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Navy Medical Department
Pocket Guide to

MALARIA PREVENTION AND CONTROL

BUREAU OF MEDICINE AND SURGERY

Navy Medical Department Pocket Guide
to Malaria Prevention and Control

2007

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INTRODUCTION

The threat to health and readiness of sailors and Marines posed by malaria stimulated the creation of the Malaria "Blue Book" in 1984. Prevention and treatment of malaria is more complex due to the emergence of drug resistance,**{**xe "drug resistant"**}** pesticide resistant mosquito vector**{**xe "vector"**}**s, and large populations of infected people in many areas of the world. The World Health Organization estimates that two billion people are at risk for malaria infection. Each year, malaria causes more than 300 million clinical cases and over two million deaths. In 1995, children under the age of five accounted for 800,000 of those deaths. The direct and indirect costs associated with malaria infections are enormous; costs were over 1.8 billion dollars in 1995 in Africa alone.

Malaria strikes during war, during deteriorating social and economic conditions, and after natural disasters; all situations where the military is called to serve. Deployed forces cannot afford loss of personnel or depletion of resources for cure and convalescence. Protecting and improving the health of airmen, soldiers, sailors, and Marines while serving in such operations requires thorough understanding of the prevention and treatment of malaria. This "Malaria Pocket Guide" includes information to help service personnel:

- Understand the transmission**{**xe "transmission"**}** and life cycle**{**xe "life cycle"**}** of malaria parasites**{**xe "parasites"**}**.
- Prevent malaria.
- Diagnose and treat malaria.
- Persuade commanders**{**xe "commanders"**}** to enforce malaria preventive measures.

Command Responsibility

Malaria control depends on directed discipline by those in command. In their role as advisors, Command Responsibility

Malaria control depends on directed discipline by those in command. In their role as advisors, medical personnel must identify threats**{**xe "threats"**}**, and present countermeasures**{**xe "countermeasures"**}** and their benefits so those in command can make effective decisions. In World War II, Lieutenant General Sir

William Slim**{**xe "Slim"**}** stopped the longest, most humiliating retreat in the history of the British Army. When he assumed command in Burma in April 1942, the health of his troops was dismal. For each wounded man evacuated, 120 were evacuated with an illness. The malaria rate was 84 percent per year of total troop strength, even higher among the forward troops. In his memoirs, he describes his course of action:

> "... A simple calculation showed me that at this rate my army would have melted away. Indeed it was doing so before my eyes.
>
> Good doctors are of no use without good discipline. More than half the battle against disease is not fought by doctors, but by regimental officers. It is they who see that the daily dose of mepacrine (anti-malarial chemoprophylactic**{**xe "chemoprophylactic"**}** drug used in W.W.II) is taken. If mepacrine was not taken, I sacked the commander. I only had to sack three; by then the rest had got my meaning. Slowly, but with increasing rapidity, as all of us, commanders**{**xe "commanders"**}**, doctors, regimental officers, staff officers, and NCOs**{**xe "NCOs"**}** united in the drive against sickness, results began to appear. On the chart that hung on my wall the curves of admissions to hospitals and malaria in forward units sank lower and lower, until in 1945 the sickness rate for the whole 14th Army was one per thousand per day."

The threat to force readiness that challenged General Slim**{**xe "Slim"**}** and his army similarly confronts our forces today. In 1993, a large percentage of Marines and soldiers in certain units participating in Operation Restore Hope**{**xe "Operation Restore Hope"**}** in Somalia**{**xe "Somalia"**}** developed malaria. The explanation for the outbreak is complex, involving a number of factors. The complex life cycle of malaria, lack of command support leading to poor execution of personal protective measures**{**xe "personal protective measures"**}**, and incomplete medical intelligence**{**xe "medical intelligence"**}** of the malaria threat all contributed.

Available medical intelligence**{**xe "medical intelligence"**}** concluded that *Plasmodium falciparum***{***xe "P. falciparum"***}*** was the predominant malaria threat in Somalia**{**xe "Somalia"**}**. Task Force medical planners were influenced by the Army's policy of not performing G-6-PD**{**xe "G-6-PD"**}** screening on its personnel. The risk of precipitating a hemolytic reaction from terminal primaquine**{**xe "primaquine"**}** prophylaxis**{**xe "terminal primaquine prophylaxis"**}** had to be weighed against the chance that *P. vivax{xe "P. vivax"}* and *P. ovale{xe "P. ovale"}* were present. Based on those factors, Task Force medical planners did not recommend terminal primaquine prophylaxis.

Unfortunately, *P. vivax{xe "P. vivax"}* was endemic in Somalia**{**xe "Somalia"**}**, and 75 soldiers developed malaria infections after they returned to the United States. After the first 30 soldiers were diagnosed with *P. vivax* malaria, terminal primaquine**{**xe "primaquine"**}** prophylaxis**{**xe "terminal primaquine prophylaxis"**}** was instituted. Despite this precaution, another 45 soldiers developed malaria infections and had to be hospitalized and administered higher dosages of primaquine. Clearly *P. vivax* malaria is present in Somalia, and drug resistant**{**xe "drug resistant"**}** strains are developing. It should be just as obvious that poor execution of personal protective measures**{**xe "personal protective measures"**}** allowed these soldiers to be bitten by infective mosquitoes. Returning Marines also developed *P. vivax* infections. The reasons were difficult to quantify, but poor compliance with terminal primaquine prophylaxis and resistant strains of *P. vivax* were responsible.

The story does not end with the *P. vivax{xe "P. vivax"}* malaria outbreak in returning soldiers and Marines. During Operation Restore Hope**{**xe "Operation Restore Hope"**}**, medical surveillance**{**xe "surveillance"**}** revealed that half of all malaria and dengue**{**xe "dengue"**}** cases were occurring in a single Marine battalion located in the Baardera**{**xe "Baardera"**}** area. Investigation of these outbreaks found that the Marine commander did not enforce recommended countermeasures**{**xe "countermeasures"**}**. Fortunately, consequences were minimal. The ill Marines recovered, and the unit was not involved in any significant engagements in its weakened condition.

The examples presented show that malaria is a formidable and deceptive foe to military units deployed into endemic areas. Resistant plasmodia strains exist in most areas of the world, and some species lie dormant**{**xe "dormant"**}** and attack long after the threat is perceived to be absent. Drugs once commonly used to prevent and treat malaria are no longer effective. Persuading commanders**{**xe "commanders"**}** to enforce personal protective measures**{**xe "personal protective measures"**}** is difficult. No vaccine is yet available, though a promising *P. falciparum* malaria**{**xe "falciparum malaria"**}{**xe "falciparum malaria"**}** vaccine is being tested.

However, all the necessary tools are present for successful prevention of malaria. Medical personnel must successfully communicate the threat. After convincing their commanders**{**xe "commanders"**}**, medical personnel must teach, supervise, and practice personal protective measures**{**xe "personal protective measures"**}**. At the same time, they must be able to diagnose and treat personnel stricken with malaria. **It cannot be emphasized enough, as General Slim{xe "Slim"} demonstrated, that success against malaria requires a unified effort enforced by commanders.**

CHAPTER ONE

MALARIA: Disease, Life Cycle, Distribution

Definition

Malaria is both an acute and chronic disease caused by protozoa of the genus *Plasmodium*.**{**xe "Plasmodium"**}** Four species cause human malaria: *P. falciparum***{**xe "P. falciparum"**}**, *P. vivax***{**xe "P. vivax"**}**, *P. malariae***{**xe "P. malariae"**}**, and *P. ovale***{**xe "P. ovale"**}**. The protozoa are transmitted to humans by female mosquitoes of the genus *Anopheles*.**{**xe "Anopheles"**}** Transmission**{**xe "Transmission"**}** can also occur by direct inoculation of infected red blood cells via transfusion**{**xe "transfusion"**}**, needles, or congenitally. Some signs**{**xe "Signs"**}** and symptoms**{**xe "symptoms"**}** of the illness are high fever**{**xe "fever"**}**, chills**{**xe "chills"**}**, headache, anemia**{**xe "anemia"**}**, and splenomegaly**{**xe "splenomegaly"**}**. Most serious and fatal complications are caused by *P. falciparum*.

Life Cycle

The life cycle**{**xe "life cycle"**}** of malaria is complex (see Fig. 1-1) with developmental stages and corresponding symptoms**{**xe "symptoms"**}** differing according to the Plasmodium**{**xe "Plasmodium"**}** species involved (see Table 1-1). Sporozoites, the infective stage of plasmodia, are injected from the salivary glands of infected mosquitoes during feeding. Following inoculation, the sporozoites**{**xe "sporozoites"**}** disappear from the blood within 30 minutes. Many are destroyed by white blood cells, but some enter liver cells.

Exoerythrocytic{xe "Exoerythrocytic"} Phase. Sporozoites that enter liver cells multiply asexually in a process called exoerythrocytic schizogony**{**xe "schizogony"**}**. Thousands of uninucleate merozoites**{**xe "merozoites"**}** form, displacing the nucleus of the liver cell, but causing no inflammatory reaction in the liver. Eventually, invaded liver cells rupture, releasing thousands of merozoites into the bloodstream. This occurs 6 to 16 days after initial infection depending on the infecting Plasmodium**{**xe "Plasmodium"**}** species.

Dormant or Hypnozoite Phase. All infections due to *P. falciparum****{****xe "P. falciparum"****}*** and *P. malariae****{****xe "P. malariae"****}***

have a single exoerythrocytic form. All infected liver cells parasitized with *P. falciparum* and *P. malariae* rupture and release merozoites**{**xe "merozoites"**}** at about the same time.

In contrast, *P. vivax***{***xe "P. vivax"***}** and *P. ovale***{***xe "P. ovale"***}** have two exoerythrocytic forms. The primary type develops, causes liver cell rupture, and releases merozoites**{**xe "merozoites"**}** just as described for *P. falciparum***{***xe "P. falciparum"***}** and *P. malariae***{**xe "P. malariae"**}**. The other form, which develops concurrently, is known as the hypnozoite**{**xe "hypnozoites"**}**. Sporozoites that enter liver cells differentiate into hypnozoites that remain dormant**{**xe "dormant"**}** for weeks, months, or years. At some future time, the hypnozoites activate and undergo exoerythrocytic schizogony,**{**xe "schizogony"**}** forming a wave of merozoites that invade the blood and cause a delayed case or a clinical relapse**{**xe "relapse"**}**.

Table 1-1. Selected Characteristics of the Four Species of Human Malaria

	*P. falciparum***{***xe "P. falciparum"***}**	*P. vivax***{***xe "P. vivax"***}**	*P. ovale***{***xe "P. ovale"***}**	*P. malariae***{***xe "P. malariae"***}**
Incubation days (range)	12 (9-14)	13 (12-17) or up to 6-12 months	17 (16-18) or longer	28 (18-40) or longer
Exoerythrocytic **{**xe "Exoerythrocytic"**}** cycle (days)	5.5-7	6-8	9	12-16
No. of merozoites per liver cell	40,000	10,000	15,000	2,000
Erythrocytic**{**xe "Erythrocytic"**}** cycle (hours)	48	42-48	49-50	72
Red blood cell preference	younger cells, but can invade cells of all ages	Reticulocytes	Reticulocytes	Older cells
Relapses	No	Yes	Yes	No
Fever periodicity (hours)	none	48	48	72

Febrile paroxysm{xe "paroxysm"} length (hours)	16-36 or longer	8-12	8-12	8-10
Severity of primary attack	severe in non-immune	mild to severe	mild	mild
Drug Resistance	++	+	-	-

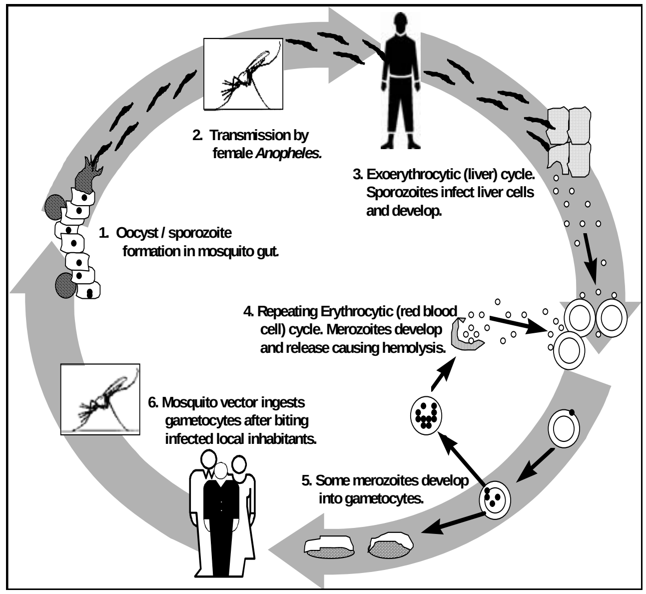
Erythrocytic{xe "Erythrocytic"} Phase. Released merozoites{xe "merozoites"} invade red blood cells (erythrocytes{xe "erythrocytes"}), where they develop into trophozoites{xe "trophozoites"}. After a period of growth, the trophozoites divide and develop, eventually forming 8-24 merozoites in each red blood cell. When this process is complete, the host{xe "host"} red blood cells rupture, releasing mature merozoites. The symptoms{xe "symptoms"} associated with malaria occur at this point.

