Malaria Field Guide

The Prevention, Diagnosis and Treatment of Malaria in U.S. Africa Command (USAFRICOM)

APHC
ARMY PUBLIC HEALTH CENTER
(Provisional)

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Table of Contents

Table of Contents 3
Introduction 5
Background 7
Transmission 9
Prevention 11
Mosquito Surveillance and Control.....23
Diagnosis 33
Treatment 43
Disposition 49
Consult Information 53
Glossary 55

Use of trademarked name(s) does not imply endorsement by the U.S. Army but is intended only to assist in identification of specific products.

Introduction

Purpose

This technical guide (TG) is for medical personnel operating in the USAFRICOM area of responsibility (AOR) for the prevention, diagnosis and treatment of malaria. Check with approving physician before implementing care and treatments described in this TG. The TG is not a definitive source of current medical intelligence. Refer to the National Center for Medical Intelligence (NCMI), https://www.intelink.gov/ncmi/index.php for the most current medical intelligence.

Sources

The APHC (http://phc.amedd.army.mil/) has produced this TG by integrating instructional material contributed by military physicians and scientists. The TG is comprised of updated excerpts specific to USAFRICOM AOR from existing U.S. Army publications including USAPHC TG 273, Diagnosis and Treatment of Diseases of Tactical Importance to U.S. Central Command; and the U.S. Navy Medical Department Pocket Guide to Malaria Prevention and Control, Environmental Health Center Technical Manual; NEHC-TM PM 6250.1; (2007). Refer to United States Africa Command Manual 4200.03, Health and Medical: Force Health Protection Procedures for Deployment and Travel, for force health protection (FHP) requirements and standardized procedures for health surveillance in the

USAFRICOM AOR. Refer to Department of Defense (DoD) Health Affairs Memorandum: Guidance on Medication for Prophylaxis of Malaria for guidance and best practices for the chemoprophylaxis of Services members serving in malaria endemic regions http://www.health.mil/Policies/2013/04/15/Guidance-on-Medications-for-Prophylaxis-of-Malaria.

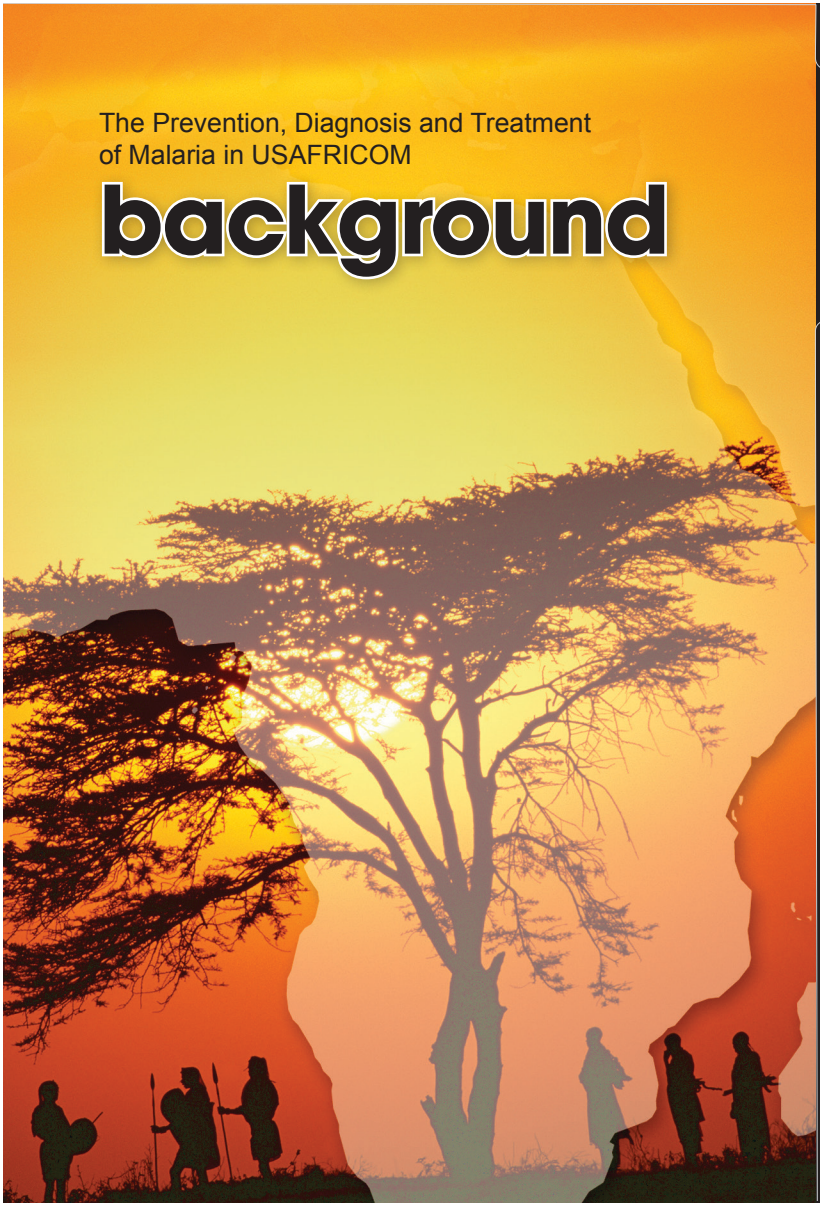
Background

Malaria is a serious mosquito-borne illness caused by a microscopic parasite which infects red blood cells. There are four primary species of malaria parasites that can infect humans: *Plasmodium (P.) falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. There are other species of Plasmodium that infect animals. In recent years, a fifth species, *P. knowlesi*, has been identified as a cause of human malaria in Southeast Asia. While infection with any of the malaria species can make a person very ill, *P. falciparum*, the predominant strain of malaria in Africa, causes severe disease and, without treatment, death.

U.S. military personnel are increasingly involved with missions in countries where malaria is present. Prompt diagnosis and treatment of malaria, particularly *P. falciparum*, is critical to prevent severe disease and death. Personnel need to strictly adhere to all countermeasures in malaria-infected areas, including chemoprophylaxis (malaria pills) and personal and unit protective measures.

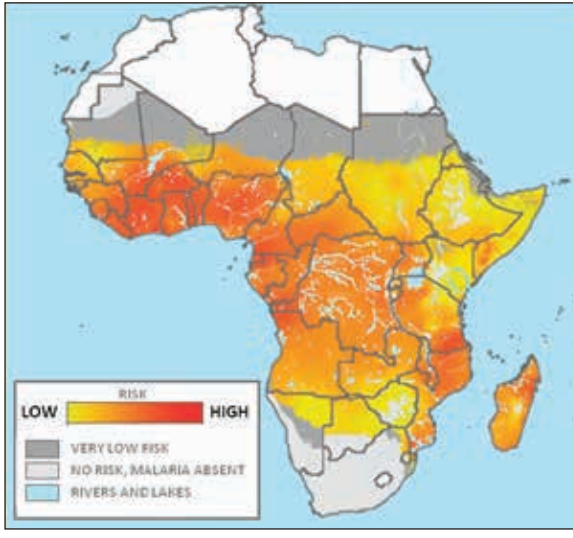
The Prevention, Diagnosis and Treatment of Malaria in USAFRICOM

background



background

Risk of Contracting Falciparum Malaria in Africa (2009)

