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

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These guidelines were developed by the Division of Global Migration and Quarantine (DGMQ), CDC and the Office of Refugee Resettlement (ORR) Health Work Group. Please see the HHS Office of Refugee Resettlement page for more information regarding the special health challenges of refugees. In order to address such needs, ORR provides guidance, resources and oversight for refugee medical assistance, initial refugee medical screening, and refugee health/mental health technical assistance and consultation. For technical questions regarding the guidelines, please contact DGMQ at 404-498-1600.

Summary and Background

Each year 50-70,000 refugees are accepted for resettlement to the United States. Refugees from sub-Saharan Africa account for an increasing proportion of these newly arriving refugees and now constitute more than a third of new arrivals. (Figure 1) The proportion of newly arriving refugees who originate in Africa has climbed from 9%, in 1998 to 39% in 2005. This shift in population has been accompanied by changing patterns of infection and illness in newly arriving refugees. Because of its potential virulence and dynamic epidemiology, including its high prevalence, malaria has emerged as a disease of particular concern in this population.

Plasmodium infection causes clinical disease in 350-500 million persons a year resulting in >1 million deaths, predominantly in sub-Saharan Africa. The acute clinical consequences of infection and disease are most severe in persons who are non-immune;

as a result, in highly endemic areas young children account for most deaths due to malaria. 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 in <12 hours following the onset of symptoms. In contrast, in highly endemic (hyper-, holoendemic) areas a majority of the older individuals in the population have acquired partial immunity and thus may have few symptoms or subclinical infection. Areas with high endemnicity include most of West and Central and portions of East Africa. *Plasmodium malariae* and the relapsing species of human malaria, *P. vivax* and *P. ovale*, also occur in sub-Saharan Africa; however, these species are found less frequently and generally do not result in severe disease or death.

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 hyper- or holoendemic levels. These areas also have varying ratios of *P. falciparum* and non-falciparum, although many areas outside sub-Saharan Africa have higher percentages of non-falciparum malaria, particularly *P. vivax*.

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 under favorable conditions. Local U.S. vector-borne transmission has resulted in 156 known malaria cases in 63 U.S. outbreaks over the past 50 years. [1,2] In addition, more than 1000 cases of malaria are reported annually in the U.S. with migration playing an important role in the importation of these cases. [3,4,5,6]

In endemic areas, malaria has historically plagued displaced populations, and this situation continues in many contemporary refugee camps. [6,7] Refugees are often not included in the host country's national health programs, which may lead to higher rates of many diseases, including malaria and other parasitic infections.

Malaria pre-departure presumptive therapy in US-bound refugees

Several studies have demonstrated that many refugees arrive in North America with asymptomatic or sub-clinical malaria. [7,8,9] There is data showing that certain refugees who are infected but arrive without disease will develop clinical malaria, on average, approximately 3 months after arrival, however it is unclear why certain refugees will develop disease while others will not. [11] Lack of knowledge of malaria among health care professionals in the United States frequently leads to delay in diagnosis and inappropriate treatment. [12,13] This lack of familiarity has been linked with fatal outcomes. [13] Furthermore, malarial illness may interfere with a refugee's successful integration into a host community due to issues such as physical incapacity, added financial stresses, and social stigmatization.

Refugees resettling from areas of high endemnicity could potentially act as reservoirs for malaria; because of the severity of disease, *P. falciparum* is of greatest concern. Although sustained malaria transmission would be unlikely, single autochthonous cases or small outbreaks would be possible with the potential for fatal outcomes, given that persons in the general U.S. population have no immunity to *P.*

falciparum. To date however, no transmission has been conclusively traced to a newly arrived refugee.

Data collected from 1997 to 1999 showed that 60% of Liberian refugees, arriving from 4 primary countries of asylum in West Africa, were parasitemic 4 weeks after arrival. [10] In another study of untreated refugees arriving in Canada from an area of lower transmission in Tanzania, 18% of refugees had evidence of infection 3 months after their arrival. [8] In the late 1990's, concerns about the high prevalence of *Plasmodium* infection in this population led the Centers for Disease Control and Prevention (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 to organizations and clinicians performing pre-departure examinations and management ("panel physicians") in May 1999. The treatment recommendation issued at that time was for a presumptive treatment course of sulfadoxine-pyrimethamine (SP, Fansidar™).

Since the implementation of pre-departure presumptive antimalarial treatment in 1999, few data have been specifically collected on *Plasmodium* imported to the United States by newly arriving refugees. In one recent study of 103 newly arrived Liberian refugees who were treated with SP prior to resettlement in the United States, the prevalence of *P. falciparum* infection was 8.7% measured 4 weeks following arrival. [9] A retrospective study examining newly arrived refugees who developed clinical malaria prior to and following implementation of pre-departure presumptive therapy with SP estimated that there is cost-savings for the host-community if there is a parasite prevalence rate >1.5% in departing populations. The study estimated that the number of

refugees that need to be treated to prevent one case of clinical malaria was 12 for West African refugees. [11]

Because of concerns over the rising rates of resistance of *P. falciparum* to SP in Africa with clinical failure being reported in newly arrived refugees, and most refugees originating from locations with rates of malaria of >1.5%, the CDC is issuing the following new guidelines for presumptive therapy and medical screening of malaria in refugees relocating to the U.S. from sub-Saharan Africa.