The merozoites{xe "merozoites"} then invade fresh erythrocytes{xe "erythrocytes"} and another generation of parasites{xe "parasites"} develops in the same manner. This process occurs repeatedly during the course of infection and is called eryrthrocytic schizogony{xe "schizogony"}. The length of this development cycle differs according to the species of parasite, varying from 48 hours in *P. vivax*, *P. ovale*, and *P. falciparum* malaria{xe "falciparum malaria"}, to 72 hours in *P. malariae{xe "P. malariae"}* infections. In the early stages of infection there is no characteristic periodicity as groups of parasites develop at different times. The febrile episodes{xe "febrile episodes"} caused are inconsistent. Later, the erythrocytic schizogony development cycle becomes synchronized, and the febrile paroxysm{xe "paroxysm"}s{xe "febrile paroxysms"} become more consistent. Some merozoites differentiate into sexual forms (female macrogametocytes{xe "macrogametocytes"}, male microgametocytes{xe "microgametocytes"}) and develop in invaded red blood cells.

Vector Phase. *Anopheles{xe "Anopheles"}* mosquitoes feeding on infected host{xe "host"}s ingest sexual forms developing in red blood cells. The female macrogametocytes{xe "macrogametocytes"} and male microgametocytes{xe "microgametocytes"} mature in the mosquito's stomach and combine forming a zygote that undergoes mitosis. The products of mitosis are ookinetes**{**xe "ookinetes"**}**, which force themselves between the epithelial cells to the outer surface of the stomach, and form into small spheres called oocysts. The oocysts enlarge as the nucleus divides, eventually rupturing and releasing thousands of motile sporozoites**{**xe "sporozoites"**}** into the body cavity. The sporozoites migrate to the salivary glands, making the female mosquito infective. The vector**{**xe "vector"**}** phase of the life cycle**{**xe "life cycle"**}**, called sporogony**{**xe "sporogony"**}**, is complete in 8 to 35 days depending on species and environmental conditions.

Environmental Factors. *Anopheles**{**xe "Anopheles"**}*** mosquitoes are essential for development, multiplication, and spread of plasmodia. Therefore, any area harboring *Anopheles* mosquitoes may be at risk for malaria transmission. **{** XE "transmission" **}**Specific environmental conditions optimal for anopheline mosquito vector and parasite development include temperature between 20^0 and 30^0C and a mean relative humidity of 60%. The sporogony phase requires temperatures between 16^0 and 33^0C. High relative humidity increases mosquito life-span, thereby increasing the probability of mosquitoes becoming infective. Areas with high rainfall have increased malaria incidence because of an increase in breeding sites. The accompanying high humidity increases survival rates of female anopheline mosquitoes. Elevation, along with cooler temperatures and lower humidity, is also a factor as transmission rarely occurs above 2000-2500 meters.

Figure 1-1. Malaria Life Cycle



Distribution. The worldwide distribution of malaria is illustrated by the map in Fig 1-2. This is a general representation and not intended for threat assessment or countermeasure planning. Country-specific information can be obtained from the Medical Environmental Disease Intelligence and Countermeasures (“MEDIC”**{**xe "MEDIC"**}**) compact disc, and the Navy Environmental and Preventive Medicine Unit responsible for a particular world area. (Further intelligence can be obtained from the agencies listed in Appendix One).

Malaria transmission**{**xe "transmission"**}** occurs in more than 100 countries. Regions include Africa, Asia, islands of the South, west, and central Pacific Ocean, Latin America, certain Caribbean islands, and Turkey. These areas, all between 45^0 N and 40^0 S latitude (see Fig. 1-2) possess tropical or subtropical zones wherein anopheline mosquito habitats exist.

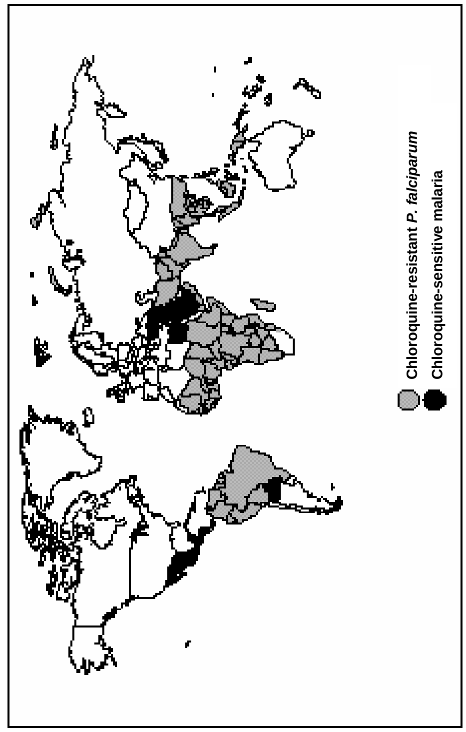


Figure 1-2. Worldwide Distribution of Malaria

CHAPTER TWO

PREVENTION

Systematic applications of four tactics are essential to planning and carrying out disease and injury prevention in field and combat operations. Listed in order, they are applicable for prevention of malaria (or any other threat):

1) Determine disease and injury threats**{**xe "threats"**}** in the area of operation before deployment.
2) Identify or develop countermeasures**{**xe "countermeasures"**}** to reduce threats**{**xe "threats"**}** to an acceptable level.
3) Educate personnel regarding threats**{**xe "threats"**}** and train in correct use of countermeasures**{**xe "countermeasures"**}**.
4) Command enforcement of countermeasures**{**xe "countermeasures"**}**.

The next three sections of this chapter review effective malaria countermeasures**{**xe "countermeasures"**}** available. Preventive countermeasures are divided into three sections: **Personal Protective Measures{xe "Personal Protective Measures"}, Chemoprophylaxis{xe "Chemoprophylaxis"},** and **Unit Protective Measures{**xe "Unit Protective Measures"**}**. Medical personnel must seek information to answer the questions outlined below and determine which countermeasures to employ, and make recommendations for the same to commanders**{**xe "commanders"**}**:

- What type(s) of malaria is (are) present?
- Which countermeasures**{**xe "countermeasures"**}** will be effective in the area and situations the unit will encounter?
- How will the unit obtain the necessary supplies, personnel, and equipment needed?
- Do unit personnel know how to apply the countermeasures**{**xe "countermeasures"**}** chosen? Will they apply them? What training is needed?

- Does the entire chain of command understand its role and accountability in enforcing the countermeasures{xe "countermeasures"}?

Section I. Personal Protective Measures{xe "Personal Protective Measures"}

This section presents measures that prevent mosquitoes from biting and transmitting malaria. **Applications of personal protective measures{xe "personal protective measures"} are effective against a wide range of disease vector{xe "vector"}s, not solely for prevention of malaria.** In many military operations, they will be the only means of protection against biting arthropods{xe "arthropods"}. They are the first line of defense, are simple to teach and perform, and enable personnel to remain in endemic areas while maintaining their operational capabilities. The major drawback of personal protective measures{xe "personal protective measures"} is dependence on service member compliance{xe "compliance"}. Persuasion by medical personnel and enforcement by NCOs{xe "NCOs"} and commanders{xe "commanders"} is necessary for their continuous proper application. Medical personnel must circulate among units teaching, examining, and improving personal protective measure practice, and also reporting their findings to those in charge. Commanders and NCOs must ensure compliance and lead via personal example.

DEET{xe "DEET"}

Topical repellents{xe "Repellents"} are natural or synthetic compounds that repel arthropods{xe "arthropods"}. The use of vapor-active skin repellents by U.S. Armed Forces has a long history. It began with the use of oil of citronella{xe "citronella"} in 1910, continued with the discovery of dimethyl phthalate during WW II, and led to the development of diethyl toluamide{xe "diethyl toluamide"} or “DEET{xe "DEET"}” in 1957. The duration of a repellent’s effectiveness decreases with activity, heat, and humidity{xe "humidity"}. Since Anopheles{xe "Anopheles"} mosquitoes inhabit warm tropical environments, military personnel need to re-apply repellent frequently to prevent biting. These products were selected based on their effectiveness. Contrary to public opinion, Avon Skin So Soft^{R} and flea collars are not effective. In fact, human use of flea collars can cause serious localized skin reactions and therefore never should be used. **As with all repellents and insecticides, carefully read and comply with the label requirements.**

Available Military Supplies{xe "Military Supplies"}: Insect/Arthropod Repellent Lotion (NSN 6840-01-284-3982) is a 33 % DEET**{**xe "DEET"**}** lotion developed to last 12 hours, has low odor, and less damaging to plastics than previous formulations. Apply in the same manner as skin lotion; neglected skin is not protected. This product is the most effective and longest lasting formulation available.

Various other personal application DEET products are available through the stock system. Cutter Repellent Stick (NSN 6840-00-142-8965) is a 30% DEET formulation that comes in a 1oz. stick. There are other functional products that include DEET formulations; DEET/SPF 15% sunscreen (NSN 6840-01-228-2188 (2 oz. tube) and NSN 6840-01-452-9582 (individual packets)), and camouflage face paint that includes 30% DEET (NSN 6840-01-493-7334).

Permethrin{xe "Permethrin"} Uniform{xe "Uniform"} Impregnants{xe "Impregnants"}

Impregnants**{**xe "Impregnants"**}** are compounds very similar to topical repellents. They are longer lasting, and cannot be applied to skin. Permethrin**{**xe "Permethrin"**}** is an impregnant for fabric only,**{**xe "impregnant"**}** used by the military to treat tents and clothing. It is also a contact insecticide capable of reducing the biting population and attack rate in the immediate area of use. Permethrin is a synthetic compound modeled from a naturally occurring insecticide found in certain plants. It is quick acting, long lasting (12 years in unwashed, stored clothing), nearly odorless, and non-staining. Permethrin is resistant to degradation when exposed to heat, sunlight, wear, laundering, rinsing, and immersion in water. It is effective against crawling arthropods**{**xe "arthropods"**}** such as ticks**{**xe "ticks"**}**, and flying insects such as mosquitoes and biting flies.

Available Military Supplies{xe "Military Supplies"**}**: Permanone 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 and mosquito netting. It is odorless, non-irritating, and can last through 3-5 washings or 6 weeks. Apply the same way as spray paint (slow sweeping motion 6-8 inches from object) until the surface of the fabric appears moistened. Allow to dry for 2 hours before wearing. Do not apply to caps, socks or undergarments or while clothing is being worn.

IDA Kit, “Insect Repellent, Clothing Application” (NSN 6840-01-345-0237) is a field kit in which shirt and trousers are treated in separate plastic bags containing a 40% permethrin and water mixture. Treatment lasts through about 50 washings.

Protective Clothing{xe "Protective Clothing"} and Netting{xe "Netting"}

The basic utility or camouflage uniform treated with permethrin and worn with sleeves down, collars closed and trousers bloused over boots offers excellent protection from mosquitoes. Other types of protective clothing and netting are also available.

Available: An improved Insect Repellent Mesh Parka (DEET jacket) is now available (small, medium, large, extra large, extra extra large: NSN 8415-01-483-2988; -3002; -3004; -3007; -3008 respectfully) that is effective without applying repellent, unlike the previous jacket.