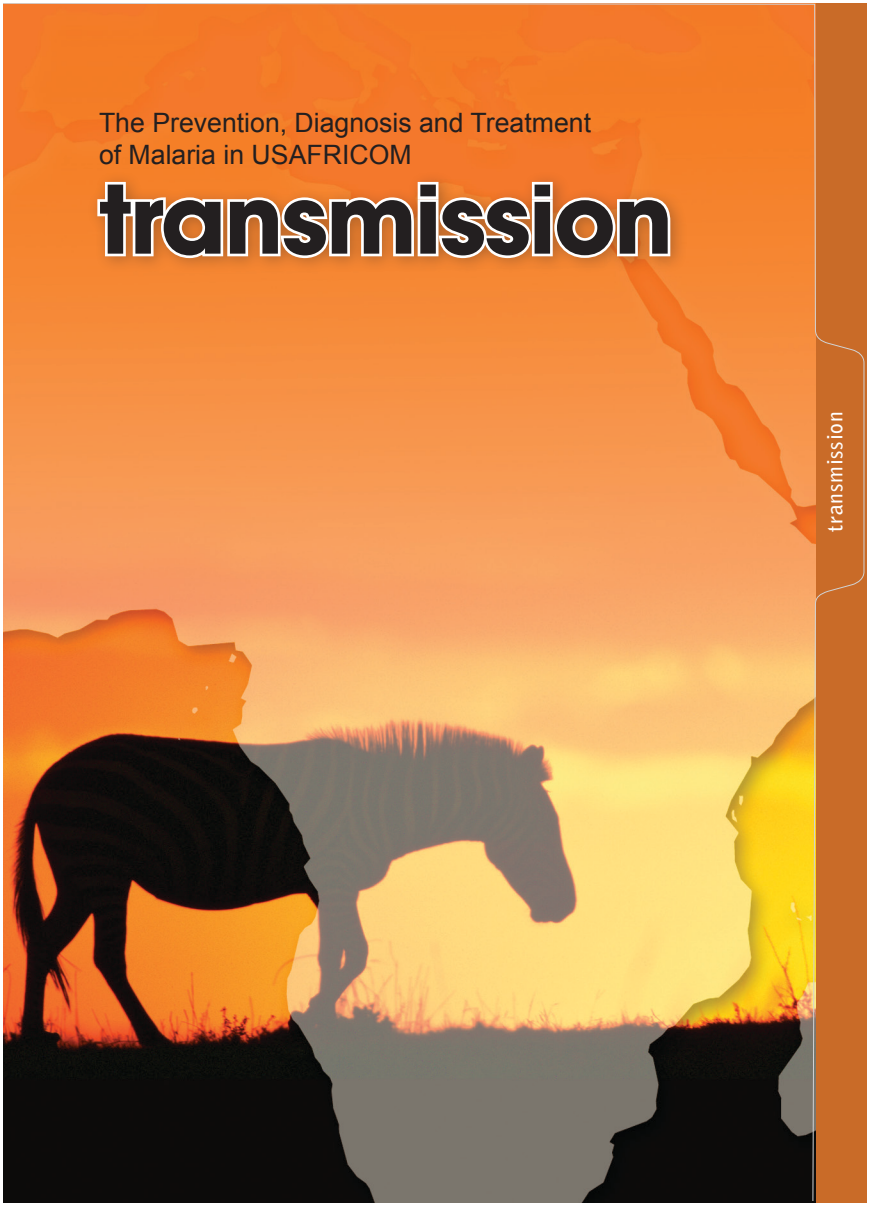


Based on Spatial Distribution of *P. falciparum* Malaria Predictions Stratified by Endemicity Class from Hay, S.I. et al (2009). A World Malaria Map: *Plasmodium falciparum* Endemicity in 2007. PLoS Medicine 6(3): e10000048.

For malaria threat in a specific location, please visit the CDC interactive malaria map at http://www.cdc.gov/malaria/map/.

The Prevention, Diagnosis and Treatment of Malaria in USAFRICOM

transmission



transmission

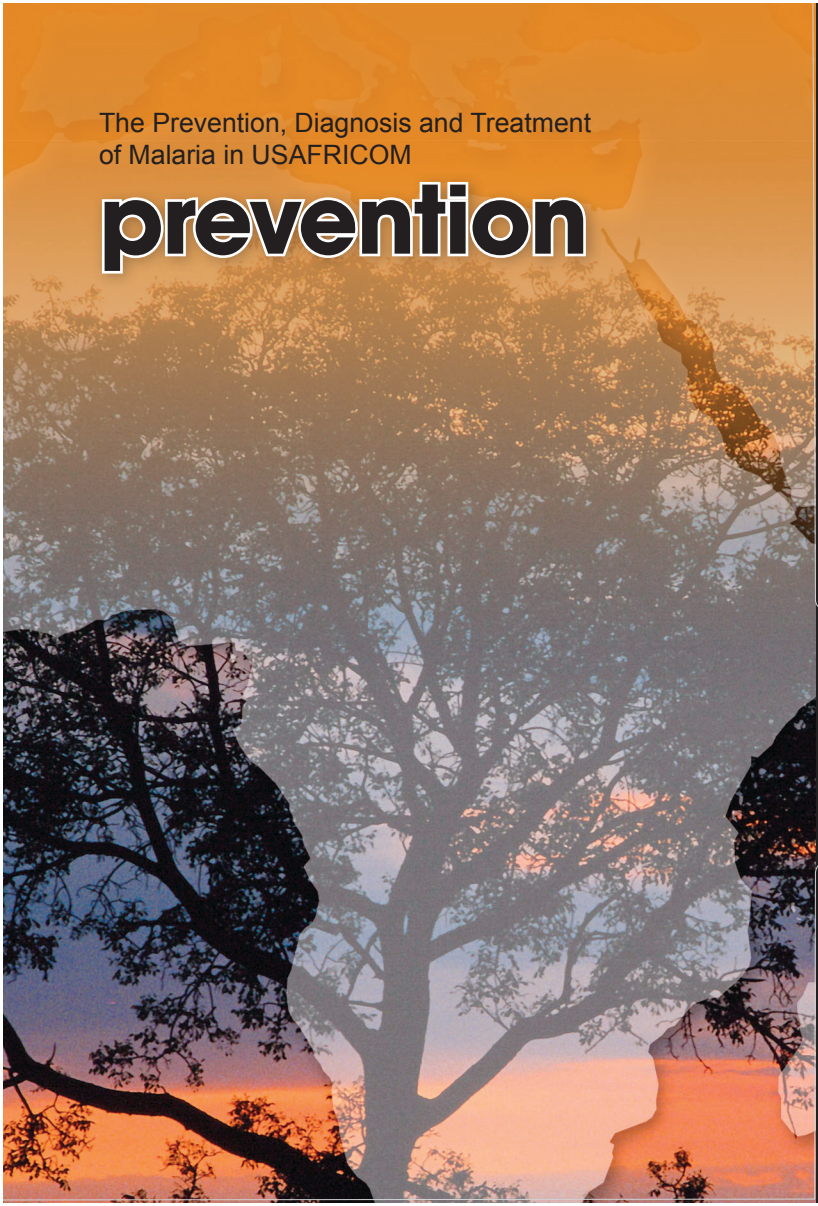
Transmission

The malaria parasite is transmitted by bites of infected female *Anopheles* species (spp.) mosquitoes. *Anopheles* mosquitoes (image below) are primarily nighttime biters, including evening and early morning. Malaria cannot be transmitted from person-to-person like a cold or the flu. You cannot get malaria through casual contact with an infected person such as touching or kissing a person with the disease. Rarely, transmission occurs by blood transfusion, organ transplantation, needle sharing, or congenitally from mother to fetus. Medical personnel should use standard precautions when in contact with malaria-infected patients. Utilize environmental controls to ensure patients are not exposed to mosquitoes.

Anopheles spp. Mosquitoes, Vectors of Malaria. CDC Public Health Image Library

The Prevention, Diagnosis and Treatment of Malaria in USAFRICOM

prevention



prevention

Prevention

Overview

There were an estimated 198 million cases of malaria worldwide (range 124-283 million) in 2013, and an estimated 584,000 deaths (range 367,000-755,000). Ninety percent of all malaria deaths occur in Africa (World Health Organization (WHO), Factsheet on the World Malaria Report 2014, http://www.who.int/malaria/media/world_malaria_report_2014/en/). Personnel from malaria-free areas are very vulnerable to the disease due to lack of immunity when they travel to countries where malaria is endemic. Protection from mosquito bites, chemoprophylaxis (malaria pills), and mosquito control are essential in reducing malaria transmission. Deployment health risk assessment addresses specific malaria prevention interventions, including use of mosquito repellents and chemoprophylaxis. Recommendations for chemoprophylaxis are based on information concerning parasite drug susceptibility for a specific location and season (see Centers for Disease Control and Prevention (CDC)), http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html and NCMI, https://www.intelink.gov/ncmi/index.php. When in areas with malaria, personnel need to adhere strictly to all countermeasures, including chemoprophylaxis and personal and unit protective measures.

Personal Protective Measures

Wear a factory-treated Army Combat Uniform (ACU Permethrin) .*

Apply DEET or Picaridin repellent to all exposed skin.

Wear your uniform properly

Use a permethrin-treated bed net.

Take your malaria pills before, during and after your deployment.

*The Army Physical Fitness Uniform (APFU) is not treated with permethrin. It does not protect Soldiers from insects.

Skin

Use repellents that have been approved by the U.S. Environmental Protection Agency (USEPA). The duration of repellent effectiveness is impacted by the levels of activity, heat, and humidity, and the intensity of mosquito population in that location. Topical repellents available to the military are designed to remain effective for 8 to 12 hours. The user should check the product label to determine how often reapplication is necessary. Use one of the following DoD-approved products for skin application:

- ULTRATHON™, a 33% DEET lotion (NSN: 6840-01-284-3982), provides protection for up to 12 hours. This product is the most effective and long-lasting formulation in the military standard stock system.
- Ultra 30™, also referred to as Lipo-Deet, a 30% DEET lotion (NSN 6840-01-584-8393), lasts up to 12 hours.

- Cutter® pump spray, 25% DEET (NSN 6840-01-584-8598), repels mosquitoes up to 10 hours.
- Natrapel® pump spray, 20% Picaridin (NSN 6840-01-619-4795), repels mosquitoes up to 8 hours.
- SUNSECT™ is a combination of sunscreen (15 SPF) and 20% DEET (NSN 6840-01-288-2188). Duration of protection is not available for this product.
- For label, MSDS, product price and shipping information, please visit the Armed Forces Pest Management Board (AFPMB) website: http://www.afpmb.org/content/department-defense-insect-repellents.