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 1-404-498-1600).

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.

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. [8,9] 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-Malaria™) 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. [9] 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). [8,10] However, when thrombocytopenia

or splenomegaly are present among individuals in these populations, they frequently indicate malaria (high specificity and positive predictive value). [10] Refugees with these clinical signs, even when not symptomatic, should receive appropriate evaluation for clinical malaria.

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. See overseas guidelines for dosing)

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.

Strategies to prevent non-falciparum malaria in newly arriving refugees

Non-falciparum malaria (caused by *P. ovale, P. vivax and P. malariae*) is rarely 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 emerging to cause blood stage infection and subsequent clinical disease. Primaquine is the only FDA-approved medication in the United States to treat hypnozoites, and must be administered for 14 days. Furthermore, prior to the use of primaquine, additional testing for glucose-6-phosphate dehydogenase (G6PD) enzyme level is necessary because of the potential risk of life-threatening hemolytic anemia in G6PD deficient individuals thus making presumptive therapy more complicated. There are many variants of *P. vivax;* depending on the sub-type and the geographic location, and 14 days of primaquine dosed at 15 mg/day may cure only 20%-80% of hypnozoite infections at the traditional dosing. However, a higher dosage (30 mg/day) has recently been recommended for better efficacy in both radical cure and presumptive anti-relapse therapy when appropriate. Laboratory testing by blood film and rapid testing 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 there is no liver dormant stage. Infected individuals are frequently asymptomatic and the parasite has been associated with blood transfusion acquired malaria in the United States years after migration. Since this organism is not common and will generally respond to currently recommended presumptive therapy for *P. falciparum* there are no additional recommendations for this infection.

Therefore, given the low prevalence of infection in most areas, the prolonged course of treatment, potential adverse effects of medication, and the lack of useful laboratory screening tools, CDC does not currently recommend that newly arriving refugees receive presumptive treatment for non-falciparum malaria or laboratory diagnostic evaluation on arrival to the United States. CDC will monitor non-falciparum prevalence rates among future arriving refugee populations, and will update this guidance if indicated.

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				
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 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)	• 600 mg in one dose • Except pregnant women in 1st trimester	• 600 mg in one dose • Except children <2 years of age

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		
Atovaquine-Proguanil (adult tab = 250 mg atovaquone/100 mg proguanil Pediatric tab = 62.5 mg atovaquone/25 mg proquanil)	**5-8 kg:** two pediatric tabs po once a day for 3 days **9-10 kg:** three pediatric tabs po once a day for 3 days **11-20 kg:** One adult tablet once a day[1] for 3 days **21-30 kg:** two adult tablets once a day[1] for 3 days **31-40 kg:** three adult tablets once a day[1] for 3 days **>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*		
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		
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.

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 Negative	Yes No	Discuss with CDC None, monitor for clinical disease