{xe "Military Supplies"**}{**xe "DEET"**}** Insect Head Net (NSN 8415-00-935-3130) is a fine mesh nylon screen and cover that can be worn over a helmet, cap, or bare head. It is designed to be fastened to the uniform shirt collar and breast pocket buttons. For maximum protection, use with an application of DEET repellent on face and neck. **{**xe "DEET"**}**

Mosquito Bed Nets**{**xe "Bed Nets"**}**, (NSN 7210-00-266-9736), and poles (NSN 7210-00-267-5641) are a protective measure with a long history of use in tropical areas. They are designed for use with cots, bedrolls, hammocks, steel beds, and shelter half tents. Personnel should receive bed nets and be trained in their use before entry into an endemic area. Bed nets should be treated with permethrin, set up before dusk and checked for tears or other spots where mosquitoes can enter. If bed nets are set up properly, they will not interfere with quick night exits. A training team to coach, inspect, and advise on the application of personal protective measures**{**xe "personal protective measures"**}** including bed net use should be established for each unit. There are now also available self contained pop-up bed nets that are pretreated with permethrin. They area available in green; NSN:

3740-01-516-4415 and coyote brown; NSN: 3740-01-518-7310.

More information on these products and personal protective measures can be can be found in the Armed Forces Pest Management Board Technical Guide No. 36, Personal Protection Against Insects and Other Arthropods of Military Significance (www.afpmb.org).

Section II. Chemoprophylaxis{xe "Chemoprophylaxis"}

This section presents three frequently used chemoprophylactic**{**xe "chemoprophylactic"**}** regimens. Choice of regimen is determined by two factors:

⇒ Drug resistance in specific locations.
⇒ Any allergic or other reaction to the anti-malarial drug of choice, or restriction by job (mefloquine**{**xe "mefloquine"**}** is not authorized for prophylaxis in aviators and divers**{**xe "aviators"**}**).

Primary sources of information regarding malaria drug resistance**{**xe "drug resistance"**}** are the Armed Forces Medical Intelligence Center (AFMIC) and the Navy Environmental and Preventive Medicine Unit responsible for that area of the world. AFMIC distributes the MEDIC CD and offers up to date information on their website. (Agencies dedicated to supplying such information, along with all needed contact information and protocol are listed in Appendix 1).

Unit personnel must be screened before malaria chemoprophylaxis is initiated. Personnel who had prior reactions or risk factors, and those in certain occupations, personnel on flight status and divers, need to be identified and provided with an appropriate regimen.

Chemoprophylaxis{xe "Chemoprophylaxis"}: Before, During, After. One of the least appreciated aspects of chemoprophylaxis is the requirement for taking the drug before, during, and after exposure**{**xe "exposure"**}** to malaria. Chemoprophylaxis should begin 2 weeks before travel to endemic areas to allow adequate blood levels to develop. This is true for all malaria prophylaxis drugs except for doxycycline**{**xe "doxycycline"**}**, which should be initiated 1-2 days before exposure. The two-week lead-time is also useful to monitor personnel for any drug reactions. Prophylaxis must be continued for four weeks after leaving an endemic area to ensure that suppressive cure results. The required four week time period is to ensure drug therapy exceeds the length of time needed for the incubation period in the liver. If a mosquito bites on the last day of deployment, protection is needed 2-3 weeks later, when parasites emerge into the blood stream.

Directly Observed Therapy{xe "Directly Observed Therapy"} (DOT{xe "DOT"}). Directly observed therapy is recommended for all regimens. Chain of command support is required to carry out this method. A fellow service member supervised by a chain of command authority observes weekly or daily drug dosage.

Chemoprophylactic{xe "chemoprophylactic"} Regimens.

For areas where chloroquine**{**xe "chloroquine"**}** resistant *P. falciparum***{***xe "chloroquine resistant P. falciparum"***}{***xe "P. falciparum"***}** has NOT been reported:
Chloroquine taken weekly, starting 1-2 weeks prior to entering the area of risk. Continue weekly dosing while the area of risk and four weeks after leaving. Chloroquine is usually well tolerated, and the few personnel who have side effects**{**xe "side effects"**}** may tolerate the drug better by taking it with meals, or in divided twice-weekly doses. Hydroxychloroquine**{**xe "Hydroxychloroquine"**}**, is an alternative and may be better tolerated. It is available by open purchase under the trade name Plaquenil [R].
Atovaquone/proguanil, doxycycline, or mefloquine are also effective alternatives.**{**xe "Plaquenil"**}**

For areas where chloroquine**{**xe "chloroquine"**}** resistant *P. falciparum***{***xe "chloroquine resistant P. falciparum"***}{***xe "P. falciparum"***}** exists:
<u>Mefloquine (Lariam[R]), taken weekly, starting 1-2 weeks prior to entry into area of risk. Continue weekly dosing while in the area and for four weeks after leaving</u> Mefloquine is usually well tolerated at prophylactic dosage, but should not be taken by personnel with a history of seizures**{**xe "seizures"**}**, severe psychiatric disorders, or those with cardiac conduction abnormalities. Aviators are prohibited from using it. Mefloquine 250 mg/wk should begin 2 weeks before entering endemic areas of operation, taken once a week while deployed, and once a week for four weeks after

leaving. Personnel on flight status and divers are prohibited from using Mefloquine.
OR
Doxycycline, 100mg daily, starting 1-2 days prior to enty into area of risk. Continue daily dosing while in area of risk and for four weeks after leaving. Daily dose should be taken at the same time of day. One of the most common side effects**{**xe "side effects"**}** of doxycycline**{**xe "doxycycline"**}** is adverse gastrointestinal**{**xe "gastrointestinal"**}** symptoms**{**xe "symptoms"**}**, usually nausea**{**xe "nausea"**}** or vomiting**{**xe "vomiting"**}**. This often leads to compliance**{**xe "compliance"**}** problems. These side effects may be avoided by taking doxycycline with a meal. Other side effects include photosensitivity manifested by a severe sunburn reaction, and an increased frequency of monilial vaginitis. The sunburn reaction can be prevented by avoiding prolonged exposure**{**xe "exposure"**}** to sunshine, or sunscreen use. Females taking doxycycline should be supplied with nystatin suppositories to treat possible yeast infections when they occur.
OR
Atovaquone+Proguanil (Malarone[R]), 250mg/100mg, 1-2 days prior to entering area of risk. Continue daily dosing while in area of risk and for 7 days after leaving. Not recommended for children < 5 kg, pregnant women, and women breastfeeding infants weighing <5kg.

For areas where chloroquine and mefloquine resistant *P falciparum* exists:
Doxycycline or atovaquone+proguanil are recommend at the doses given above.

Terminal Prophylaxis: Primaquine is the only available drug for prevention of P. vivax**{**xe "P. vivax"**}** and P. ovale**{**xe "P. ovale"**}** relapse**{**xe "relapse"**}**. As most endemic areas of the world have at least one of these species, terminal primaquine prophylaxis is recommended to eradicate hypnozoites**{**xe "hypnozoites"**}**. Primaquine, 30mg, is taken daily during the last 14 days of the post-exposure prophyaxis when chloroquine, doxycycline, or mefloquine are being used for the prophylaxis. Primaquine can be taken during the 7 days of post-exposure prophylaxis when atovaquone/proguanil is used and for 7 additional days. This ensures an overlap of medication to eradicate parasites of any stage that may be present. No other medication eliminates

Plasmodia merozoites in the liver. Without primaquine**{**xe "primaquine"**}** therapy, personnel can harbor dormant**{**xe "dormant"**}** parasites in the liver long after leaving the risk area. Terminal primaquine prophylaxis**{**xe "terminal primaquine prophylaxis"**}** is given to ensure a complete cure.

Personnel should be screened for G-6-PD**{**xe "G-6-PD"**}** deficiency before given primaquine**{**xe "primaquine"**}**. See Chapter 6 for details and recommendations. In certain instances, terminal primaquine prophylaxis may not be indicated. Consult with the cognizant Navy Environmental and Preventive Medicine Unit**{**xe "Navy Environmental and Preventive Medicine Unit"**}** or other authorities for recommendations on need for terminal primaquine prophylaxis**{**xe "terminal primaquine prophylaxis"**}**.

Prophylaxis During Pregnancy{xe "Pregnancy"**}**:
For areas where chloroquine**{**xe "chloroquine"**}** resistant P. falciparum**{**xe "chloroquine resistant P. falciparum"**}{**xe "P. falciparum"**}** has NOT been reported:

When travel must occur, <u>chloroquine</u> is safe to use in pregnancy**{**xe "pregnancy"**}**. No harmful fetal**{**xe "fetal"**}** effects have been reported when given in the recommended doses for malaria prophylaxis. <u>Proguanil**{**xe "Proguanil"**}**</u> has been used for several decades without adverse effects on the pregnancy or fetus.

For areas where chloroquine**{**xe "chloroquine"**}** resistant *P. falciparum***{***xe "chloroquine resistant P. falciparum"***}{***xe "P. falciparum"***}** exists:

Mefloquine**{**xe "mefloquine"**}** may be considered for use by females who are pregnant when exposure**{**xe "exposure"**}** to chloroquine**{**xe "chloroquine"**}**-resistant *P. falciparum***{***xe "P. falciparum"***}** is unavoidable. A review of clinical trials and reports of inadvertent use during pregnancy shows no association with adverse fetal**{**xe "fetal"**}** or pregnancy outcomes when used at prophylactic doses during the second and third trimesters. Use of mefloquine during the first trimester for prophlyaxis appears to be safe but the data is more limited. <u>Doxycycline</u> is contraindicated for malaria prophylaxis during pregnancy. Fetal effects include discoloration and dysplasia**{**xe "dysplasia"**}** of teeth and inhibition of bone growth. Tetracycline**{** XE "Tetracycline:tetracycline" **}**s are only indicated to treat life-threatening infections due to multi-drug resistant**{**xe "drug resistant"**}** *P. falciparum.*

Primaquine should not be used during pregnancy**{**xe "pregnancy"**}**, as it can be passed transplacentally to a G-6-PD**{**xe "G-6-PD"**}** deficient fetus, causing in utero hemolytic anemia**{**xe "anemia"**}**. Chloroquine can be given**{**xe "chloroquine"**}** once weekly until delivery, at which time primaquine**{**xe "primaquine"**}** can be given.

Pediatric Prophylaxis:
For areas where chloroquine**{**xe "chloroquine"**}** resistant *P. falciparum***{***xe "chloroquine resistant P. falciparum"***}{***xe "P. falciparum"***}** has NOT been reported:

Chloroquine is recommended for prophylaxis in children.

For areas where chloroquine**{**xe "chloroquine"**}** resistant *P. falciparum***{***xe "chloroquine resistant P. falciparum"***}{***xe "P. falciparum"***}** exists:

Children should avoid travel to areas with chloroquine**{**xe "chloroquine"**}**-resistant *P. falciparum***{**xe "P. falciparum"**}**, unless a highly effective drug such as doxycycline**{**xe "doxycycline"**}** or mefloquine**{**xe "mefloquine"**}** can be administered. Indications and dosage schedules are the same as for adults; dose is based on age or weight (see Table 2-1).

Doxycycline is contraindicated in children under 8 years of age. Mefloquine can be used for infants and children of all ages and weights. Chloroquine and proguanil**{**xe "Proguanil"**}** are safe for pediatric use.

Chloroquine is manufactured in the U.S. in tablet form only, and has a very bitter taste. Pharmacists can pulverize tablets into powder for mixing in food or drink, or prepare gelatin capsules. Oral suspensions of chloroquine**{**xe "chloroquine"**}** are available overseas; parents should calculate dose because preparations vary. Overdose of anti-malarial drugs can be fatal. They must be stored in child proof containers out of children's reach.

Table 2-1. Drugs Used for Malaria Proplylaxis*

Drug	Adult Dosage	Pediatric Dosage
Mefloquine (Lariam[R])	250 mg base (250 mg salt)/week	5-10kg: 1/8 tablet/wk 10-20 kg: 1/4 tab/wk 20-30 kg: 1/2 tab/wk 30-45 kg: 3/4 tab/wk > 45 kg: 1 tab/wk
Doxycycline	100 mg/daily	> 8 yr. of age: 2 mg/kg once daily, up to adult dose of 100 mg/day
Chloroquine phosphate (Aralen[R])	300 mg base (500 mg salt)/wk	5 mg/kg base (8.3 mg/kg salt)/wk up to adult dose 300 mg base
Primaquine	30 mg base (52.6 mg salt) once/day for 14 days	0.5 mg/kg base (0.8 mg /kg salt) up to adult dose, once/day for 14 days (maximum 15 mg base)
Hydroxychloroquine**{**xe "Hydroxychloroquine"**}** **{**xe "chloroquine"**}** sulfate (Plaquenil**{**xe "Plaquenil"**}**[R])	310 mg base (400 mg salt) once/week	5 mg/kg base (6.5 mg/kg salt), once/week up to maximum adult dose of 310 mg base
Atovaquone/proguanil (Malarone™)	250 mg/100mg (adult tablet) Once/day	62.5mg/25mg (pediatric tablet) 5-8 kg: 1/2 tablet ≥ 8-10 kg: 3/4 tablet daily ≥10-20 kg: 1 tablet daily ≥20-30 kg: 2 tablets daily ≥30-40 kg: 3 tablets daily ≥40 kg: 1adult tablet daily

*all are oral doses.