Always follow label directions. Do not apply to skin that is underneath clothing. Do not apply to cuts, wounds, or to broken, irritated, or sunburned skin. When making separate applications of sunscreen and insect repellent products, apply sunscreen first followed by repellent. To apply to your face, dispense a small amount of repellent onto your hands, and then rub them carefully over your face, avoiding your eyes and mouth. When using pump spray, do not spray directly on face. Spray on hands first, and then apply sparingly to face, avoiding eyes. Wash off skin with soap and water when returning indoors and the exposure to mosquitoes or other biting insects has ended. Some of the repellent products may damage some synthetic fabrics, plastics, and painted or varnished surfaces. Avoid smearing on plastic eyeglasses, goggles, watch crystals, computer or phone screens and similar surfaces.

Clothing

Clothing is the first direct line of personal defense against arthropods. Proper wearing of the field uniform is essential to minimize skin exposure. A loose fitting uniform with pants tucked into boots, sleeves pulled down, and undershirt tucked into pants will provide protection from mosquitoes and other biting insects and ticks.

Uniforms should be treated with permethrin, which acts as a repellent and residual insecticide. Permethrin is the U.S. military's standard repellent for application to fabric and is considered the most effective clothing impregnate available. The currently issued Army Combat Uniforms (ACUs) and Marine Corps Combat Utility Uniforms are factory treated with permethrin. Factory treated uniforms provide effective protection from mosquitoes, ticks, and other biting insects through 50 launderings, the estimated field life of the uniform. Do not dry clean uniforms – this process will remove permethrin from the fabric.

Other cloth items such as civilian clothing, mosquito netting, camouflage helmet covers, ground covers, and tentage (with the exception of vinyl-coated temper tents) can also be treated with permethrin. Do not treat underwear, including undershirts, physical training uniforms or uniform caps with permethrin because of the potential for excessive permethrin absorption.

Civilian clothing that is factory-impregnated with permethrin may also be purchased commercially. Permethrin will withstand numerous launderings.

Permethrin should only be used on clothing, never on skin. Treat clothing with permethrin repellent BEFORE putting it on and strictly follow product instructions.

Factory-treated uniforms have a label on the inside of the garment that indicates the garment has been treated and how long the treatment will last. Uniforms and civilian clothing that have not been treated with permethrin can be treated with one of the following methods:

- Permethrin Arthropod Repellent, aerosol spray "Insect Repellent, Clothing Application" (NSN 6840-01-278-1336) is a formulation of 0.5% permethrin in 6-oz aerosol cans for use on uniforms, mosquito netting, and other clothing. One treatment can last six weeks or six washings.
- Individual Dynamic Absorption (IDA) Kit, "Insect Repellent, Clothing Application" (NSN 6840-01-345-0237) is a field kit in which shirts and trousers are treated in separate plastic bags containing a 40% permethrin and water mixture. Treatment lasts about 50 washings.
- Insect Repellent, clothing application, 40% permethrin, liquid (2-gal sprayer) (NSN 6840-01-334-2666) is commonly used to treat large numbers of uniforms at one time. Two gallons of finished spray will treat eight uniforms. Treatment lasts about 50 washings. This method of treating uniforms may only be performed by personnel trained and certified in pesticide application.

You need to know ……

- Dry cleaning removes permethrin from the uniform.
- Flame-Resistant Army Combat Uniforms (FRACUs) and Nomex® cannot be field treated with permethrin. (Nomex® is a registered trademark of E.I. du Pont de Nemours and Company. DuPont Canada Inc. is a licensee).

Other personal and unit countermeasures:

- When possible, stay inside well-screened areas at dawn, dusk, and nighttime. Anopheline mosquitoes are most active at these times.
- Eliminate mosquito breeding sites by draining standing water.
- Make sure door and window screens do not have holes.
- Educate personnel on malaria threats and the correct use of countermeasures.
- Adhere strictly to prescribed malaria medication regimen.
- Sleep under a permethrin-impregnated bed net (see AFPMB website for Pop-Up Bed Nets, NSN 3740-01-516-4415; 3740-01-518-7310; 3740-01-543-5652), or the Egret™ bed net (NSN 3740-01-644-4953). If not available, use the insect net protector (NSN 7210-00-266-9736) olive drab, nylon canopy that can be used with the folding cot, hammock, steel bed, or shelter half-tent (see below

images). Another nylon insect protector (NSN 7210-00-266-9740) is also available; this item has slightly smaller dimensions yet can also be used with the folding cot. Treat an untreated bed net with permethrin using aerosol can (NSN 6840-01-278-1336). Follow label directions. Spray the outside surface of the net prior to setting up the bed net. Permethrin will help prevent mosquitoes from being able to gain entry or bite through the net.

- Once the permethrin-treated bed net has dried, erect net so that there are no openings. Tuck edges of the net under your mattress pad or sleeping bag. Do not allow the net to drape on the ground. Don't leave your net open during the day.
- Don't let the net touch your skin while you sleep because insects may bite you through the netting.
- Check the bed net for tears, holes, and other damaged areas where mosquitoes could enter.

Permethrin-Treated Lightweight, Self-Supporting, Pop-Up Bed Net, NSN 3740-01-516-4415 OD Green.

Insect Net Protector (Mosquito Bed Net Not Treated With Permethrin), NSN 7210-00-266-9736.

Chemoprophylaxis

The use of chemoprophylaxis should be anticipated for operations in most regions. Malaria, particularly chloroquine-resistant *P. falciparum*, is endemic to most of Sub-Saharan Africa. Specific recommendations by country/region are available from the NCMI (https://www.intelink.gov/ncmi/index.php).

Recommended Regimen

Malaria in Africa may be transmitted year round or seasonally depending on the location, so an understanding of local epidemiology is important. The choice of a particular regimen is based on a risk-benefit assessment of each regimen and the deployment-specific infection risk. Infection risk is determined by multiple factors, including the operational situation, length of exposure, prevalence of drug resistance, individual factors and any Service-specific policies. While basic chemoprophylaxis guidance is provided in this guide, always follow current Theater policy and consult NCMI for specific location guidance. The Food and Drug Administration (FDA)-approved regimens for Force Health Protection in the AFRICOM AOR include:

- Atovaquone-proguanil. Take 1 adult tablet by mouth (PO) per day (QD) starting 1-2 days before arrival in the at-risk region and continuing 7 days after departure from the region. Take this medication daily with food or a glass of milk. Atovaquone-proguanil is well-tolerated and side effects are rare.

- Doxycycline. Take one 100 milligrams (mg) tablet PO daily, beginning 1-2 days before arrival in the at-risk region and continuing daily for 4 weeks after departure. Doxycycline comes as many products. Doxycycline monohydrate causes less gastrointestinal (GI) upset than doxycycline hyclate. Doxycycline is best taken in the morning with lots of water; do not recline or lie down for at least one hour after taking the medication. Doxycycline may increase the likelihood of sunburn; ensure individuals use sunscreen and protective clothing when taking this medication.
- Mefloquine. Take one 250 mg tablet PO once weekly, beginning 1-2 weeks before arrival in the at-risk region and continuing for 4 weeks (4 doses) after departure. Initiating mefloquine earlier (e.g., 3-4 weeks prior to travel) may provide additional time to determine if the medication is well-tolerated. Mefloquine is a third-line chemoprophylaxis drug and should only be considered in individuals who cannot tolerate atovaquone-proguanil or doxycycline. Mefloquine must NOT be used in anyone with contraindications, including active or recent history of depression, anxiety disorder, psychosis, or other major psychiatric disorder; history of seizures; history of recent traumatic brain injury; aircrew members, and divers. Providers must complete mefloquine training at Swank Health in order to be granted prescribing capability. Contact your MTF pharmacist for the most current information. Anyone receiving a prescription for mefloquine must be provided the FDA-approved

medication guide for this drug. Individuals taking this medication must be instructed to immediately report any adverse reactions to a health care provider.

Presumptive Anti-Relapse Therapy (Terminal prophylaxis)

P. vivax and *P. ovale* have dormant liver stage parasites which can reactivate ("relapse") and cause malaria symptoms several months or years after initial infection.

Primaquine is the only available drug that can eradicate persistent hepatic parasites (hypnozoites) of *P. vivax* and *P. ovale* malaria.

Primaquine must not be given to glucose-6-phosphate dehydrogenase (G6PD) deficient individuals because of the risk of hemolytic anemia. Pregnant or breastfeeding G6PD-normal women should not take primaquine because fetal G6PD status is unknown. G6PD deficiency is determined by a one-time blood test. G6PD status of Service members is available in Service-specific medical readiness data systems. In individuals without documentation of G6PD status, pre-deployment testing is recommended prior to entering malaria risk areas.

Taking primaquine concurrently with another anti-malarial drug for asymptomatic patients after leaving an endemic area is referred to as presumptive anti-relapse therapy (PART) or terminal prophylaxis. Due to the low prevalence of non-falciparum malaria in Africa, terminal prophylaxis with primaquine for deployments shorter than 30 days should be based on individual risk and is not mandated.