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

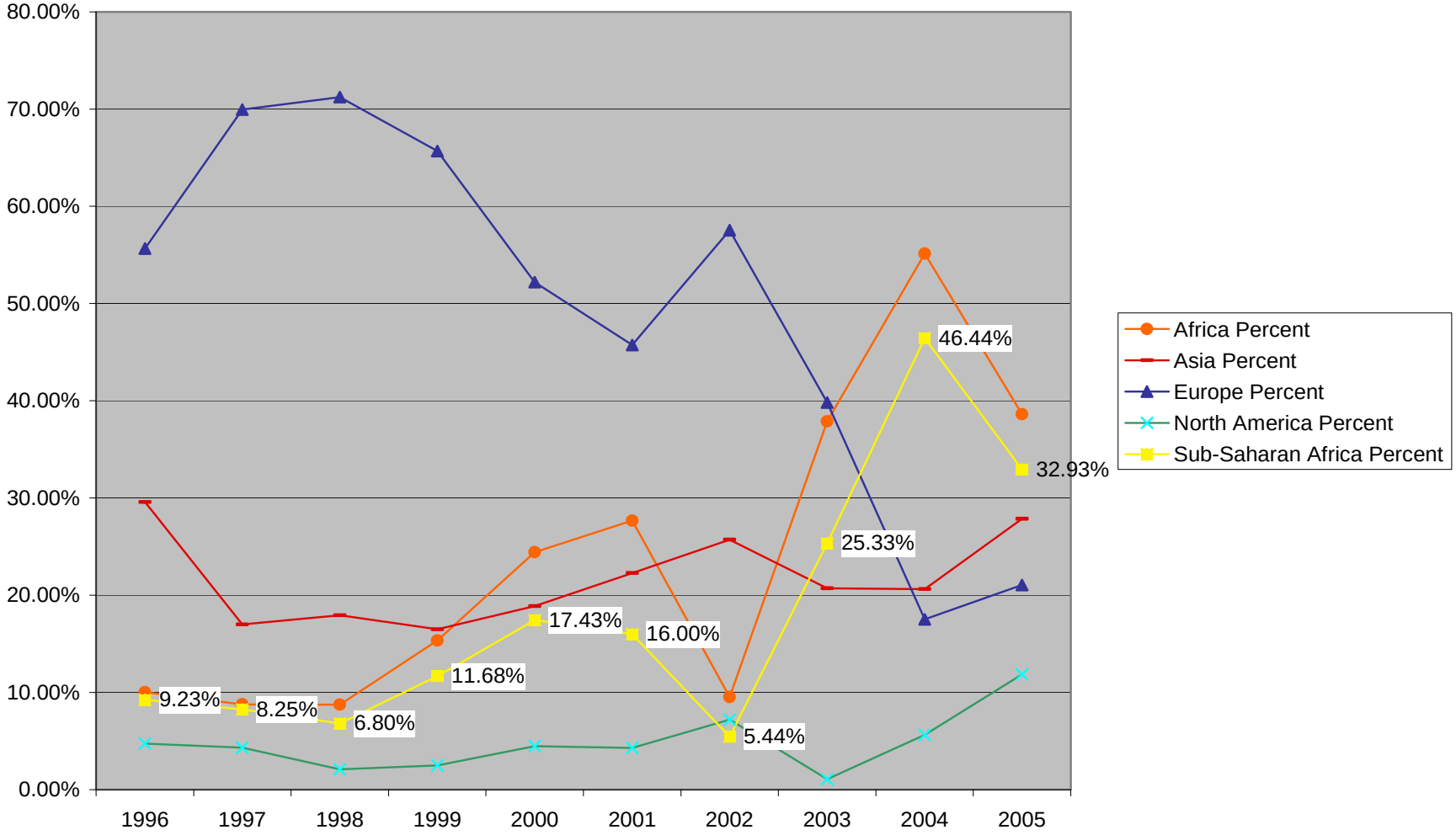
Population	PRESUMPTIVE TREATMENT WITHOUT TESTING	TESTING	TEST RESULT	TREAT	MEDICATION
All adults and children weighing ≥ 5 kilograms (except pregnant or lactating women or if known contraindication as listed in protocol)	Preferred	Malaria Smear[1]			Atovaquone-proguanil: see Annex II
Pregnant women, 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.

Figure 1. Region of Origin of United States Refugees



References

1. Zucker JR. Changing patterns of autochthonous malaria transmission in the United States: a review of recent outbreaks. Emerg Infect Dis 1996;2:37--43.
2. Centers for Disease Control and Prevention ; Filler SJ, MacArthur JR, Parise P, et al. Locally acquired mosquito-transmitted malaria: a guide for investigations in the United States. MMWR Recomm Rep 2006; 55:1-9.
3. Kambili C, Murray HW, Golightly LM. Malaria: 30 years of experience at a New York City teaching hospital. Am J Trop Med Hyg 2004;70(4):408-11.
4. Schlagenhauf P, Steffen R, Loutan L. Migrants as a major risk group for imported malaria in European countries. J Trav Med 2003;10(2):106-7.
5. Taylor-Robinson A. Population migration and malaria: terms of reference. Trends Parasitol 2001;17(7):315.
6. Mertans P, Hall L. Malaria on the move: human population movement and malaria transmission. Emerg Infect Dis 2000;6(2):103-9.
7. Rowland M, Nosten F. Malaria epidemiology and control in refugee camps and complex emergencies. Ann Trop Med Parasitol 2001;95(8):741-54.
8. 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.
9. 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-Now™). Pediatr Infect Dis J. 2006;25(10).

10. 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.
11. Collinet-Adler S, Stauffer WM, Boulware DR, Larson LL, Rogers TB, Williams DN. Financial implications of refugee malaria: The impact of pre-departure anti-malarial presumptive therapy. Am J Trop Med Hyg. In Press.
12. Kain KC, Harrington MA, Tennyson S, Keystone JS. Imported malaria: prospective analysis of problems in diagnosis and management. Clin Infect Dis 1998;27:142-149.
13. Newman RD, Parise ME, Barber AM, Steketee RW. Malaria-related deaths among U.S. travelers, 1963-2001. Ann Int Med 2004 ;141(7) :547-55.
14. Paxton LA, Slutsker L, Schultz LJ, Luby SP, Meriwether R, Matson P, Sulzer AJ. Imported malaria in Montagnard refugees settling in North Carolina: Implications for prevention and control. Am J Trop Med Hyg 1996;54(1):54-7.