Section III. Unit Protective Measures{xe "Unit Protective Measures"}

Unit malaria protective measures consist of the following:

- Discipline and training.
- Treatment of equipment with permethrin.**{**xe "Permethrin"**}**
- Camp selection.
- Vector control measures.

Discipline and Training

Avoiding malaria, other diseases, and non battle injuries is a team effort that must be supported by command authority. Medical personnel must be prepared to decisively advise those in command of such threats**{**xe "threats"**}** and their countermeasures**{**xe "countermeasures"**}**, train personnel in the use of protective measure and monitor their application and effectiveness. Disciplined and correct use of the personal protective measures**{**xe "personal protective measures"**}** thus far presented is very effective in preventing malaria and other diseases.

Equipment Treatment

Units should institute a program to treat uniforms, netting, and tents with Insect Repellent, Clothing Application, 40% Permethrin, Liquid (2-gallon sprayer) (NSN 6840-01-334-2666). This is a 40% Permethrin concentrate in 5.1 oz. bottles that is mixed with water and applied using a 2-gallon sprayer to uniforms, netting, or tents. Other gear (camouflage netting, ground covers, sleeping bags, hammocks, and window drapes) should also be treated.

Treat tents while erected, and uniforms and miscellaneous items while spread on the ground. Treated uniforms**{**xe "Uniform"**}** are ready to wear when dry; do not treat underwear or caps. Mark date of treatment on items. Permethrin**{**xe "Permethrin"**}** is very long lasting (12 years in unwashed, stored clothing), and such treatment could be done during routine field exercises. This approach would effectively prepare unit equipment months or years before use in an actual contingency.

Effectiveness in uniforms lasts through 50 washings. Tents and netting should be retreated every 6-9 months if regularly used. The impregnation of miscellaneous items (camouflage netting, ground covers, sleeping bags, hammocks, window drapes, and barrier nets) for protection is very effective.

Note: Application of the 40% permethrin product can only be done by DoD certified pesticide applicators, usually Preventive Medicine Technicians or Navy Medical Entomologists.

Camp Selection

If the tactical situation permits, base camps should be located in areas where there is low risk of exposure**{**xe "exposure"**}** to infected mosquitoes.

The following factors affect the risk of exposure:

- Presence of mosquito breeding sites**{**xe "breeding sites"**}**.
- Direction of prevailing winds.
- Proximity of settlements with malaria infected inhabitants**{**xe "inhabitants"**}**.
- Length of time unit will be present in area.

Breeding areas vary depending on the specific species of *Anopheles***{**xe "Anopheles"**}** mosquito responsible for malaria transmission**{**xe "transmission"**}**. Sunlit streams, shaded lagoons, rice fields, and marshes are all breeding habitats for different species of *Anopheles* mosquitoes. Campsite selection close to possible breeding sites**{**xe "breeding sites"**}** of the mosquito known to transmit malaria in that region should be avoided. When camping near an area where a high density of *Anopheles* mosquitoes is unavoidable, camp where the prevailing winds will blow the mosquitoes away from camp.

A host**{**xe "host"**}** population of infected humans is necessary to infect mosquitoes. If possible, locate base camps distant enough from settlements with infected inhabitants**{**xe "inhabitants"**}** so as to be beyond normal flight range (2-3 kilometers) of the Anopheles**{**xe "Anopheles"**}** mosquito vector**{**xe "vector"**}** **{**xe "transmission"**}**.

Duration of deployment in the area is also important for planning permanent mosquito control measures**{**xe "mosquito control measures"**}**. If military presence may be prolonged, establishment of a long-term base should be done with the preceding factors in mind or where elimination of mosquito breeding areas through engineering and control projects is feasible. Entomologists should be consulted to find the site most amenable for development by determining mosquito activity and identifying breeding areas. Improvement projects that impound water should be screened by entomologists**{**xe "entomologists"**}** and preventive medicine personnel to prevent creation of mosquito breeding areas.

Another unit protective measure to consider when operating in endemic areas is reducing troop exposure**{**xe "exposure"**}** during peak biting times (dusk till dawn for most Anophelines). Examples include:

- Restrict showers and baths to hours when the mosquitoes are not biting.
- Reschedule work parties and unit formations.
- Allocate available screening material to buildings that protect the largest number of personnel during peak mosquito biting times.

Malaria Vector Control Measures

Vector control includes two stages: surveillance**{**xe "surveillance"**}** and control. First, mosquito surveillance and analysis**{**xe "lysis"**}** of collected data are performed. The analysis leads to choice of control measures most applicable to area and situation. Mosquito control is the employment of chosen vector**{**xe "vector"**}** control measures.

Preventive medicine teams deployed in contingency situations are prepared to survey campsites for mosquitoes and other vector**{**xe "vector"**}**s, determine their breeding areas, and establish programs to control them. They are experienced at implementing sanitation and other public health measures and prepared to supervise and provide technical guidance to unit personnel (medical and non-medical) on unit protective measure management, if needed. These teams include medical entomologists**{**xe "entomologists"**}**.

Medical entomologists**{**xe "entomologists"**}** supervise the two-stage process, first determining mosquito species, their abundance, and breeding sites**{**xe "breeding sites"**}**. A control plan is then recommended, including specific control methods and their evaluation. Descriptions of common vector surveillance**{**xe "vector surveillance"**}** and control techniques used by medical entomologists follow.

Mosquito Surveillance Techniques

Larval Mosquito Surveys. The goals of sampling for mosquito larvae**{**xe "larvae"**}** are to identify their habitats, and later to evaluate control measures. All possible breeding areas are checked by sampling a uniform volume of water, and counting and identifying larvae present. From these data, the larval index, or average number of larvae collected per sample is calculated and recorded. This information is used to justify the use of permanent control measures such as filling or draining.

Anopheles larvae**{**xe "larvae"**}** are found in areas of heavy surface vegetation where debris accumulates, usually in water less than one meter deep. In larger ponds or lakes, they are found close to the shore.

Adult Mosquito Surveys**{**xe "Adult Mosquito Surveys"**}**. These are most frequently done because adult mosquitoes are often easier to collect and identify. These surveys determine the species present and their relative abundance, and the potential of a disease outbreak. For example, if no species of *Anopheles***{**xe "Anopheles"**}** mosquitoes are collected, the risk of malaria transmission**{**xe "transmission"**}** will probably be low.

Landing Counts**{**xe "Landing Counts"**}**. A landing count survey is done to rapidly assess mosquito biting activity and abundance when populations are high. An index (landing rate) is obtained by recording the number of mosquitoes that land on clothing within a certain time interval (usually one minute). **{**xe "vector"**}{**xe "host"**}** Mosquitoes are vacuumed into a container when they land for later identification. Success of mosquito control measures**{**xe "mosquito control measures"**}** can be evaluated by comparing landing counts before and after application of mosquito control measures.

Resting Sites. Daytime inspections are useful for some Anopheline mosquitoes. They rest in cool, dark, humid places protected from the wind during the day. From these sites, they are vacuumed into a container and provide a representative sample of the population.

Pyrethrum Spray/Sheet Collection. Spread white sheets on the floor of a human or animal shelter and spray the overhead spaces above with pyrethrum or 2% d-phenothrin. Any mosquitoes resting overhead will be killed, and can be collected from the sheets and identified. For best results, the technique should be used during midmorning hours.

Light Traps{xe "Light Traps"}. Light traps are the most widely used method to sample adult mosquito populations. The New Jersey light trap has limited use in military situations because of its size and need for a 110 or 220 volt power source. The solid state Army miniature light trap is more often used in the military setting. Traps are hung near wooded areas, swamps, or potential breeding sites{xe "breeding sites"}, 5-6 feet above ground and 30 feet away from buildings, avoiding areas exposed to strong winds or artificial light sources. They are scheduled a specific number of nights per week, and results are tabulated as to species, sex, and total number collected per night, per location. A trapping index (total females divided by number of trap nights) will detect changes in the population density of mosquitoes in an area.

Some *Anopheles*{xe "Anopheles"} mosquito species are not attracted by light, but by carbon dioxide (CO_2){xe "carbon dioxide (CO_2)"}. If so, light traps are baited with a perforated container of dry ice mounted above the trap. Light traps and adult mosquito resting counts are initially unsatisfactory to monitor populations of *Anopheles* mosquitoes because these methods may not identify all potential vector{xe "vector"} species. Mosquito collections from landing counts should be done until medical entomologists{xe "entomologists"} are satisfied that they have identified all *Anopheles* species present in the area. Then, they determine which collection methods are sufficient to monitor area species.

Mosquito Control Measures

The goal of malaria vector{xe "vector"} control is to eliminate the Anopheline population or reduce it below the number required to sustain disease transmission{xe "transmission"}. There are three main methods used to reduce mosquito populations:

- Biological control{xe "Biological control"}.
- Elimination of breeding sites{xe "breeding sites"}.
- Insecticides.{xe "Insecticides"}

The use of insecticides to kill larvae{xe "larvae"} and adult mosquitoes has been practiced in many military operations. Elimination of breeding sites and{xe "breeding sites"} employment of biological control methods may take too long to have an effect or are too resource intensive to be practical in most military operations. However, they are quite effective as public health measures for control of malaria and may be employed in humanitarian operations.

Biological control{xe "Biological control"}. Several methods of biological control currently exist. One involves the introduction of *Bacillus thuringiensis israelensis*, a mosquito bacterial pathogen, into a targeted mosquito population. Another requires the introduction of mosquito larvae{xe "larvae"}-eating fish, *Gambusia spp.*, into breeding areas.

Elimination of breeding sites{xe "breeding sites"}. Breeding sites can be made unsuitable for mosquito larvae through a variety of methods. They include increasing water flow or ditching, removing protective aquatic vegetation, or other actions that completely destroy breeding areas (filling or draining). Aside from limiting water containers in bivouac areas or simple ditching to provide drainage, permanent removal of breeding sites requires careful and thorough engineering, heavy equipment, and personnel usually not available to an engaged military force.

Insecticides{xe "Insecticides"}: Chemical Control of Larvae. Treatment of standing water with larvicides{xe "larvicides"} provides temporary control of mosquitoes and is more effective than adult control techniques. Unfortunately, the adult mosquito population is not immediately affected. Therefore, this may be a cost effective control method if troops are going to be located in the area for an extended period.

Solutions, emulsifiable concentrates, and suspensions are effective with ground operated or aerial dispersal equipment. They are also available in forms that can be applied by hand (briquettes or biodegradable plastic pouches). Medical entomologist supervision is essential. Considerations include larvicide formulation, delivery method, and amount and application rate. Method, amount, and formulation vary depending on geography, vegetation, species, level of insecticide resistance, and possible toxic effects on local inhabitants{xe "inhabitants"} and troops in the treatment area.

Insecticides{xe "Insecticides"}: Chemical Control of Adult Mosquitoes: Outdoor Control. The treatment of choice to control adult mosquitoes is ultra-low-volume{xe "Ultra-low-volume"} spraying (ULV{xe "ULV"}). ULV spraying provides adequate protection for limited periods of time. To provide continuous protection in large areas with many breeding sites{xe "breeding sites"**}**, ULV insecticides must be applied on a repetitive schedule, typically twice daily, daily, or every other day.

ULV**{**xe "ULV"**}** insecticides should be applied when winds are calm (less than 6 knots or 10 mph), and when the ground is cooler than the air. Such temperature conditions usually occur at sunrise and sunset. However, many *Anopheles***{**xe "Anopheles"**}** mosquitoes are most active later in the evening. As ULV insecticides are most effective against flying insects, spraying operations should be planned for dusk, after dark, and early morning (near sunrise). When properly applied, ULV treatments do not leave dangerous or unsightly deposits on trees, bushes, or terrain.

Aerial application of insecticide requires special consideration. It requires the authorization of certified Department of Defense entomologists**{**xe "entomologists"**}** or applied biologists, and qualified pest control personnel must supervise the operation. Factors considered before use include size of treatment area, vegetation cover (canopy) and density, suitability of alternate measures, prevalence of vector**{**xe "vector"**}** borne diseases, and the prospects of increasing troop effectiveness.