Primaquine Dosing for PART (Terminal Prophylaxis) and Radical Cure

The current FDA-approved dose regimen for primaquine for both anti-relapse therapy and radical cure (see Treatment tab: Treatment of Relapsing Malaria section) is 15 mg (base) PO QD for 14 days. This regimen was approved in 1952 and has not been revisited since. Since 2003, the CDC-recommended, first-line regimen, based on accumulated evidence, is a higher dose of 30 mg (base) PO QD for 14 days. Use of the higher-dose primaquine regimen for PART is now recommended for military personnel. This recommendation is consistent with the spirit of DoD issuance 6200.02 (February 17, 2008), in that the higher-dose recommendation for primaquine when used as PART is “standard medical practice in the United States.”

Directly Observed Therapy

Directly Observed Therapy (DOT) is strongly recommended to ensure personnel are taking chemoprophylaxis as directed. DOT is the assignment of personnel to watch as individuals take their pills at the same time (e.g., while in formation). Missing as little as one dose of doxycycline can put personnel at risk for infection. Chain of command support is critical for DOT to be executed effectively.

The Prevention, Diagnosis and Treatment of Malaria in USAFRICOM

mosquito surveillance and control

mosquito surveillance and control

Basic Information on Mosquitoes

There are approximately 3,500 species of mosquitoes. Human malaria is transmitted only by females of the genus *Anopheles*. Of the approximately 430 Anopheles species, only 30-40 transmit malaria in nature. Understanding the biology and behavior of *Anopheles* mosquitoes can help understand how malaria is transmitted and can aid in designing appropriate control strategies. Factors that affect a mosquito's ability to transmit malaria include its innate susceptibility to *Plasmodium*, its host choice, and its longevity. Factors that should be taken into consideration when designing a control program include the susceptibility of malaria vectors to insecticides and the preferred feeding and resting location of adult mosquitoes.

In African countries where malaria is endemic, disease transmission is typically intense, and transmission is influenced by local ecological factors such as proximity to bodies of water.

Mosquito Life Stages

Like all mosquitoes, anophelines go through four stages in their life cycle: egg, larva, pupa, and adult. The first three stages are aquatic and last 5-14 days, depending on the species and the ambient temperature. The adult stage is when the female *Anopheles* mosquito acts as a malaria vector.

Eggs: Anopheline mosquitoes lay their eggs singly directly on water and are unique in having floats on either side. Eggs are not resistant to drying and hatch within 2-3 days, although hatching may take up to 2-3 weeks in colder climates.

Larvae: In contrast to other mosquitoes, *Anopheles* larvae lack a respiratory siphon and for this reason position themselves so their body is parallel to the surface of the water to breathe air (image below).

CDC Public Health Image Library

The larvae occur in a wide range of habitats, but most species prefer clean, unpolluted water. Larvae of *Anopheles* mosquitoes have been found in diverse habitats such as fresh or salt-water marshes, lagoons, mangrove swamps, rice fields, grassy ditches, the

edges of streams and rivers, temporary rain pools, sunlit pools and man-made containers. Many species prefer habitats with vegetation. Some breed in open, sun-lit pools while others are found only in shaded habitats.

Pupae: The pupa (image below) is comma-shaped when viewed from the side. After a few days as a pupa, the adult mosquito emerges.

CDC Public Health Image Library

Adults: Like all mosquitoes, adult anophelines have slender bodies with 3 sections: head, thorax and abdomen. The head is specialized for acquiring sensory information and for feeding. The head contains the eyes and a pair of long, many-segmented antennae. The antennae are important for detecting host odors as well as odors of breeding sites where females lay eggs. The head also has an elongate, forward-projecting proboscis used for feeding and two sensory palps. *Anopheles* mosquitoes can be distinguished from other mosquitoes by the palps, which are as long as the proboscis and by the presence of discrete blocks of black and white scales on the wings. Adult *Anopheles* can also be identified

by their typical resting position: males and females rest with their abdomens sticking up in the air rather than parallel to the surface on which they are resting.

Anopheline Mosquito Resting Position. CDC Public Health Image Library

Mosquito Surveillance and Control

A general knowledge of anopheline mosquito biology is valuable in instituting a successful malaria prevention and control program. Mosquito surveillance is a prerequisite to an effective, efficient, and environmentally sound mosquito control program. Mosquito surveillance includes the collection and interpretation of data on the presence and sources of mosquito species and testing collected specimens for the presence of pathogens/parasites.

Mosquito Surveys: Surveys should be a continuing part of a control program in order to evaluate the adequacy of control methods. Mosquito surveys are usually a responsibility of preventive medicine personnel. Since mosquito collection methods differ in their effectiveness for sampling different species, more than one collection method may be used to accurately determine the seasonality and abundance of all the important mosquito species in an area. Multiple surveillance techniques for larvae and adult mosquitoes should be used to accurately quantify mosquito abundance. Captured adult anopheline mosquitoes can be tested for presence of malaria by using a Malaria Detection test kit (MAL-K020) with follow-up confirmatory submission to an entomology laboratory. The MAL-K020 (NSN 3740-6550-01-551-5327) is available in the DoD supply system along with an instructional video for use of the kit. http://www.youtube.com/watch?v=8aJUPRdGIB8&list=UUYbnT9j9n5KZ3fvp8REKycw&index=1&feature=plcp. For additional information on mosquito surveillance

and the malaria detection kit, visit AFPMB TG 48, Contingency Pest and Vector Surveillance at http://www.afpmb.org/sites/default/files/pubs/techguides/TG48/TG48.pdf.

Larval Surveys: Larval surveys are conducted to determine the areas in which mosquitoes breed and their relative abundance. For these reasons, they are of special value in the guidance of control operations. Chemical treatment to kill larvae can then be limited to only those areas where significant mosquito populations are found. The mosquito dipper is a simple tool for conducting larval mosquito surveillance. It consists of a white plastic cup attached to a handle approximately 3 feet long.

Mosquito dipper

Adult Surveys: The methods used in sampling adult mosquito populations include the use of light traps, resting station collections, biting collections and landing counts. Because one method is not sufficient for all mosquitoes, a combination of methods is desirable, particularly when several species with different biting preferences or reactions to light are present in the area. Adult surveys are most frequently conducted because adult mosquitoes are easier to locate and identify. These surveys indicate various

species present and their relative abundance. Information obtained from adult surveys includes: (1) determining the need for a control program, including when and where control measures should be applied and by what method; (2) determining if a disease potential may exist and (3) evaluating control measures previously applied. The CDC light trap provides a reliable and portable sampling device for the collection of mosquitoes. These traps are small, lightweight, and battery-operated. Carbon dioxide can be supplied by a regulated compressed gas container or through placement of dry ice in a padded envelope or insulated container that is suspended above the trap. Ideally, several CDC traps should be used in an area to conduct mosquito surveillance.

CDC light trap. Christina Graber, APHC

Biting Collections and Landing Counts: Collecting mosquitoes as they bite is the simplest and most direct method of determining which vector and pest species feed on man and their relative abundance. The mosquitoes are collected with a kill tube or an aspirator for a designated period of time as they land on exposed skin area such as the back or legs. The favored procedure is to sit on a box or stool with the trouser legs rolled to the knees and with shoes and socks removed. This method should not be employed by untrained personnel and should only be used in carefully controlled settings due to the risk of acquiring mosquito-borne diseases.

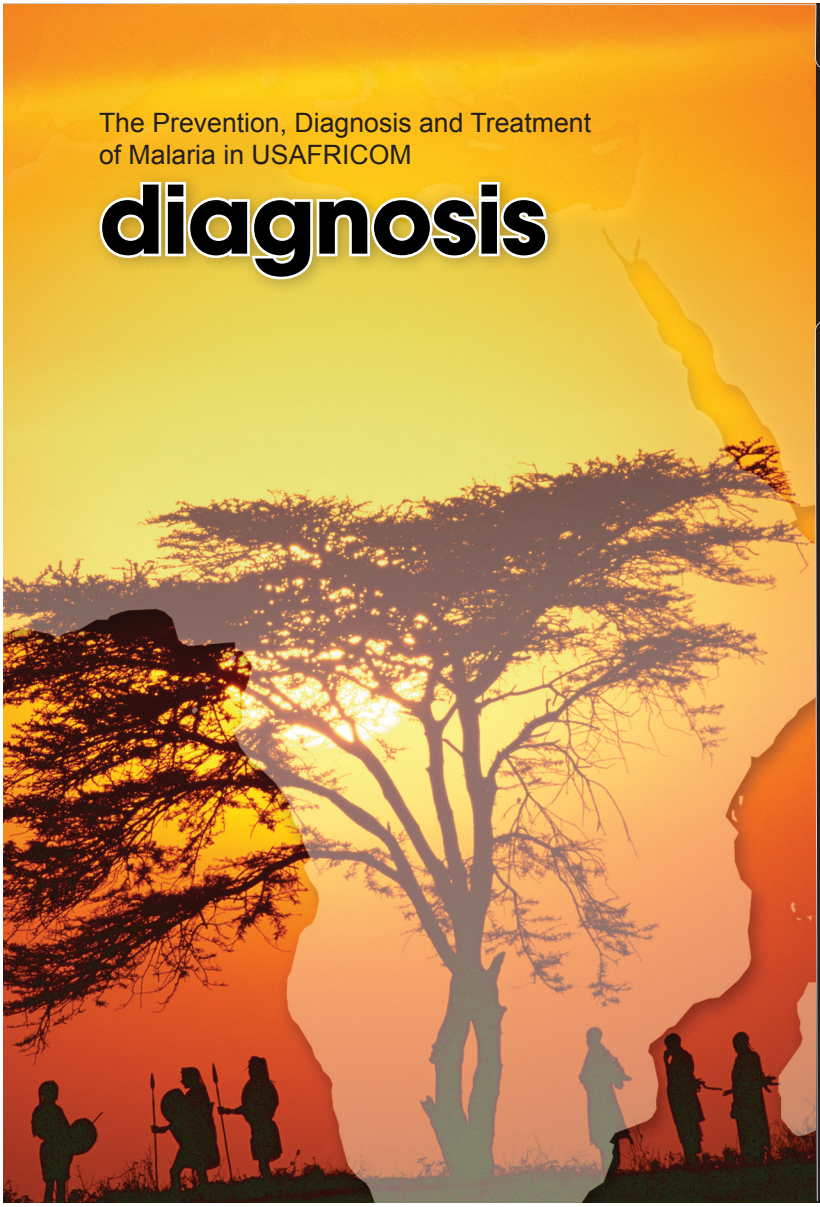
Resting Stations: Many species of mosquitoes are inactive during the day and may be found resting in dark, cool and humid places protected from the wind. Comparative data on the densities of adult mosquitoes may be obtained by daytime inspection of these natural resting sites. Resting mosquitoes can be collected using a variety of devices such as vacuum aspirators, sweepers, suction traps, and hand-held, battery-operated flashlight aspirators.

