by the refugees to the U.S. If treatment was not administered, this should be clearly documented on the paperwork along with the reason that treatment was not administered.

4. Electronic monthly summary reports of treatment, and testing (including number of persons positive and negative) and adverse events by nationality, age group and camp should be sent to CDC by the end of following month. A standard format will be provided for completion.
5. Although there is no known contraindication to co-administration of these malaria treatment medications with the parasitic intestinal treatment regimens (praziquantel, ivermectin and albendazole), CDC is recommending a spacing of these regimens in order to better monitor effects of treatment and tolerability. Intestinal parasite regimens should be administered first. The malaria treatments should be administered at least 2 days after completion of the intestinal parasite regimen. The malarial treatment should be completed at least 2 days prior to departure for the U.S.

SUMMARY AND BACKGROUND

Recently studies have demonstrated high rates of malaria in refugees arriving in the U.S. and Canada from sub-Saharan Africa. ^{1 2} In some areas of sub-Saharan Africa prevalence rates of *P. falciparum* malaria exceed 75%. Worldwide, the *Plasmodium falciparum* malaria parasite has rapidly developed resistance to many drugs used for treatment. In many parts of Africa, *P. falciparum* is resistant to chloroquine and sulfadoxine-pyrimethamine (SP, FansidarTM), and this resistance has increased to levels where these drugs are no longer effective. Until recently, SP was used throughout many parts of Africa for treatment of uncomplicated malaria. However, based on efficacy studies showing SP failure and guidance from the World Health Organization, many African countries have adopted artemisinin-based combinations as the national standard for treatment.

The current pre-department treatment recommendation for U.S.-bound African refugees is SP. In addition to data in Africa, a recent study in newly arrived refugees suggests that SP alone is not eradicating *P. falciparum* in this population. ³ Therefore, this recommendation must be revised to consider more effective treatment and to be consistent with WHO guidance and national policies in the host countries.

Currently, no refugee populations relocating to the U.S. from non-sub-Saharan African countries are in areas of hyper- or holoendemic malaria, making asymptomatic *P. falciparum* very unlikely. Therefore, refugee populations relocating to the U.S. from areas other than sub-Saharan Africa should be tested for malaria if symptomatic and residing in an endemic area. Currently, no empiric therapy is recommended in these populations.

RECOMMENDATIONS

The recommendations in this document provide revised guidance for presumptive treatment for asymptomatic malaria in refugees relocating to the U.S. The revised regimen for pre-departure presumptive treatment is artemisinin-based combination therapy. Artemisinin-derivatives are obtained from the sweet wormwood plant (Chinese: 青蒿 or qīnghāo), which are currently in short supply. The optimal regimen is the artemisinin-based combination therapy, artemether-lumefantrine (Annex I). However, due to the worldwide shortage of artemisinin-based combinations, a second option (Annex I) is presented until artemether-lumefantrine can be obtained. Option 2 consists of amodiaquine-artesunate. Special populations, delineated below, require directed treatment after diagnostic testing and should not receive empiric treatment for

asymptomatic malaria. These populations including pregnant and lactating women, very young infants and persons with medication allergies may have to receive a third option (Annex I) of anti-malarial consisting of seven days of oral quinine after the diagnosis of malaria has been confirmed.

Precautions and Contraindications to Presumptive Treatment

Certain exclusions apply to both regimens; these special populations, pregnant women, lactating women, children weighing less than 5 kilograms and persons with other contraindications, should have diagnostic testing first, and if positive, receive directed treatment. Diagnostic testing should be performed with blood smears or rapid diagnostic tests with a kit recommended by DGMQ for IOM use for medical screening of U.S.-bound refugees, as consistent with the Quality Assurance Program for Panel Physicians. Lactating women and children weighing less than 5 kilograms who test positive can be treated with amodiaquine-artesunate. If they have a contraindication to amodiaquine-artesunate, they can be treated with a 7-day course of oral quinine. Pregnant women who test positive should be treated with a 7-day course of oral quinine. A summary table and detailed explanation of the recommendations are provided in the document (Table 1 and Annex I).

For information regarding domestic management of malaria (screening and presumptive treatment) for refugees relocating from sub-Saharan Africa to the United States, please see Domestic Refugee Health Guidelines.

Table 1: Summary Treatment and Testing

Population	PRESUMPTIVE TREATMENT WITHOUT TESTING	TEST BY BLOOD SMEAR OR RAPID DIAGNOSTIC TEST APPROVED BY CDC	TEST RESULT	TREAT	MEDICATION
All children weighing more than 5 kilograms (except if known contraindication as listed in protocol)	Yes	No			<u>Option 1</u> : artemether-lumefantrine; <u>Option 2</u> (Only if option 1 is not available): amodiaquine-artesunate
All adults (except pregnant or lactating women, and persons with known contraindication as listed in	Yes	No			<u>Option 1</u> : artemether-lumefantrine; <u>Option 2</u> (Only if option 1 is not available): amodiaquine-