<u>Insecticides</u>**{**xe "Insecticides"**}**: <u>Chemical Control of Adult Mosquitoes: Indoor Control</u>. Indoor control of mosquitoes relies on aerosol space sprays that have only a short-term effect. They must be re-applied whenever new mosquitoes enter the space.

Another method of indoor control is application of residual sprays to surfaces where mosquitoes rest. Use permethrin or a long lasting spray recommended by a medical entomologist. For porous surfaces such as brick or unfinished wood, use a suspension made with a water-mixable powder or a microencapsulated formulation.

<u>Insecticides</u>**{**xe "Insecticides"**}**: <u>Chemical Control of Adult Mosquitoes: Barrier Treatments</u>. Residual spray treatment of all vegetation surfaces within 30 meters of small camps or bivouac areas can establish a barrier against mosquito re-infestation. Apply with backpack or hand held sprayers.

CHAPTER THREE

DIAGNOSIS

The definitive diagnosis of malaria is made by the identification of malaria parasites**{**xe "parasites"**}** in a peripheral blood film. However, U.S. medical professionals are inexperienced in malaria diagnosis and treatment because they rarely encounter the disease. When confronted with malaria, Navy medical personnel have misdiagnosed it as “viral illness”, “gastroenteritis”, or “flu.” Malaria also may not be considered because it shares signs and symptoms**{**xe "symptoms"**}** with other tropical illnesses including typhoid fever**{**xe "fever"**}**, rheumatic fever, and bacterial meningitis. Therefore, diagnosis of malaria requires a raised level of suspicion and diligent screening.

Screening. Screen all febrile patients possibly exposed to malaria transmission**{**xe "transmission"**}**. This includes personnel who took malaria chemoprophylaxis medication while deployed to endemic areas, or air crew or travelers briefly exposed at airports in malaria endemic zones.

The screening tool of choice for malaria diagnosis is microscopic examination of thick and thin blood smears**{**xe "blood smears"**}{**xe "thin blood smears"**}**. Thick**{**xe "Thick"**}** smear examination detects the presence of any organisms; thin smear examination identifies the specific infecting Plasmodium species. Thick and thin smears**{**xe "thin smears"**}** can be prepared on the same microscope slide; see Appendix 3 for description of this technique and further information on preparing and interpreting peripheral blood smears.

Timing of Screening. Symptoms often precede detectable parasitemia**{**xe "parasitemia"**}** by 1-2 days. Therefore, screen blood obtained through fingersticks**{**xe "ticks"**}** or other techniques several times a day (frequency is more important than timing) until a diagnosis of malaria is made or ruled out. Thin smear diagnosis for causal species is crucial, as P. falciparum**{**xe "P. falciparum"**}** infections are life threatening and require specific treatment. After diagnosis, blood smears**{**xe "blood smears"**}** should continue to be monitored for response to therapy. Decreasing parasite count (concentration) signifies favorable response to therapy; frequency of testing depends on therapeutic response and severity of illness. For example, seriously ill patients should be tested 2-3 times daily until they significantly improve, then daily until parasite level is zero.

Early diagnosis and treatment is lifesaving; falciparum malaria**{**xe "falciparum malaria"**}** kills 25% of non-immune adults within 2 weeks if treatment is not started early in the infection. If the diagnosis of malaria is suspected, treat, then arrange for definitive diagnosis. The rest of this chapter describes the clinical manifestations of malaria to aid in early diagnosis and understanding of disease processes.

Clinical Manifestations

Symptoms (Table 3.1). Patients present with a variety of symptoms**{**xe "symptoms"**}** depending on the stage of infection and the infecting species. Fever is virtually always present, and fever**{**xe "fever"**}** plus any other symptom might be malaria if exposure**{**xe "exposure"**}** occurred. Common complaints include mild to moderate malaise**{**xe "malaise"**}**, fatigue, muscle aches**{**xe "muscle aches"**}**, back pain**{**xe "back pain"**}**, headache**{**xe "headache"**}**, dizziness**{**xe "dizziness"**}**, loss of appetite**{**xe "loss of appetite"**}**, nausea**{**xe "nausea"**}**, vomiting**{**xe "vomiting"**}**, abdominal pain**{**xe "abdominal pain"**}**, and diarrhea**{**xe "diarrhea"**}**. Dry cough**{**xe "cough"**}** and shortness of breath have been reported in some patients. Gastrointestinal complaints can be considerable, suggesting a diagnosis of gastroenteritis. Young children and semi-immune individuals may complain of fever and headache as their only symptoms.

Signs{xe "Signs"}. Physical examination usually demonstrates an increased temperature, tachycardia**{**xe "tachycardia"**}**, and warm flushed skin. The spleen**{**xe "spleen"**}** is often palpable in initial infection, but this is more likely in subsequent attacks. It is usually soft and may be tender. The liver is often enlarged and may be tender; jaundice is not unusual. Orthostatic hypotension**{**xe "hypotension"**}** often occurs during initial infections. Mental confusion**{**xe "Mental confusion"**}** and cyanosis**{**xe "cyanosis"**}** are sometimes encountered.

Laboratory Findings (Table 3.2). Abnormal laboratory findings reflect the severity of hemolysis**{**xe "lysis"**}{**xe "hemolysis"**}**. Blood. A normocytic, normochromic anemia**{**xe "anemia"**}** with leukopenia**{**xe "leukopenia"**}** and thrombocytopenia**{**xe "thrombocytopenia"**}** is sometimes present on initial screening, but is almost always present following medication therapy with the resultant clearing of parasitemia**{**xe "parasitemia"**}**. Massive P. falciparum**{**xe "P. falciparum"**}** infections cause acute decreases in hemoglobin**{**xe "hemoglobin"**}**, hematocrit**{**xe "hematocrit"**}**, and an increase in reticulocyte**{**xe "reticulocyte"**}** count. Kidneys. Trace to moderate protein, urobilinogen, and conjugated bilirubin may be found on urinalysis**{**xe "urinalysis"**}**. In severe *P. falciparum* infections, massive hemolysis combined with circulating immune complexes produces acute renal insufficiency**{**xe "acute renal insufficiency"**}** or failure ("blackwater fever**{**xe "blackwater fever"**}{**xe "fever"**}**") with laboratory findings of hemoglobin**{**xe "hemoglobin"**}**uria**{**xe "hemoglobinuria"**}**, proteinuria**{**xe "proteinuria"**}**, and an elevated serum creatinine. **{**xe "lysis"**}{**xe "hemolysis"**}**

Table 3-1. Malaria Clinical Findings{xe "Clinical Findings"**}**

Sign or Symptom	Percent with Finding
• Fever & Chills**{**xe "Chills"**}**	96
• Headache	79
• Muscle Pain	60
• Palpable Liver	33
• Palpable Spleen	28
• Nausea & Vomiting	23
• Abdominal Cramps/Diarrhea	6

Fever and dehydration**{**xe "dehydration"**}** may cause an increase in BUN and creatinine, but if serum creatinine rises disproportionately higher than BUN (BUN to creatinine ratio is normally 10 or 12 to 1), renal failure must be considered.

Liver. Liver impairment may occur, though hyperbilirubinemia normally results from hemolysis**{**xe "lysis"**}{**xe "hemolysis"**}**. Abnormalities in liver function tests, increased ALT, AST, and prolonged prothrombin time**{**xe "prothrombin time"**}**, sometimes occur causing diagnostic confusion with viral hepatitis. Serum albumin is usually decreased.

Hypoglycemia, commonly seen in *P. falciparum***{**xe "P. falciparum"**}** infections and pregnancy**{**xe "pregnancy"**}**, is due to the 75-fold increase in glucose**{**xe "glucose"**}** consumption by parasitized red blood cells. In addition, quinidine{xe "quinidine"} or quinine{xe "quinine"} may stimulate insulin{xe "insulin"} secretion, causing clinically significant hypoglycemia{xe "hypoglycemia"} when used for treatment, especially when given intravenously{xe "intravenously"}. If a patient deteriorates during convalescence, especially with a deterioration in neurologic{xe "neurologic"} function, hypoglycemia should be considered as a possible cause.

False positive serologic tests may be present, including syphilis (VDRL{xe "VDRL"}, RPR{xe "RPR"}), rheumatoid factor{xe "rheumatoid factor"}, heterophil agglutinins{xe "heterophil agglutinins"}, and cold agglutinins. These result from a polyclonal increase in both IgG and IgM immunoglobulins, which are associated with appearance of specific malarial antibodies and reduced complement levels. Malaria does not cause eosinophilia{xe "eosinophilia"}.

Table 3-2. Malaria Laboratory Findings

Finding	Normal Range	Percent with Abnormal Findings
• Reticulocytosis	3 - 18%	42
• Thrombocytopenia	12K-150K	36
• Bilirubin Increased	1 - 1.8	33
• VDRL{xe "VDRL"} Positive	(-)	28 (+)
• Anemia	5.8 - 12 (Hgb)	28
• Leukopenia	3,000 - 4,700	26
• Alk. Phos. Increased	11-27	17
• SGOT Increased	40 - 108	10

Hyperparasitemia{xe "parasitemia"}. Patients with *P. falciparum{xe "P. falciparum"}* infections that are hyperparasitemic{xe "hyperparasitemic"} have a higher risk of death. Hyperparasitemia is defined as a parasite count of greater than 250,000 per microliter (>250,000/l), or as having greater than 5% of red blood cells parasitized. Risk of death is due to extensive microvascular{xe "microvascular"} disease, and severe metabolic effects from the parasite load.{xe "parasites"}

Pathophysiology and Clinical Presentation

Clinical symptoms{xe "symptoms"} and signs of malaria occur shortly before or at the time of red blood cells lysis{xe "lysis"}. Fever is caused by the release of merozoites{xe "merozoites"}, malarial pigment, parasite proteins and cellular debris. Chills{xe "Chills"} or rigor{xe "rigor"}, followed by high fever{xe "fever"} occur in a cyclical pattern in infections due to *P. vivax{xe "P. vivax"}, P. ovale{xe "P. ovale"},* and *P. malariae*{xe "P. malariae"}, but not *P. falciparum*, which is more likely to show continuous fever with intermittent temperature spikes. Clinical signs and symptoms described are those experienced by non-immune patients, such as will be seen in most U.S. military personnel. Clinical manifestations are not as severe in persons living in endemic areas. They are infected intermittently and develop partial immunity.

The malaria paroxysm{xe "paroxysm"} is the defining clinical feature of the disease. That being said, it is often not present. Fever caused by malaria can have any pattern, and falciparum infections often present with a constant fever{xe "fever"}. The classic paroxysm typically has three stages, and is preceded in some patients by an initial period of nonspecific symptoms{xe "symptoms"}. Those symptoms include fatigue, muscle aches{xe "muscle aches"}, loss of appetite{xe "loss of appetite"}, headache{xe "headache"}, and a slight fever of 2-3 day's duration.

A paroxysm{xe "paroxysm"} begins with the “cold” or “chilling” stage lasting 15 minutes to several hours during which the patient feels cold and has shaking chills{xe "chills"}. The second “hot” stage lasts several hours and coincides with red blood cell rupture and merozoite release. During the second stage temperatures rise to 40^{O}C (104^{O}F) or higher. There is minimal sweating{xe "sweating"} and the patient is at risk of febrile seizures{xe "seizures"} or hyperthermic{xe "hyperthermic"} brain{xe "brain"} damage. Clinical signs and symptoms{xe "symptoms"} include tachycardia{xe "tachycardia"}, hypotension{xe "hypotension"}, cough{xe "cough"}, headache{xe "headache"}, backache{xe "backache"}, nausea{xe "nausea"}, abdominal pain{xe "abdominal pain"}, vomiting{xe "vomiting"}, diarrhea{xe "diarrhea"}, and altered consciousness{xe "altered consciousness"}. Within 2-6 hours, the patient enters the third “sweating” stage of the paroxysm with generalized sweating, resolution of fever{xe "fever"}, and marked exhaustion, usually giving way to sleep. Paroxysms occur in regular intervals, but take several days to emerge.

As previously stated, the classic paroxysm{xe "paroxysm"} described above is generally not how *P. falciparum*{xe "P. falciparum"} infections present. *P. falciparum* malaria{xe "falciparum malaria"} is more severe and qualitatively different from the other plasmodia that infect humans, and is the only type that causes microvascular{xe "microvascular"} disease. For those reasons, it will be discussed separately and in more detail.