Aspirator, 1.5V Powered, NSN 3740-01-210-2368

Mosquito Control: Anopheline species that are indoor feeders are readily controlled by indoor spraying of residual insecticides on resting surfaces using thermal fog or cold fog application. Mosquito larvae are controlled by source reduction (destruction of the breeding sites) and the use of larvicides. Ultra Low Volume (ULV) space treatments are ideal for outdoor mosquito control. For larger areas where ULV treatments are not possible, residual spray should be applied to vegetation surfaces within a radius of 100 feet or more around the site to protect people and kill mosquitoes resting in the vegetation. The decision to recommend and/ or implement mosquito control measures should be made in consultation with a medical entomologist. For specific guidance on mosquito control products, refer to Contingency Pest Management Guide at http://www.afpmb.org/sites/default/files/pubs/techguides/tg24.pdf.

The Prevention, Diagnosis and Treatment of Malaria in USAFRICOM

diagnosis



diagnosis

Diagnosis

Malaria MUST be considered in all febrile patients who have spent any time in an area where malaria is present. If not diagnosed and treated promptly, *P. falciparum* is often fatal. While *P. falciparum* causes the most severe disease, other species of *Plasmodium* also have the potential to cause severe illness and even death. Symptoms can occur before parasites are detectable by blood smear, but critically ill patients will have a detectable parasitemia at some time in their illness. A reported history of compliance with chemoprophylaxis and/or personal and unit protective measures does not exclude a patient from having malaria.

Signs and Symptoms

Symptoms are non-specific and vary depending on malaria type but generally include the following at the onset of clinical illness:

- fever
- shaking chills
- sweats
- headache
- muscle aches
- exhaustion
- nausea
- vomiting
- diarrhea

Patient ill with fever > 101 °F and is/has been in a malarious area.

YES

MUST rule out malaria. Start empiric treatment if malaria is suspected. Consider rapid medical evacuation.

YES

Perform blood smears or rapid diagnostic test (RDT). If initial smear or RDT is negative, test again in 8-12 hours. If smear is not available, a repeat RDT can be performed. If tests are again negative, either repeat the smear a third time or consider transferring to a location that can perform malaria smears.

- Malaria can only be excluded after three properly spaced diagnostic tests. Repeat RDT testing alone cannot rule out malaria--at least one test should be a smear.
- Negative tests that are clinically considered possible false-negative should be treated even as testing continues.

If accurate and reliable diagnostic testing is not available within 1-2 hours OR if clinical symptoms worsen during serial testing and no alternative diagnosis has been confirmed, empiric treatment for chloroquine-resistant falciparum malaria is recommended.

YES

If smear or RDT positive, treat (see Treatment section). Report confirmed and empirically treated cases to preventive medicine authorities.

Infection with *P. falciparum*, if not promptly treated, may advance to complicated (severe) malaria and lead to —

- kidney failure
- seizures
- coma
- acute respiratory distress syndrome (ARDS)
- death

Complicated malaria occurs when there is evidence of organ failure or serious abnormalities of the patient's blood and/or metabolism. This condition is a medical emergency requiring prompt evacuation, hospitalization and intensive treatment.

See Table 1 for additional information.

Symptoms of untreated, non-falciparum malaria may continue for weeks or months, with recurring episodes of fever and chills. *P. vivax* and *P. ovale* have dormant liver-stage parasites that can reactivate ("relapse") and cause malaria symptoms several months or years after initial infection.

P. malariae may produce a long-lasting infection that can persist without symptoms for years, or even a lifetime.

Malaria in pregnant women can be more severe than in non-pregnant women and can cause adverse pregnancy outcomes, including —

- prematurity
- miscarriage
- stillbirth
- maternal death

Persons on chemoprophylaxis or using antibiotics, especially macrolides, sulfa drugs, and quinolone antibiotics, may have delayed presentations, low parasitemia, and atypical presentations.

Table 1. Manifestations of Complicated (Severe) Malaria

Major Findings	Description
Impaired consciousness	Failure to localize or abnormal response to painful stimuli; unarousable coma persisting for >30 minutes after generalized convulsion
Seizures	More than two generalized convulsions in 24 hours
Severe anemia (normochromic, normocytic)	Hematocrit <15%, or hemoglobin <5 grams per deciliter (g/dL) in children; <20% or <7g/dL in adults
Severe bleeding abnormalities	Significant bleeding from gums, nose, GI tract, and/ or evidence of disseminated intravascular coagulation
Pulmonary edema/ Acute Respiratory Distress Syndrome	Shortness of breath; fast labored respiration; rales
Renal impairment	Serum creatinine >3.0 mg/ dL (>265 micromoles per liter (μmol/L))
Hemoglobinuria	Black, brown, or red urine; not associated with effects of drugs or red blood cell enzyme defects (e.g., primaquine administration, G6PD deficiency)

Table 1. Manifestations of Complicated (Severe) Malaria (continued)

Major Findings	Description
Hypoglycemia	Glucose <40 mg/dL (<2.2 millimoles per liter (mmol/L))
Hypotension/ shock	Systolic blood pressure (BP)<50 mmHg in children or <80 mmHg in adults
Metabolic acidosis	Plasma bicarbonate <15 mmol/L

Adapted from *Management of Severe Malaria: A Practical Handbook*, 3rd edition. World Health Organization, 2012.

Diagnostic Testing

Patients with suspected malaria should have a total of three blood smear exams or rapid diagnostic tests (RDTs), one every 8-12 hours, to exclude malaria. At least one of these should be a malaria smear before excluding malaria. Infected patients may have negative diagnostic testing due to low parasitemia early in the infection or due to chemoprophylaxis. RDTs also frequently miss *P. ovale* infection. Other RDTs are available internationally but may perform differently than the BinaxNOW® Malaria test.

Rapid Diagnostic Tests: BinaxNOW® Malaria Test

1. The BinaxNOW® Malaria test is a rapid laboratory antigen test that can detect *Plasmodium* parasites using a whole blood sample drawn from a vein or obtained by a finger stick. This is the only FDA-cleared product for detection and identification of the parasites that cause malaria. (BinaxNOW® is a registered trademark of Alere).

- First-line diagnostic tool **when a skilled microscopist is not available.**
- Rapidly (within 15 minutes) diagnoses malaria infection and can distinguish between *P. falciparum* and non-falciparum infection. (Detection of *P. ovale*, differentiation of mixed infections or speciation of non-falciparum parasites requires microscopy).
- The lower limit of detection (with 90% sensitivity) for *P. falciparum* is 100 parasites per microliter and 1000 parasites per microliter for *P. vivax*. It does not reliably detect *P. ovale*.
- Not for malaria screening or in individuals who have no signs or symptoms of malaria or for monitoring anti-malaria therapy. Antigens may be detected for several days even after successful treatment.
- A positive test result in an ill patient must lead to immediate treatment. If a negative test result is seen in an ill patient at some risk for malaria,

empiric treatment should be considered, especially if skilled microscopy is not immediately available.

2. How the BinaxNOW® Malaria test works:

- The patient's blood sample is applied to the sample pad. If malaria antigens are present they bind to anti-malaria antibodies.
- A liquid reagent is then added to the pad allowing the antigen-antibody complexes to migrate along the test strip where they are captured by immobilized antibodies forming two test lines. A third line is formed (control line) if all of the reagents are working and migrating properly.
- The test is positive if one or both of the test lines and the control line appear. The test is negative if only the control line is visible.
- Refer to the manufacturer's test procedure card for additional information: http://www.alere.com/us/en/product-details/binaxnow-malaria.html. Consult the Product Insert for detailed instruction and performance characteristics.