Population	PRESUMPTIVE TREATMENT WITHOUT TESTING	TEST BY BLOOD SMEAR OR RAPID DIAGNOSTIC TEST APPROVED BY CDC	TEST RESULT	TREAT	MEDICATION
protocol)					artesunate
Pregnant women	No	Yes	Positive	Yes	Oral quinine, 7 day oral course
			Negative	No	None
Lactating women	No	Yes	Positive	Yes	Amodiaquine-artesunate; May also be treated with 7-day oral course, if they have a contraindication to amodiaquine-artesunate
			Negative	No	None
Children less than 5 kilograms	No	Yes	Positive	Yes	Amodiaquine-artesunate; May also be treated with 7-day oral course of quinine if they have a contraindication to amodiaquine-artesunate
			Negative	No	None
Persons with other contraindications to recommended regimen	No	Yes	Positive	Yes	Discuss with CDC
			Negative	No	

ANNEX I:

Acceptable pre-departure empiric anti-malarial therapy regimens for sub-Saharan African Refugees

A. OPTION 1

1. Dose: artemether-lumefantrine (AL) (Coartem™, Riamet Novartis™)
 - The 6-dose schedule should be used for treatment, as described below. Table 2.
2. Exceptions for the use of artemether-lumefantrine:
 - a. Children weighing less than 5 kilograms
 - b. Pregnant women. The safety of this drug in pregnancy has not yet been established
 - c. Lactating women
 - d. Persons with known hypersensitivity to either components
 - e. Persons with severe malaria
3. Alternatives for persons who cannot receive artemether-lumefantrine:
 - . Children weighing less than 5 kilograms: test with blood smear or rapid diagnostic test, using a test kit approved by DGMQ, CDC in accordance with Quality Assessment Program for panel physicians. Children who test positive for malaria should be treated with amodiaquine-artesunate or, if they have a contraindication to amodiaquine-artesunate, they can receive a 7-day course of oral quinine.
 - a. Pregnant or lactating women: test with blood smear or rapid diagnostic test, using a test kit approved by DGMQ, CDC in accordance with Quality Assessment Program for panel physicians. Pregnant women who test positive for malaria should be treated with a 7-day course of oral quinine. Lactating women who test positive for malaria should be treated with amodiaquine-artesunate unless they have a known contraindication to amodiaquine-artesunate, in which case they can be treated with a 7-day course of oral quinine. Pregnant or lactating women who test negative do not require treatment.
 - b. Persons with known hypersensitivity to either artemether or lumefantrine should be treated with a 7-day course of oral quinine. Instructions for artesunate-amodiaquine and quinine are provided in Option 2 and 3.
4. Formulation of artemether-lumefantrine: Tablets containing 20 mg of artemether plus 120 mg of lumefantrine
5. Other instructions: administer with food
6. Adverse effects: dizziness, fatigue, anorexia, nausea, vomiting, abdominal pain, palpitations, myalgia, sleep disorders, arthralgia, headache, rash.
7. 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.

Table 2: Artemether-lumefantrine dosing

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

B. OPTION 2

1. Artesunate-amodiaquine (ASAQ) combination therapy is dosed as (Table 3 & 4):
 - o Artesunate 4 mg/kg once a day for three days plus
 - o Amodiaquine 10 mg/kg once a day for three days

2. Exceptions for the use of artesunate(AS)-amodiaquine(AQ):
 - a. Children weighing less than 5 kilograms (AS)
 - b. Pregnant women. The safety in pregnancy has not yet been established. (AS)
 - c. Persons with known hypersensitivity to either components (ASAQ)
 - d. Persons with hepatitis disorders (AQ)
 - e. For use as chemoprophylaxis (AQ)

3. Alternatives for persons who cannot receive artesunate and/or amodiaquine:
 - . Children weighing less than 5 kilograms: test with blood smear or rapid diagnostic test, using a test kit approved by DGMQ, CDC in accordance with Quality Assessment Program for panel physicians. Children who test positive for malaria should be treated with amodiaquine-artesunate, or, if amodiaquine-artesunate is contraindicated, they may receive a 7-day course of oral quinine.
 - a. pregnant women: test with blood smear or rapid diagnostic test, using a test kit approved by DGMQ, CDC in accordance with Quality Assessment Program for panel physicians. Women who test positive for malaria should be treated with a 7-day course of oral quinine. Women who test negative do not require any treatment.
 - b. Lactating women: test with blood smear or rapid diagnostic test, using a test kit approved by the Division of Global Migration and Quarantine, CDC in accordance with Quality Assessment Program for panel physicians. Women who test positive for malaria can be treated with amodiaquine-artesunate. If they have a known contraindication to amodiaquine-artesunate, they can be treated with a 7-

day course of oral quinine. Lactating women who test negative do not require any treatment.

c. Persons with known hypersensitivity to either artesunate or amodiaquine should be treated with a 7-day course of oral quinine. Instructions for quinine are provided under Option 3.