Malaria due to *Plasmodium{xe "Plasmodium"} falciparum* Infection

Plasmodium{xe "Plasmodium"} falciparum malaria{xe "falciparum malaria"} is a microvascular{xe "microvascular"} disease with a substantial metabolic element that damages tissue in the following manner: *P. falciparum*{xe "P. falciparum"} parasites{xe "parasites"} mature in red blood cells causing knobs{xe "knobs"} to form on their surface in effect making them “sticky”. This stickiness causes parasitized red blood cells to adhere to endothelial cells,{xe "endothelial cells"} lining capillaries{xe "capillaries"} and postcapillary venules{xe "venules"} of brain{xe "brain"}, kidneys{xe "kidneys"}, and other organs, obstructing blood flow. In addition to being “sticky," infected red blood cells are less flexible, adding to their obstructive potential. In obstructed capillaries and postcapillary venules, parasites consume glucose{xe "glucose"} and produce lactate-causing acidemia{xe "acidemia"} and release of tissue necrosis factor-{xe "tissue necrosis factor-□"} (a cytokine produced by the immune system). Lack of oxygen and increased concentrations of toxic metabolites cause capillaries to become more permeable, allowing leakage of protein and fluids. This results in tissue edema and further anoxia{xe "anoxia"} due to the edema, leading to organ damage and death. In some cases, diagnosis of *P. falciparum* infection is made difficult because no parasites are seen on peripheral blood smears{xe "blood smears"}, as they are sequestered in the host{xe "host"}’s microvasculature.

Cerebral Malaria{xe "Cerebral Malaria"}. The principal manifestations of cerebral malaria are seizures{xe "seizures"} and impaired consciousness, usually preceded by a severe headache{xe "headache"}. Neurologic examination may be unremarkable, or have findings that include contracted or unequal pupils, a Babinski{xe "Babinski"} sign, and absent or exaggerated deep tendon reflexes. Cerebrospinal fluid{xe "Cerebrospinal fluid"} examination shows increased pressure, increased protein, and minimal or no pleocytosis. High fever{xe "fever"}, 41^0 to 42^0C (106^0 to 108^0F), with hot, dry skin as seen in heat stroke can occur.

Manifestations of cerebral malaria are caused by microvascular{xe "microvascular"} obstruction that prevents the exchange of glucose{xe "glucose"} and oxygen at the capillary level, hypoglycemia{xe "hypoglycemia"}, lactic acidosis, and high-grade fever{xe "fever"}. These effects impair brain{xe "brain"} function, yet cause little tissue damage in most cases, as rapid and full recovery follows prompt treatment. Ten to twelve percent of patients surviving cerebral malaria have persistent neurologic{xe "neurologic"} abnormalities upon hospital discharge.

Renal Failure. Renal failure, due to acute tubular necrosis, is a common complication of severe *P. falciparum*{xe "P. falciparum"} infections in non-immune persons{xe "acute tubular necrosis"}. Acute tubular necrosis in severe *P. falciparum* infections is caused by two mechanisms: renal tubules become clogged with hemoglobin{xe "hemoglobin"} and malarial pigment released during massive hemolysis{xe "lysis"}{xe "hemolysis"}, and microvascular{xe "microvascular"} obstruction causes anoxia{xe "anoxia"} and glucose{xe "glucose"} deprivation at the renal capillary or tissue level. Failure of urine production is a poor prognostic sign, requiring peritoneal or hemodialysis{xe "hemodialysis"}.

Pulmonary Edema. Often fatal, acute pulmonary{xe "acute pulmonary"} edema can develop rapidly and is associated with excessive intravenous fluid therapy. Fast, labored respiration, with shortness of breath, a non-productive cough{xe "cough"}, and physical findings of moist rales and rhonchi are usually present. Chest X-rays usually show increased bronchovascular{xe "bronchovascular"} markings. It is thought that the pulmonary edema is more related to release of tissue necrosis factor{xe "tissue necrosis factor-□"}, than to the effects of microvascular{xe "microvascular"} obstruction.

Gastroenteritis. Most patients with falciparum malaria{xe "falciparum malaria"} complain of loss of appetite{xe "loss of appetite"} and nausea{xe "nausea"}. However, in some patients (especially young children), additional symptoms{xe "symptoms"} including vomiting{xe "vomiting"}, abdominal pain{xe "abdominal pain"}, watery diarrhea{xe "diarrhea"}, and jaundice are present leading to misdiagnosis of viral gastroenteritis or hepatitis. Clinical manifestations are associated with the adherence of parasitized red blood cells in the microvasculature of the gastrointestinal{xe "gastrointestinal"} tract.

Anemia. Destruction of red blood cells upon merozoite release, and inhibition of hematopoesis{xe "hematopoesis"} by tissue necrosis factor-{xe "tissue necrosis factor-□"} cause the severe anemia{xe "anemia"} often seen in P. falciparum{xe "P. falciparum"} infections. Also, *P. falciparum* parasites{xe "parasites"} can infect red blood cells of all ages, which theoretically allows infection of all circulating red blood cells. Whereas, *P. vivax* and *P. ovale* require young red blood cells (reticulocyte{xe "reticulocyte"}s) and *P. malariae* requires mature blood cells for infection.

Severe anemia{xe "anemia"} is defined as a hematocrit{xe "hematocrit"} of less than 21%, and clinical manifestations may include dark brown or red urine (hemoglobin{xe "hemoglobin"}uria{xe "hemoglobinuria"}), decrease in urine production, and jaundice. Renal failure, as previously discussed, may be a complication. Another cause of hemolysis{xe "lysis"}{xe "hemolysis"} and hemoglobinuria in patients with malaria is destruction of G-6-PD{xe "G-6-PD"} deficient red blood cells by oxidant{xe "oxidant"} anti-malarial drugs such as primaquine{xe "primaquine"}.

Malaria due to *P. vivax*{xe "P. vivax"} (or *P. ovale*{xe "P. ovale"}) Infection

Infections due to P. vivax**{**xe "P. vivax"**}** and P. ovale**{**xe "P. ovale"**}** are virtually the same. Both are less severe than falciparum malaria**{**xe "falciparum malaria"**}**, and parasite blood levels are lower. Parasitized red blood cells do not develop knobs**{**xe "knobs"**}**, therefore no microvascular**{**xe "microvascular"**}** obstruction with resultant brain**{**xe "brain"**}**, kidney, lung, or other organ complications occur in malaria due to *P. vivax* or *P. ovale.*

*P. vivax***{**xe "P. vivax"**}** and *P. ovale{xe "P. ovale"}* form a dormant**{**xe "dormant"**}** stage in liver cells called hypnozoites**{**xe "hypnozoites"**}**. These parasites**{**xe "parasites"**}** activate and cause delayed infections or a relapse (Table 3-3). A relapse usually occurs**{**xe "relapse"**}** within 6 months of an acute attack. Some hypnozoites remain dormant much longer, and are virtually undetectable. If there is any suspicion that *P. vivax{xe "P. vivax"}* or *P. ovale{xe "P. ovale"}* is endemic in the area of exposure, presumptive treatment must be given to prevent illness**{**xe "exposure"**}**. Currently, the only available treatment is primaquine**{**xe "primaquine"**}**; dosages are listed in Chapters 4, 5, and Appendix 4.

As previously stated, fever**{**xe "fever"**}** is virtually always present, and fever plus any other symptom might be malaria. *P. vivax***{**xe "P. vivax"**}** or *P. ovale***{**xe "P. ovale"**}** fevers may be erratic or continuous in the initial phase of illness. After 3 to 4 days, if not treated, the fever then develops into a synchronous cycle of afternoon temperature increases every 48 hours. The fever can be as high as 40^{O}C (104^{O}F), and symptoms**{**xe "symptoms"**}** during this stage have been described as worse than falciparum malaria**{**xe "falciparum malaria"**}**. Physical findings usually include an enlarged, tender spleen**{**xe "spleen"**}**, and a palpable liver present by the second week of infection. Deaths have been reported due to rupture of an enlarged spleen.

Parasitemia levels are less for *P. vivax{xe "P. vivax"}* or *P. ovale***{**xe "P. ovale"**}** because they infect only young red blood cells, unlike *P. falciparum***{**xe "P. falciparum"**}** which can infect red blood cells of all ages. Fewer red blood cells are hemolyzed, but their loss stimulates replacement. This increases the number of young red blood cells (reticulocyte**{**xe "reticulocyte"**}**s), which are susceptible to infection, leading to parasitemia**{**xe "parasitemia"**}** levels greater than 1 to 2% in *P. vivax* or *P. ovale* infections.

Malaria due to P. malariae{xe "P. malariae"} Infection

P. malariae{xe "P. malariae"} infection is the mildest and most chronic of all the human malaria infections. Invasion of red blood cells builds up slowly, so blood parasite levels are low, and symptoms{xe "symptoms"} are usually mild. Patients may have several febrile paroxysm{xe "paroxysm"}s{xe "febrile paroxysms"} before parasites{xe "parasites"} are seen in the peripheral blood. As in *P. vivax{xe "P. vivax"}* and *P. ovale*{xe "P. ovale"} infections, febrile paroxysms develop in the afternoon, but cycle every 72 hours. *P. malariae* and *P. falciparum*{xe "P. falciparum"} do not have the hypnozoite stage, therefore relapse{xe "relapse"}s do not occur in infections with these species. Recrudescence{xe "recrudescence"} can be seen with P. malariae infections many years after the initial infection. This is due to an increase in parasites after a chronic, low level of parasitemia in infected red blood cells that have persisted in tissue microcapillary circulation. Low-grade infections can persist up to 20-30 years. Splenomegaly is a common complication in those patients with low-grade infections of long duration.

P. malariae{xe "P. malariae"} infection may produce a unique immune complex glomerulonephritis{xe "glomerulonephritis"} . Low-level parasitemia{xe "parasitemia"} causes continuous antigen stimulation of host{xe "host"} antibodies and formation of immune complexes, causing an immune complex glomerulonephritis. This manifestation usually presents 3-6 months after malaria transmission{xe "transmission"} season, and can lead to nephrotic syndrome. Half the people who develop nephrotic syndrome had their first symptoms before the age of 15. Classic findings include persistent proteinuria, hypoalbuminemia, edema, and ascites. Patients who develop this complication do not respond to anti-malarial therapy, and response to corticosteroids is variable.

Table 3-3. Characteristics of malaria relapse and recrudescence.

	Relapse or Delayed Illness	Recrudescence
Species	*P. vivax, P. ovale*	*P. malariae*
Cause	hypnozoites (persistent	persistent undetectable

	liver cell stage)	parasitemia

Malaria in Pregnancy{xe "Pregnancy"}

Because of the immune suppression associated with pregnancy**{**xe "pregnancy"**}**, recrudescence**{**xe "recrudescence"**}** and relapse**{**xe "relapse"**}** are frequent in the second and third trimester. Malaria can potentiate the anemia**{**xe "anemia"**}** of pregnancy, and cause acute renal insufficiency**{**xe "acute renal insufficiency"**}** and hypoglycemia**{**xe "hypoglycemia"**}** in *P. falciparum***{**xe "P. falciparum"**}** infections. It is associated with increased numbers of abortions, miscarriage**{**xe "miscarriage"**}**s, stillbirths, and neonatal deaths.

Malaria in Children

In non-immune children,**{**xe "children,"**}** the initial attack can vary widely. Common symptoms**{**xe "symptoms"**}** include drowsiness**{**xe "drowsiness"**}**, anorexia, thirst, headache**{**xe "headache"**}**, nausea**{**xe "nausea"**}**, vomiting**{**xe "vomiting"**}**, and diarrhea**{**xe "diarrhea"**}**. Common early signs include increased temperature (may be greater than 40^{O}C), pallor, and cyanosis**{**xe "cyanosis"**}**; enlarged liver and spleen**{**xe "spleen"**}** occur later. Convulsions**{**xe "Convulsions"**}** are frequent, and cerebral malaria is the most frequent complication. Anemia is a complication with repeated infections.

Children living in endemic areas develop limited immunity. Symptoms are milder and more difficult to detect. They include low-grade anemia**{**xe "anemia"**}**, restlessness, loss of appetite**{**xe "loss of appetite"**}**, weariness, sweating**{**xe "sweating"**}**, and intermittent fever**{**xe "fever"**}**.