Blood Smear Exam

Blood smears identify parasites on smears of peripheral blood. Blood smears remain the gold standard for malaria diagnosis. They not only detect malaria but can also estimate the degree of parasitemia, determine the species of malaria and identify mixed infections. If RDTs are used initially,

a malaria smear should be done before malaria is excluded.

Thick smears are 20-40 times more sensitive than thin smears for detecting parasites. Thin smears are more accurate for determining parasite species.

- Thick smear: Place one drop of blood on a slide. With the corner of another glass slide, spread the drop until it is about the size of a dime and newsprint placed below the slide can barely be read. Allow slide to dry thoroughly. DO NOT FIX WITH METHANOL. Stain with Giemsa stain.
- Thin smear: Prepare film as for normal complete blood count (CBC), fix in methanol, and stain with Giemsa stain. Wright's stain can be used if Giemsa stain is not available, but this may make species determination more difficult.

Additional laboratory findings (if available) — Hematologic:

- CBC:
    - Anemia (normochromic, normocytic, hemolytic)
    - Leukopenia
    - Monocytosis (>10%)
    - Thrombocytopenia (<150,000/mm^3)
    - Eosinophilia not usually seen

Chemistry:

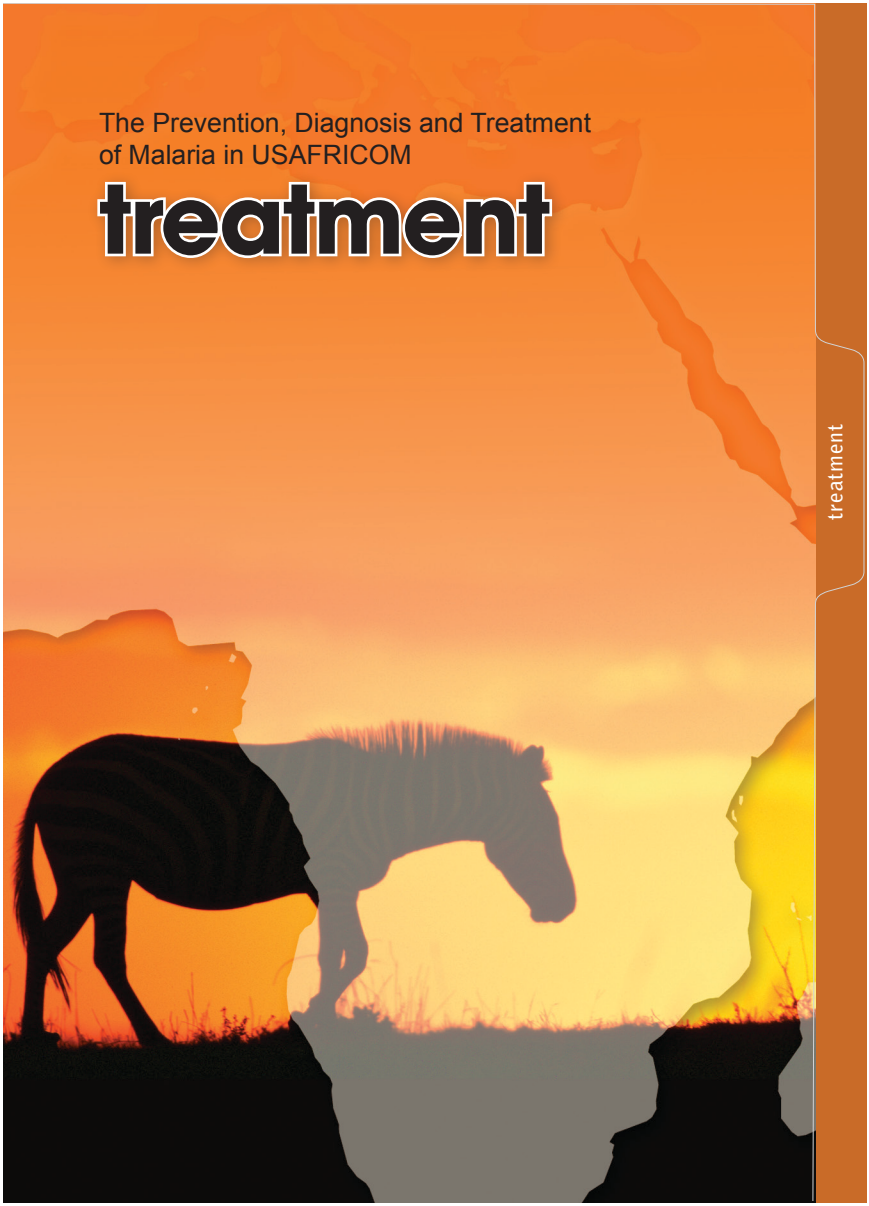
- Hypoglycemia (not uniformly seen, but may be severe and recurrent).
- Hyperlactatemia, associated with worse outcomes in severe malaria.
- Electrolyte abnormalities, including hyperkalemia (from RBC lysis) and hyponatremia (from reduced free water clearance).
- Elevated aspartate transaminase (AST) > alkaline phosphatase (ALT).
- Azotemia (pre-renal).
- Hyperbilirubinemia.
- Urinalysis: may be normal; however, increased protein, urobilinogen, and conjugated bilirubin may occur.
- Coagulation: normal in uncomplicated disease; prolonged prothrombin time (PT) and partial thromboplastin time (PTT) with disseminated intravascular coagulation (DIC) may be seen in late stage disease.

X-ray: nonspecific; pulmonary infiltrates may be seen.

Diagnostic confirmation: Identification of parasite on blood smears or RDT.

The Prevention, Diagnosis and Treatment of Malaria in USAFRICOM

treatment



treatment

Treatment

Note: Malaria medications should always be obtained from approved sources. NEVER procure malaria medications from local pharmacies or other local vendors due to very high levels of counterfeit and tainted products in developing countries.

Uncomplicated (Non-severe) Malaria

P. falciparum resistance to chloroquine and sulfadoxinepyrimethamine is widespread in Sub-Saharan Africa; these drugs should not be used. *P. vivax* is relatively rare on the continent, except in parts of the Horn of Africa. *P. ovale* may be seen in mixed infections with some frequency. **Regardless of the species identified, treat for chloroquine-resistant *P. falciparum.*** Consider presumptive treatment with the addition of primaquine in those with no contraindication to cover the possibility of *P. vivax* or *P. ovale* infections. After diagnosis, blood smears should be monitored for response to therapy. Decreasing parasite count signifies a favorable response to therapy. Frequency of testing depends on therapeutic response and severity of illness. Antigen-based RDTs should not be used to assess response to treatment.

- **Initial treatment for adult patients with uncomplicated malaria** who are able to tolerate oral medication —
  - Artemether/lumefantrine (Coartem®) 20/120 mg per tab, 4 tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice daily (morning and evening) for the following two days (total course of 24 tablets). (Coartem® is a registered trademark of Novartis AG).

    or

  - Atovaquone-proguanil (AP) 250/100 mg per tab, 4 tablets PO QD for 3 days. AP should not be used for treatment if the patient was taking the medication for chemoprophylaxis.

Alternatives:

- Quinine 650 mg (2 tabs) PO three times per day (TID) for 3 days PLUS doxycycline 100 mg PO twice per day (BID) for 7 days. Substitute clindamycin (20 mg/kg/d divided TID for 7 days) for doxycycline in pregnant women.

  or

- Mefloquine 750 mg once followed by 500 mg 8-12 hours later.

Complicated (Severe) Malaria

Complicated malaria is a medical emergency requiring immediate treatment and prompt evacuation to an appropriate high level of care. Most treatment options require a baseline electrocardiogram and blood pressure, glucose, and cardiac monitoring.

Patients presenting with any of the clinical manifestations listed in Table 1 (page 37) should be treated for complicated malaria.

- Start treatment as soon as diagnosis is suspected as conditions allow.
- Calculate dosage according to patient weight.
- Give medication intravenously.
- Give loading dose of medication per treatment regimen (below).
- If patient is comatose, place on his/her side and give lorazepam or diazepam to prevent seizures.
- Measure parasite count and hematocrit every 6-12 hours.
- Switch to oral medication as soon as patient can tolerate tablets and response to treatment is confirmed.
- Observe patients carefully for drug toxicity and complications.

The treatment of confirmed or suspected severe malaria in Sub-Saharan Africa is a significant challenge. As prompt therapy is critical to survival, you should use whichever intravenous antimalarial medication is readily available. The only FDA-approved drug with an indication to treat severe malaria is intravenous quinidine but intravenous artesunate is available through the CDC under a treatment protocol (and locally in Europe and Africa). Intravenous (IV) artesunate has been shown to reduce complications and mortality compared to IV quinine, which is a stereoisomer of quinidine. Unfortunately, IV quinidine gluconate is often not available and carries a risk of severe adverse events such as cardiac dysrhythmias leading to sudden cardiac death if used improperly in settings without cardiac monitoring capability.