4. Artesunate Component:

- . Dose: 4 mg/kg once a day for 3 days.
- a. Formulation of artesunate: tablets containing 50 mg of sodium artesunate or 200 mg sodium artesunate.
- b. Special attention should be given to package labeling for formulation dose.
- c. Adverse effects: similar to artemisinin.
- d. Metabolism of drug: Similar to artemisinin with mean peak plasma concentrations of 1-2 hours.

Table 3: Artesunate Dosing

Artesunate
4 mg/kg once a day for three days

5. Amodiaquine Component:

- a. Use as part of combination therapy with artesunate; see table 4 for dose
- b. Formulation of amodiaquine: tablets containing 200 mg of amodiaquine base as hydrochloride or 153 mg of base as chlorohydrate. Suspension containing 10 mg of amodiaquine base as hydrochloride or chlorohydrate per ml.
- c. Special attention should be given to package labeling for formulation dose.
- d. Adverse effects: Similar to chloroquine. Nausea, vomiting, abdominal pain, diarrhea, itching, bradycardia (less common). Can induce toxic hepatitis and fatal agranulocytosis following use for malaria chemoprophylaxis.
- e. Overdosage: syncope, spasticity, convulsions, involuntary movements.

Table 4: Amodiaquine Dosing

Weight (kg)	AGE (Years)	Amodiaquine Number of Tablets					
		Tablets, 153 mg of base			Tablets, 200 mg of base		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5-6	< 4 months	0.5	0.5	0.25	0.5	0.25	0.25
7-10	4-11 mos	1	0.5	0.5	0.5	0.5	0.5
11-14	1-2	1	1	1	1	0.5	0.5
15-18	3-4	1.5	1	1	1	1	1
19-24	5-7	1.5	1.5	1.5	1.5	1	1
25-35	8-10	2.5	2.5	2	2	2	1.5

Weight (kg)	AGE (Years)	Amodiaquine Number of Tablets					
		Tablets, 153 mg of base			Tablets, 200 mg of base		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
36-50	11-13	3	3	3	3	2	2
50+	14+	4	4	3	3	3	3

C. Option 3. For use only in refugees with a contra-indication for empiric therapy who have proven asymptomatic *P. falciparum* malaria.

1. Dose: Oral dose: 8.3 mg base per kilogram (10 mg salt per kilogram) three times a day (every 8 hours) for 7 days. [Table 5](#).
2. Formulations: tablets of quinine hydrochloride, quinine dihydrochloride, or quinine sulfate containing 82%, 82% and 82.6% quinine base respectively. Tablets are usually 300 mg for dihydrochloride and 200 mg for the sulphate hydrochloride. Special attention should be given to package labeling for formulation dose.
3. Special pregnancy instructions: Quinine is safe in pregnancy. However, the risk of quinine-induced hypoglycemia is greater than in non-pregnant women, particularly in severe disease. Patients should be monitored for symptoms of hypoglycemia and blood sugar should be tested if the patient is symptomatic.
4. Adverse effects: The triad of quinine toxicity is cinchonism, hypoglycemia and hypotension. Cinchonism (a symptom complex characterized by tinnitus, hearing impairment, postural hypotension, and vertigo or dizziness) occurs in a high proportion of treated patients. These symptoms that are usually reversible, tend to develop during the second or third day of treatment, and rarely constitute a reason for discontinuing the drug. Dose-related cardiovascular, gastrointestinal and central nervous system effects may occur after excessive infusion or from accumulation after oral administration. Gastrointestinal effects include nausea, vomiting and diarrhea. Severe hypotension, primarily occurs with administration of intravenous quinine, if injected too rapidly. Quinine may enhance cardiosuppressant effects and should be used with caution in persons taking beta-adrenergic blocking agents, digoxin and calcium blocking agents. Visual disturbances may include blurred vision, distorted color perception, photophobia, diplopia and night blindness. Other effects include cutaneous flushing, pruritis, rashes, fever, dyspnea. Black water fever has been observed in patients with G6PD enzyme deficiency; it is characterized by hemolysis, hemoglobinuria and renal failure.
5. Overdosage: A single dose of quinine of > 3 g can cause serious and fatal overdosage in adults, resulting in central nervous system depression and seizures. Smaller doses can be fatal in children. Other symptoms of overdose include dysrhythmias, hypotension, cardiac arrest, visual disturbances, blindness. Induce emesis and gastric lavage as soon as possible.
6. Metabolism of drug: Rapidly absorbed after oral administration with peak plasma concentrations within 1-3 hours. Metabolized by liver and excreted in the urine.

Table 5: Quinine Dosing for 7-day course

QUININE – oral, 7-day course					
8.3 mg base (10 mg of salt) per kg three times daily for 7 days					
Weight (kg)	Number of tablets		Weight (kg)	Number of tablets	
	200 mg salt			300 mg salt	
≤ 12	0.5		≤ 18	0.5	
13-22	1		19-33	1	
23-32	1.5		34-48	1.5	
33-42	2		49-63	2	
43-52	2.5		64-78	2	
53-62	3		79-92	2	

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