CHAPTER FOUR

TREATMENT

Overview

After establishing the presence of a malaria infection, treatment should be initiated as soon as possible. Specific treatment regimen depends on whether the case is diagnosed as complicated**{**xe "complicated"**}** or uncomplicated**{**xe "uncomplicated"**}** malaria. Severity of clinical illness and level of parasitemia determine this distinction. In addition, steps must be taken to identify the responsible species, and the area where transmission**{**xe "transmission"**}** occurred as those factors influence treatment. Patients diagnosed with complicated malaria are at risk for morbidity and death. Prompt treatment minimizes this risk. If possible, treatment of malaria should be done in consultation with a physician trained and experienced in treatment, with access to a tertiary care center.

Choice of treatment regimen, drug type, and selection of oral or intravenous administration, is based on the above factors. Two types of drugs are used to treat malaria. *Blood schizonticides***{**xe "Blood schizonticides"**}**, which attack parasites**{**xe "parasites"**}** in red blood cells, are used in acute infection to prevent or terminate the clinical attack. *Tissue schizonticides**{**xe "Tissue schizonticides"**}*** are medications that act on the exoerythrocytic parasite stages (forming merozoites**{**xe "merozoites"**}** and hypnozoites**{**xe "hypnozoites"**}**) in liver cells to prevent relapse**{**xe "relapse"**}**. Treatment with *tissue schizonticides*, known as “radical” cure**{**xe "radical cure"**}**, is required for infections of *P. vivax**{**xe "P. vivax"**}*** and *P. ovale***{**xe "P. ovale"**}**.

During treatment, patients must be monitored for response to therapy and complications from the infection or treatment. Repeated clinical assessment is important in cases of severe malaria, where early detection of complications and immediate intervention may be lifesaving.

Uncomplicated{xe "complicated"} Malaria

P. falciparum or species unknown:

In chloroquine sensitive areas; chloroquine 1000mg loading dose then 500 mg at 6, 24, and 48 hours after the initial dose. In areas of chloroquine resistance; one of the following three options should be used:

1) Quinine sulfate + doxycycline, or tetracycline, or clindamycin. Doxycycline or tetracycline are recommended over clindacycline due to more data regarding efficacy of the treatments. Quinine combinations should be prescribed for 7 days for infections acquired in Southeast Asia and for 3 days in other areas.
2) Atovaquone/proguanil.
3) Mefloquine. Recommended as a treatment only when the above two options cannot be used. Mefloquine is associated with an increased risk of neuropsychiatric side effects when taken at treatment doses.

Pediatric patients have the same three treatment options. Dosage should be calculated by using the patient's weight. Only quinine + clindamycin combination is recommended for children less than eight years of age. Doxycycline and tetracycline are contraindicated for use in this age group and should be used by this age group when the other options are not available and the benefits clearly outweigh the risk.. Quinine for seven days not in combination is another option for infections acquired in chloroquine resistant areas for pediatric patients.

P. malariae:

Chloroquine is recommended for all P. malariae infections as there is little evidence of chloroquine resistance found in this species.

P. vivax and P. ovale:

Chloroquine is recommended for *P. vivax* and *P. ovale* infections. For *P. vivax* infections not responding to chloroquine treatment and patients acquiring *P. vivax* infections in Papua New Guinea or Indonesia treatment should be either:

1) quinine + doxycycline or tetracycline
2) mefloquine

At present not enough data exists to support use of atovaquone/proquanil for use in treating chloroquine resistant *P. vivax* infections.

Febrile, acutely ill patients are prone to vomiting**{**xe "vomiting"**}** anti-malarial drugs, which are very bitter tasting. Administer an antipyretic such as Tylenol[R] (acetominophen**{**xe "acetominophen"**}**). This eases symptoms**{**xe "symptoms"**}** and helps patients tolerate anti-malarial drugs. Patients continuing to vomit require treatment by injection, administration of crushed tablets via nasogastric**{**xe "nasogastric"**}** tube, or suppository. After administering an effective dose by one of these routes, patients can usually complete their course of therapy by mouth.

Complicated Malaria

Complicated malaria is almost always due to *P. falciparum*, and is associated with a mortality rate between 15 and 25%. Most deaths from malaria occur within the first 24 -48 hours so the goal of treatment is to reach therapeutic concentrations quickly. Its diagnosis is based on the severity of clinical manifestations and a parasitemia**{**xe "parasitemia"**}** involving more than 1% or 2% of red blood cells. Patients presenting with any of the clinical manifestations listed in Table 4-1 should be treated for complicated**{**xe "complicated"**}** malaria. It is strongly advised that consults with a cardiologist and a physician with experience in treating malaria be obtained when treating a patient with severe malaria.

Treatment approach for complicated**{**xe "complicated"**}** malaria is listed below:

- Start treatment as soon as diagnosis is suspected.
- Calculate dosage according to patient weight.
- Give medication intravenously**{**xe "intravenously"**}**.
- Give loading dose of medication (not indicated if patient has received quinine**{**xe "quinine"**}**, quinidine**{**xe "quinidine"**}**, or mefloquine**{**xe "mefloquine"**}** in the last 24 hours).
- If patient is comatose, place on his or her side and give a single parenteral dose of Phenobarbital (5-20mg/kg) to prevent convulsions.
- Measure parasite count and hematocrit every 6-12 hours.

- Exchange transfusion should be strongly considered for patients with parasitemia (>10%) and for severely ill patients if it can be provided safely.
- 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.

Patients with complicated**{**xe "complicated"**}** malaria should be treated with intravenous quinidine**{**xe "quinidine"**}** (parenteral quinine**{**xe "quinine"**}** has not been available in the U.S. since 1991). Intravenous Quinidine is a potent blood schizonticide, and therapeutic plasma concentrations can be quickly and safely achieved by administration of a loading dose. Loading doses have been shown to decrease the duration of fever**{**xe "fever"**}**, parasitemia**{**xe "parasitemia"**}**, and coma**{**xe "coma"**}**, and should be given unless the patient has received more than 40 mg/kg quinine in the previous 2 days or mefloquine in the last 12 hours. The recommendation is a loading dose of quinidine gluconate 10 mg salt/kg infused intravenously over 1-2 hours then a continuous infusion of quinidine gluconate at 0.02mg salt/kg/min. If possible, plasma concentrations of quinidine should be monitored,and quinidine levels should be maintained at 3-8 mg/L. Quinidine gluconate should be infused for at least 24 hours. An alternative regimen is 24mg salt/kg IV infused over 4 hours, as a loading dose, followed by 12 mg salt/kg IV infused over 4 hours, given every 8 hours, starting 8 hours after the loading dose. At least 3 following doses should be given.

Baseline blood pressure and ECG should be obtained before initiating therapy, and periodically throughout treatment. Therapy should be discontinued if systolic**{**xe "systolic"**}** blood pressure persists below 80 mm Hg, if either the QRS interval widens greater than 50% of baseline or the QT**{**xe "QT"**}** interval is greater than 0.6 seconds; or if a cardiac arrhythmia**{**xe "arrhythmia"**}** arises.

Overdose of quinidine**{**xe "quinidine"**}**, particularly if too rapidly infused, can cause convulsions, hypotension**{**xe "hypotension"**}**, cardiovascular collapse, heart block, and ventricular fibrillation**{**xe "ventricular fibrillation"**}**. The maintenance dose should be reduced to one-third to one-half after 48 hours to prevent accumulation and toxicity, unless the patient has improved and can tolerate oral medication. Therapeutic doses of both quinidine can cause hypoglycemia**{**xe "hypoglycemia"**}** through stimulation of insulin{xe "insulin"} release. All patients treated with intravenous quinidine should receive a continuous infusion of 5 to 10 % dextrose. Measure blood glucose {xe "glucose"}periodically during treatment, every 4 to 6 hours in unconscious patients, and give prompt treatment of intravenous dextrose if glucose levels fall below 40mg/dl (2.2mmol/l).

Table 4-1. Manifestations of Complicated Malaria

MAJOR SIGNS	DESCRIPTION
Unarousable coma{xe "coma"}	Failure to localize or abnormal response to painful stimuli; coma{xe "coma"} persisting for >30 min after generalized convulsion
Seizures	More than two generalized convulsions in 24 hours
Severe anemia{xe "anemia"} (normochromic, normocytic)	Hematocrit rapidly falling or <15%, or hemoglobin{xe "hemoglobin"} <5g/dl, with parasitemia{xe "parasitemia"} level > 10,000 per ml, or with > 1 to 2% of RBCs involved
Severe bleeding abnormalities	Significant bleeding from gums, nose, GI tract, and/or evidence of disseminated intravascular coagulation
Pulmonary edema /adult respiratory distress syndrome	Shortness of breath, fast labored respiration, rales
Renal failure	Urine output <400 ml/24 hrs (<12 ml/kg per 24 hrs in children); no improvement with re-hydration; serum creatinine >3.0 mg/dl (>265 mol/l)
Hemoglobinuria	Black, brown, or red urine; not associated with effects of drugs or red blood cell enzyme defects (primaquine{xe "primaquine"}/G-6-PD{xe "G-6-PD"})
Hypoglycemia	Glucose <40mg/dl (<2.2 mmol/l)
Hypotension/shock	Systolic BP <50 in children aged 1-5 or <80 in adults; core to skin temperature >10^{0}C difference
Acid base disturbances	Arterial pH <7.25 or plasma bicarbonate <15 mmol/l

Intravenous therapy is continued until the parasite density is <1%, the recommended minimum IV treatment has been given and the patient is able to tolerate oral therapy. Oral therapy should be quinine, 10 mg salt/kg very 8 hours until a combined treatment course of quinidine and quinine of 7 days for southeast Asia and 3 days for South America and Africa. Quinidine/quinine therapy should be comibined with doxycycline (100mg every 12 hours), tetracycline (250 mg every 6 hours) or clindamycin (20mg base/kg/day divided into three q8 hour doses). These medications should be taken for 7 days.

“Radical” Cure**{**xe "Radical Cure"**}**. To prevent relapse**{**xe "relapse"**}**, *P. vivax***{***xe "P. vivax"***}** and *P. ovale***{***xe "P. ovale"***}** infections need to be treated to eradicate tissue schizonts (persistent liver cell stages known as hypnozoites**{**xe "hypnozoites"**}**). This is known as “radical” cure**{**xe "radical cure"**}**, and currently the only available effective drug is primaquine**{**xe "primaquine"**}**. It is a potent oxidant**{**xe "oxidant"**}**, and can cause severe hemolytic anemia**{**xe "anemia"**}** in G-6-PD**{**xe "G-6-PD"**}** deficient patients. Therefore, before treating with primaquine, the G-6-PD status of patients must be checked, and an appropriate dosage regimen selected. Radical cure dosage schedules are listed in Table 4-2.

Table 4-2. Primaquine Treatment Regimens

G-6-PD**{**xe "G-6-PD"**}** NORMAL	1 tablet* per day x 14 days
G-6-PD**{**xe "G-6-PD"**}** deficiency (Mild African form)	3 tablets per week for 8 weeks
G-6-PD**{**xe "G-6-PD"**}** deficiency (More severe Mediterranean variety)	2 tablets per week for 30 weeks

* 1 tablet consists of 26.3 mg pimaquine phosphate, 15 mg primaquine base; after travel to some areas, resistant *P. vivax* strains have required a 2 tablet per day dosage.

Treatment Management

Monitoring. Complicated malaria patients are at risk for sudden decompensation and need to be closely monitored. If possible, these patients should be transferred to facilities with an intensive care unit (ICU) or equivalent. Treatment should be supervised by a physician. Initial patient monitoring should be frequent (every 1 to 2 hours), until the patient improves. Parameters to monitor include:

- Vital signs**{**xe "Vital signs"**}** (temperature, pulse, blood pressure, respiration)
- Parasite concentration.
- Urinary output.
- Serum electrolytes.
- Blood glucose.**{**xe "glucose"**}**
- Hematocrit/hemoglobin**{**xe "hemoglobin"**}**.
- ECG (required for quinidine**{**xe "quinidine"**}** treatment).

Response to therapy is monitored by serial blood smears**{**xe "blood smears"**}**. Fewer parasites**{**xe "parasites"**}** will be seen on successive smears if treatment is effective. If no improvement in clinical symptoms**{**xe "symptoms"**}** or decrease in parasitemia**{**xe "parasitemia"**}** is seen in the first 24 to 48 hours of treatment, resistance should be assumed and treatment with an alternate drug should be initiated. Providers should be vigilant and monitor other parameters to identify the common complications of malaria: cerebral malaria, hypoglycemia**{**xe "hypoglycemia"**}**, anemia**{**xe "anemia"**}**, renal failure, pulmonary edema, concurrent bacterial infection, and over-hydration. Prompt initiation of supportive measures (intravenous hydration, glucose**{**xe "glucose"**}** administration, oxygen therapy, blood transfusion**{**xe "transfusion"**}**, etc.) is important in reducing permanent injury and mortality.