Complicated (severe) malaria is usually treated in the U.S. with one of the quinidine regimens:

- Quinidine gluconate: 6.25 mg base/kg (10 mg salt/kg) loading dose IV over 1-2 hours, then 0.0125 mg base/kg/min (0.02 mg salt/kg/min) continuous infusion for at least 24 hours.
- Alternative quinidine gluconate regimen: 15 mg base/kg (24 mg salt/kg) loading dose IV infused over 4 hours, followed by 7.5 mg base/kg (12 mg salt/ kg) infused over 4 hours every 8 hours.
- Continue treatment until the parasitemia is < 1% and patient can take oral medications (switch to quinine sulfate and doxycycline regimen).

- Caution: Do not give a quinidine loading dose if the patient has received more than 40 mg/kg of quinine in the preceding 48 hours or any mefloquine within the preceding 12 hours.

Quinidine is not readily available outside the U.S. or in U.S. medical facilities abroad. Drugs available outside the U.S. to treat severe malaria include intravenous quinine and intravenous artesunate (preferred). Many U.S. embassies stock IV artesunate and are preferred sources for this medication.

- IV artesunate: 2.4 mg/kg initial dose (as IV push), then 2.4 mg/kg dose 12 hrs later, then 2.4 mg/kg dose every 24 hrs for a total of 4 doses or until patient can tolerate oral medication. A full treatment course for chloroquine-resistant falciparum malaria should then be given. Infectious disease consultation is recommended.
- IV quinine: 20 mg/kg loading dose over 4 hours, followed by 10 mg/kg every 8 hours given over 2 to 4 hours.
- Caution: Do not give loading dose if patient has received quinidine or mefloquine in the last 24 hours.

Treatment of Relapsing Malaria

P. vivax and *P. ovale* have dormant liver stage parasites (hypnozoites) which can reactivate ("relapse") and cause malaria symptoms several months or years after initial infection.

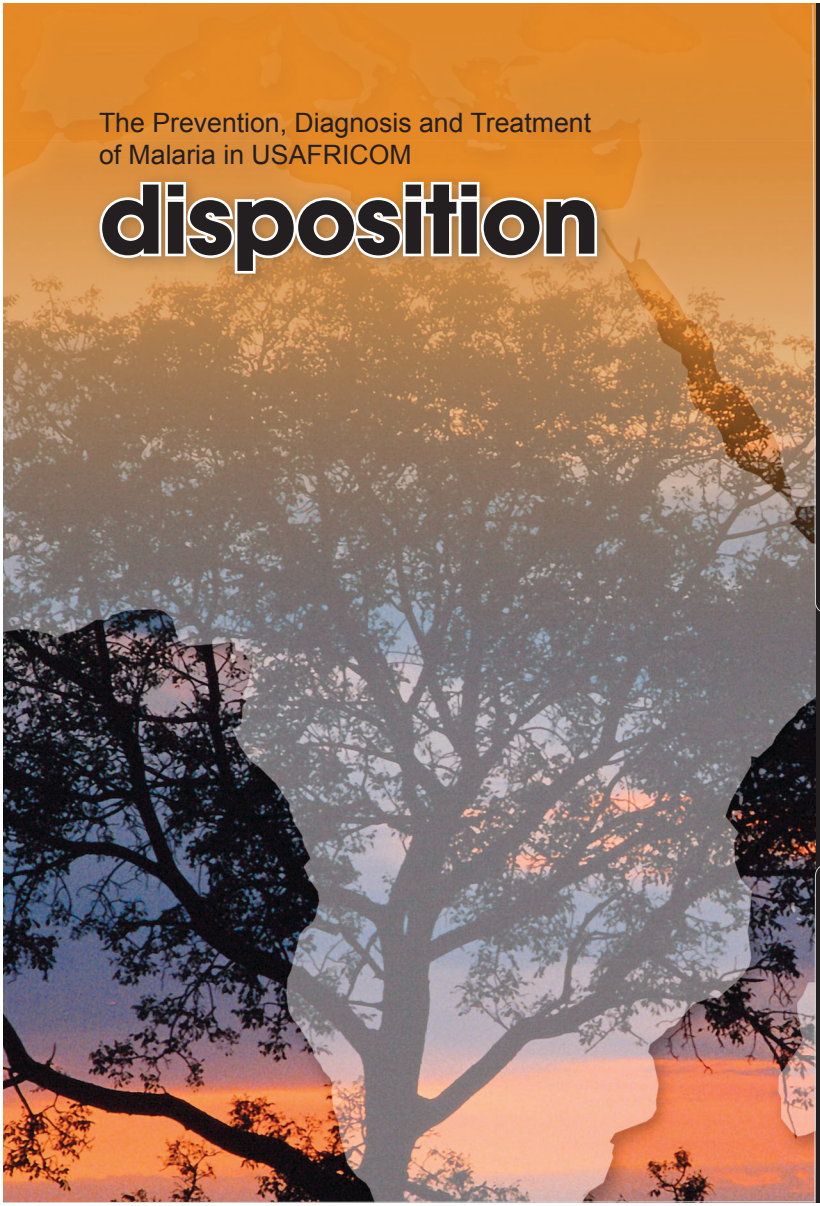
Primaquine is the only available drug that can eradicate *P. vivax* and *P. ovale* hypnozoites.

Use of primaquine combined with another appropriate antimalarial to treat *P. vivax* or *P. ovale* infection is known as radical cure. Primaquine can cause severe hemolytic anemia in G6PD-deficient patients. Therefore the G6PD status of patients must be confirmed before treating with primaquine. Consult with a specialist regarding treatment of relapsing malaria in G6PD-deficient individuals.

Note: All malaria medications should be obtained from approved sources. NEVER procure malaria medications from local pharmacies or other local vendors due to very high levels of counterfeit and tainted products in developing countries.

The Prevention, Diagnosis and Treatment of Malaria in USAFRICOM

disposition



disposition

Disposition

Duration of Illness

- Treated: 3-5 days in uncomplicated cases. *P. falciparum* cases can worsen within the first 24 hours of starting treatment and patients should be hospitalized. May recrudesce (recur) within 4 weeks in cases of treatment failure.
- Untreated: *P. falciparum* is rapidly fatal in untreated nonimmune patients. *P. malariae* is rarely fatal but may persist and recrudesce for years if not treated.
- Non-falciparum malaria is rarely fatal, but relapses can occur with *P. vivax* and *P. ovale* in up to 50% of cases without primaquine therapy. The majority of relapses occur several weeks to 1 year after the initial infection, but there are case reports of latency up to 8 years if persistent liver forms are not eliminated (see treatment tab: Treatment of Relapsing Malaria section).

Complications and Sequelae

Uncomplicated malaria responds well to appropriate treatment and is rarely associated with complications or long-term sequelae.

Complicated (severe) malaria may be associated with significant complications and, even with aggressive treatment, may lead to long-term disability. Sequelae include persistent neurologic impairment, decreased renal function, and loss of spleen (surgical removal due to rupture). Severe anemia due to hemolysis has been reported after completion of intravenous malaria therapy, likely due to damage to erythrocytes.

Return to Duty

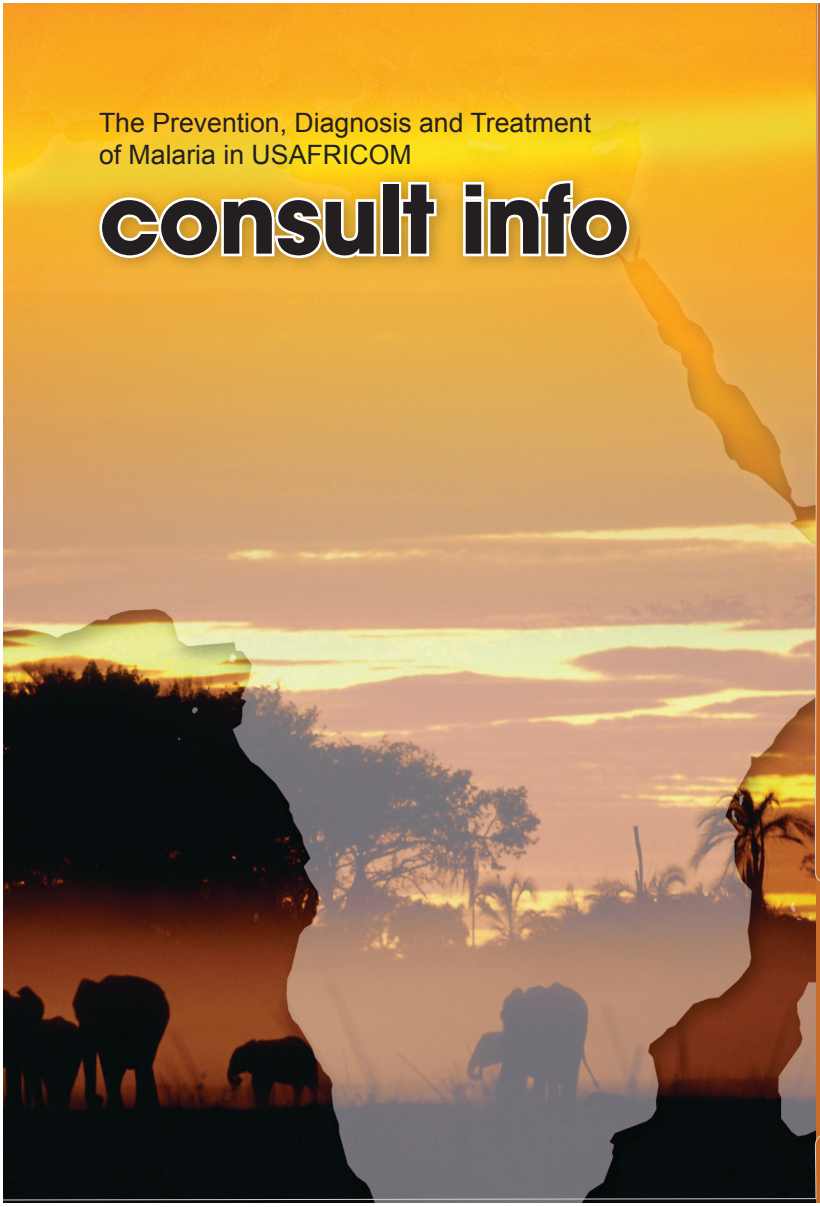
- For uncomplicated cases: local hospitalization for 48-72 hours with limited duty for several days (until drug therapy is completed). Splenomegaly must be resolved before allowing the patient to return to full duty.
- For complicated cases: patients should be evaluated on a case-by-case basis.

Air Evacuation

- Ensure plans are in place for rapid air evacuation to appropriate medical treatment facilities.

The Prevention, Diagnosis and Treatment of Malaria in USAFRICOM

consult info



consult info

Consult Information

Malaria Prophylaxis, Diagnosis and Treatment

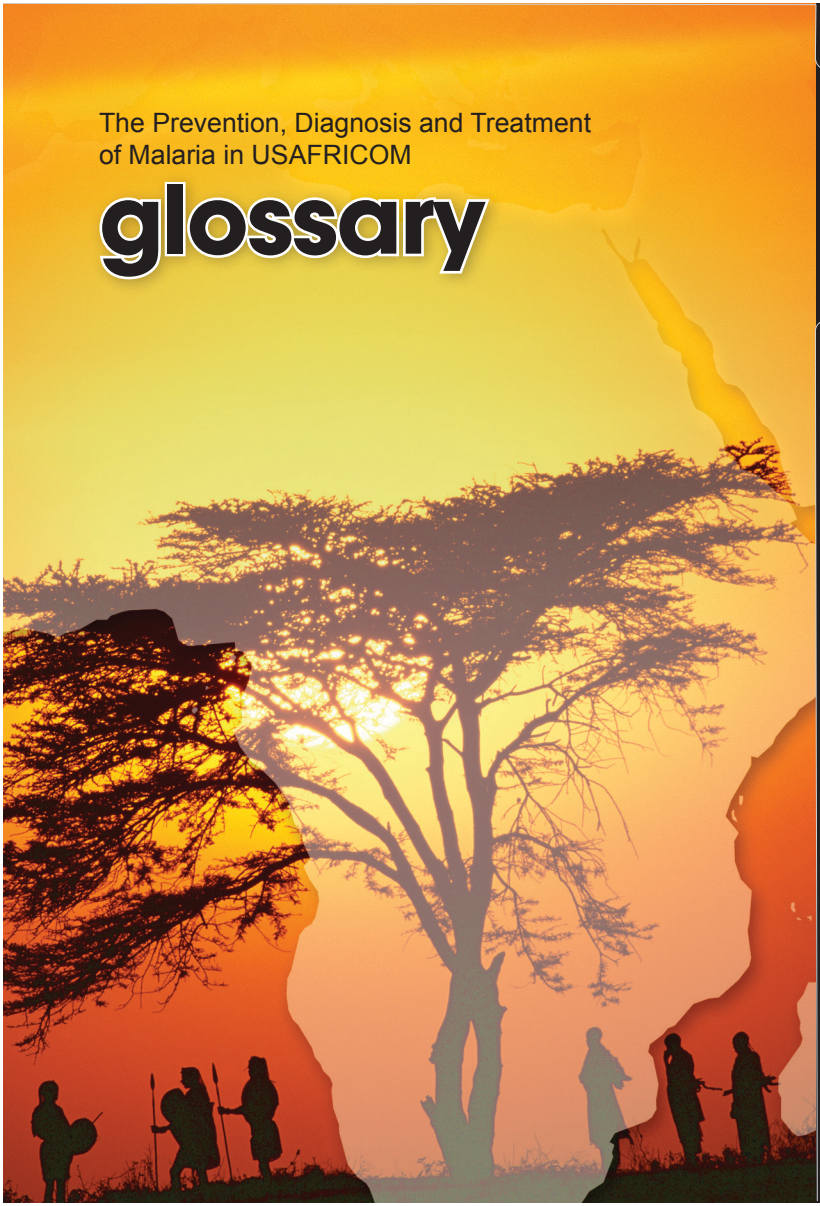
- Recommendations for malaria prevention and treatment are based on parasite drug susceptibility for a specific geographic setting. See CDC, http://www.cdc.gov/malaria/diagnosis_treatment/index.html and NCMI, https://www.intelink.gov/ncmi/index.php
- Questions about malaria prophylaxis, diagnosis and treatment guidelines should be addressed to id.consult.army@mail.mil and pmom.consult.army@mail.mil.
- Another resource is the CDC Malaria Hotline: (770) 488-7788 Monday-Friday 0800-1630 EST or (770) 488-7100 after hours, weekends and holidays.

Mosquito Control/Insect Repellent Questions

- For questions about mosquito control/insect repellents and other unit protective measures contact the DoD Pesticide Hotline: (410) 436-3773/ DSN 584-3773 or email to usarmy.apg.medcom-phc.mbx.pesticide-hotline@mail.mil.

The Prevention, Diagnosis and Treatment of Malaria in USAFRICOM

glossary



Glossary

Anemia - decrease in number of red blood cells and/ or quantity of hemoglobin. Malaria causes anemia through rupture of red blood cells.

Chemoprophylaxis - method of disease prevention by taking medication. Malaria chemoprophylaxis requires drugs to be taken before, during, and after exposure. Very effective, but not absolute because of drug resistance and poor compliance.

Dyspnea - shallow, labored breathing.

Erythrocyte - red blood cell.

Erythrocytic stage - the malaria parasite's life cycle when infecting and developing within the red blood cells.

Hematocrit - the amount of blood consisting of red blood cells, measured as a percentage. Measured after a blood sample has been centrifuged or allowed to settle. Normal hematocrit values: Males 39-49%; females 33-43%.

Hemolysis - the destruction of red blood cells. Malaria causes hemolysis when malaria parasites mature and rupture red blood cells they infected.

Hypnozoite - a stage of malaria parasites found in liver cells. After sporozoites invade liver cells, some develop into latent forms called hypnozoites. They become active months or years later, producing a recurrent malaria attack. Only *P. vivax* and *P. ovale* species that infect humans develop latent stage hyponozoites. Primaquine is the only available drug active against hypnozoites.

Hypoglycemia - blood glucose less than the lower limit of normal (70-110 mg/dL [3.9-6.1 mmol/L in International System of Units (SI) reference units]). Glucose levels of 40 mg/dL and below constitute severe hypoglycemia, a life-threatening emergency. Hypoglycemia is common in malaria as parasitized RBCs utilize glucose 75 times faster than uninfected cells. In addition, treatment with quinine and quinidine stimulate insulin secretion, which further reduces blood glucose.

Hyponatremia - serum sodium less than the lower limit of normal, which is 135-147 milliequivalent per liter (mEq/L) (135-147 mmol/L in SI reference units). Hyponatremia can be seen in malaria and is indicative of complicated malaria. A serum sodium level approaching 120 mEq/L and below constitutes a severe medical emergency.

Hypotension - low blood pressure; see also orthostatic hypotension.

Jaundice - yellow discoloration of skin and eyes due to elevated blood levels of bilirubin.

Orthostatic hypotension - decrease in blood pressure occurring when an individual arises from a seated or lying position. A small decrease in blood pressure is normal, but large decreases are abnormal, especially if accompanied by clinical manifestations such as faintness, light-headness, dizziness, or increased pulse. Orthostatic hypotension is a common finding in patients with malaria infections.

Recrudescence - a repeated attack of malaria (short-term relapse or delayed), due to the survival of malaria parasites in red blood cells. Characteristic of *P. malariae* infections.

Recurrence - a repeated attack weeks, months, or sometimes years after initial malaria infection, also called a long-term relapse. Due to re-infection of RBCs from malaria parasites (hypnozoites) that persisted in liver cells.

Relapse - a repeat attack of malaria.

Tachycardia - increased heart rate, defined as greater than 100 beats per minute.

Tachypnea - increased respiratory rate, defined as greater than 20 breaths per minute.

Thrombocytopenia - low platelet count, defined as less than 150,000. Low platelet counts can lead to impaired blood clotting, and counts below 50,000 increase the risk of spontaneous bleeding. Thrombocytopenia is typical in malaria, though spontaneous bleeding is rare.

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