Cerebral Malaria{xe "Cerebral Malaria"**}**. Generalized seizures**{**xe "seizures"**}** occur in more than 50% of patients with cerebral malaria, and can lead to sustained neurologic**{**xe "neurologic"**}**al deterioration or aspiration**{**xe "aspiration"**}** pneumonia. Patients with impaired consciousness should be placed in the lateral decubitis position**{**xe "lateral decubitis position"**}**. If patient is unconscious, intubation with an endotracheal tube or placement of a rigid oral airway is indicated to maintain the airway. Vital signs**{**xe "Vital signs"**}**, level of consciousness (modified Glasgow coma{xe "coma"} scale{xe "Glasgow coma scale"}, see Table 4-3), and seizures should be monitored and recorded frequently. Seizures must be treated promptly with a benzodiazepine drug (diazepam, chlormethiazole, or lorazepam). A nasogastric{xe "nasogastric"} tube should be placed to lower risk of aspiration pneumonia.

Deepening coma{xe "coma"} or signs of cerebral herniation{xe "cerebral herniation"} are indications for further assessment with computed tomography (CT{xe "CT"}) or magnetic resonance imaging (MRI{xe "MRI"}). If such techniques are not available, therapy to lower intracranial pressure should be attempted. Acceptable treatment measures include intravenous mannitol{xe "mannitol"}, 1.5 mg/kg of 10-20% concentration given over 30 minutes, or hyperventilation to reduce arterial pCO_2 below 4.0 pKa. Steroids have been proven ineffective when used in an attempt to lower intracranial pressure.

Seizures may be prevented with a single intramuscular dosage of phenobarbital{xe "Phenobarbital"} sodium (loading dose 15-20 mg/kg, total dose 60-200 mg/kg/day). In an ICU, an alternate method is phenytoin{xe "phenytoin"}, 10-15 mg/kg loading dose, followed by an adult maintenance dose of 100 mg every 6 hours. Plasma phenytoin concentration should be monitored daily.

Hypoglycemia. This complication should be suspected in any patient who becomes unresponsive. Frequent monitoring of blood glucose{xe "glucose"} is necessary in complicated malaria, particularly during intravenous quinine{xe "quinine"} or quinidine{xe "quinidine"} administration. Hypoglycemia can be caused by two mechanisms, stimulation of insulin{xe "insulin"} release caused by quinine or quinidine therapy, or from consumption of glucose{xe "glucose"} by large numbers of parasites{xe "parasites"}. If available, give a therapeutic trial of 50% dextrose followed by continuous infusion of 5 or 10 % dextrose solution.

Table 4-3. Modified Glasgow Coma Scale

		Score
Best Verbal Response:	Oriented	5
	Confused	4
	Inappropriate words	3

	Incomprehensible sounds	2
	None	1
Best Motor Response:	Obeys commands	6
	Localizes pain	5
	Flexion to pain:	
	Withdrawal	4
	Abnormal	3
	Extension to pain	2
	None	1
	Total	2 - 11
	Unarousable coma**{**xe "coma"**}**	≤ 7

Pulmonary Edema. This complication results from either increased capillary permeability or fluid overload and resembles Adult Respiratory Distress Syndrome (ARDS). A patient with pulmonary edema needs treatment in an ICU, as positive pressure ventilation with positive end expiratory pressure/continuous positive airway pressure (PEEP/CPAP) is needed for adequate oxygenation. Fluid overload must be prevented by maintaining the central venous pressure between zero and 10-15 cm H_2O. If an ICU setting is not available, oxygen should be delivered by the most effective means available, and a rapid acting diuretic such as furosemide**{**xe "furosemide"**}** should be given intravenously**{**xe "intravenously"**}**.

Renal Failure. Renal complications are seen in one third of adult patients with severe falciparum malaria**{**xe "falciparum malaria"**}**. Most patients will respond to cautious re-hydration with an increase in urine output. Dialysis**{**xe "lysis"**}** is indicated for hyperkalemia, uremia, metabolic acidosis, or pulmonary edema. Treatment of intravascular hemolysis**{**xe "hemolysis"**}** (blackwater fever**{**xe "blackwater fever"**}{**xe "fever"**}**) involves correction of uremia with dialysis, and avoidance of fluid overload due to blood transfusion**{**xe "transfusion"**}**. In cases of renal failure due to massive hemolysis, blood transfusion is usually necessary to prevent death.

Anemia. In most cases no intervention beyond treatment of the malaria infection is required. Transfusion should be considered if the hematocrit**{**xe "hematocrit"**}** drops below 20%, or if it is falling rapidly and associated with clinical distress. Clinical manifestations indicating need for transfusion**{**xe "transfusion"**}** include shock, cardiac failure, hypoxia, and extreme lethargy.

Transfusion has safely been used to correct anemia**{**xe "anemia"**}**, but the volume given must be included in fluid balance calculations to prevent pulmonary edema. Diuretics (furosemide**{**xe "furosemide"**}**, 1-2 mg/kg) can be given to promote urine output to maintain fluid balance during transfusion**{**xe "transfusion"**}**. Plasma expanders (colloids), and administration of oxygen can be used if transfusion is not practical or available.

<u>Exchange transfusion</u>**{**xe "<u>Exchange transfusion</u>"**}{**xe "transfusion"**}** for treatment of hyperparasitemia**{**xe "parasitemia"**}** has been used for approximately 70 patients. Though most showed clinical improvement during and after the procedure, it has not been proven superior to optimal anti-malarial medication treatment. Manual exchange transfusion (alternating phlebotomy with transfusion), or continuous cell separation (hemophoresis) are methods of exchange transfusion that have been used. Parasite density should be monitored every 12 hours. Eight to 10 units of blood can be expected to be exchanged.

Septic Shock. Secondary bacterial infection is a frequent complication in severe malarial cases. Blood, urine, and CSF fluid, etc. should be routinely cultured. Broad-spectrum intravenous antibiotics combining an aminoglycoside**{**xe "aminoglycoside"**}** and a later generation cephalosporin**{**xe "cephalosporin"**}** should be started immediately if a secondary bacterial infection is suspected. Other causes of shock to consider are hypovolemia**{**xe "hypovolemia"**}** from dehydration**{**xe "dehydration"**}**, pulmonary edema, or massive blood loss (gastrointestinal**{**xe "gastrointestinal"**}** hemorrhage or ruptured spleen**{**xe "spleen"**}**).

Ruptured Spleen. This potentially fatal complication should be considered in patients infected with P. vivax**{**xe "P. vivax"**}** or P. falciparum**{**xe "P. falciparum"**}**. Clinical manifestations include complaints of abdominal pain**{**xe "abdominal pain"**}**, especially in the left upper quadrant, left shoulder pain, and hypotension**{**xe "hypotension"**}** without other signs of blood loss. Free blood in the peritoneal cavity or a torn splenic capsule can be detected by ultrasound or CT**{**xe "CT"**}**, and confirmed by needle aspiration**{**xe "aspiration"**}** of the peritoneal cavity. A trial of conservative management is currently recommended so the spleen**{**xe "spleen"**}** and its immunological functions can be preserved. This includes blood transfusion**{**xe "transfusion"**}**, close observation in an ICU or equivalent setting, and rapid access to surgical consultation.

Pregnancy{xe "Pregnancy"}. Treatment is essential for pregnant women to save their lives and prevent miscarriage**{**xe "miscarriage"**}**s. Falciparum malaria is associated with low birth weight, fetal**{**xe "fetal"**}** distress, premature labor, miscarriage, stillbirth, and hypoglycemia**{**xe "hypoglycemia"**}**. Treat as for any adult, suspect hypoglycemia, and do not give tetracycline.

Pediatrics. Most of the 1 to 3 million deaths from malaria each year are children,**{**xe "children,"**}** primarily in Africa. Common complications are convulsions, coma**{**xe "coma"**}**, hypoglycemia**{**xe "hypoglycemia"**}**, metabolic acidosis, and severe anemia**{**xe "anemia"**}**. Severe jaundice, acute renal failure, and pulmonary edema are unusual. Children tolerate anti-malaria drugs well, and treatment is virtually the same as for adults with appropriate dosage adjustments. Tetracycline**{** XE "Tetracycline" **}** drugs cause defects in forming teeth and bone, and should not be given to children under 8 or 9 years.

Follow Up and Prognosis

Once elimination of parasites**{**xe "parasites"**}** has been documented on peripheral blood smears**{**xe "blood smears"**}**, routine repeat smears are not recommended. Patients should be advised that malaria relapse**{**xe "relapse"**}** is possible despite thorough treatment. If presenting for care with a febrile illness within a year, they should be advised to inform their provider that they were recently treated for malaria and it should be considered a potential cause of their present illness.

CHAPTER FIVE

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

Overview

The recognition of Glucose-6-Phosphate Dehydrogenase (G-6-PD**{**xe "G-6-PD"**}**) deficiency was the direct result of investigations of the hemolytic effect of the drug primaquine**{**xe "primaquine"**}** in the 1950s. G-6-PD is the first enzyme of the hexose monophosphate shunt, a biochemical pathway crucial in the protection of red blood cells. Damage done to hemoglobin**{**xe "hemoglobin"**}** molecules (See Table 5-1) by oxidizing drugs or chemicals is neutralized or reversed by substances that the hexose monophosphate shunt produces.

Primaquine is the only currently available drug able to destroy dormant**{**xe "dormant"**}** hypnozoites**{**xe "hypnozoites"**}** in liver cells and prevent relapse**{**xe "relapse"**}** of *P. vivax***{***xe "P. vivax"***}** or *P. ovale***{***xe "P. ovale"***}** malaria. Unfortunately, it is a strong oxidizing agent, and can cause severe hemolytic anemia**{**xe "anemia"**}** in G-6-PD**{**xe "G-6-PD"**}** deficient personnel. In the U.S. military population, 2 types of G-6-PD deficiency**{**xe "G-6-PD deficiency"**}** are common. Understanding the difference between these types, and the primaquine**{**xe "primaquine"**}** treatment schedules available for each, can minimize or prevent complications from drug reactions, and allow treatment of the relapsing forms of malaria.

Physiology of G-6-PD{xe "G-6-PD"} Deficiency

Red blood cells are normally protected from oxidizing**{**xe "oxidant"**}** substances in a complex chemical pathway in which G-6-PD**{**xe "G-6-PD"**}** is an essential enzyme. In G-6-PD deficient red blood cells, this protective mechanism is compromised and oxidizing substances produced by infections or oxidant drugs damage hemoglobin**{**xe "hemoglobin"**}** molecules. In this harmful process, hemoglobin is denatured irreversibly and precipitates in clumps of protein called Heinz bodies**{**xe "Heinz bodies"**}**. Heinz bodies attach to red blood cell membranes, deforming the cells, and are filtered from circulation by the spleen. Free hemoglobin is released into the blood from the destroyed red blood cells. If a large number of red blood cells are destroyed, the human body's normal compensatory mechanisms are overwhelmed. The amount of hemoglobin released into the bloodstream may be too great to be absorbed and metabolized by the liver, resulting in hemoglobinuria**{**xe "hemoglobinuria"**}** and kidney damage. Anemia may also occur if the loss of red blood cells is too great to be compensated by an increase in the rate of reticulocytosis**{**xe "reticulocytosis"**}**. The extent of hemolysis**{**xe "lysis"**}{**xe "hemolysis"**}** depends on the type and severity of G-6-PD**{**xe "G-6-PD"**}** deficiency, and the amount of exposure**{**xe "exposure"**}** to oxidizing**{**xe "oxidant"**}** substances (see Table 5-2).

Table 5-1. Summary of Hemolysis{xe "lysis"} in G-6-PD Deficiency

• Exposure of hemoglobin**{**xe "hemoglobin"**}** to oxidant**{**xe "oxidant"**}**
• Heinz body formation (denatured clumps of hemoglobin**{**xe "hemoglobin"**}** inside red blood cells)
• Deformation of red blood cells caused by attachments of red cell membranes and Heinz bodies**{**xe "Heinz bodies"**}**
• Removal and destruction of deformed red bloods cells by the spleen**{**xe "spleen"**}**
• Decline in hemoglobin**{**xe "hemoglobin"**}**, hematocrit**{**xe "hematocrit"**}**
• Increase in red blood cell production (reticulocytosis**{**xe "reticulocytosis"**}**) to compensate for decrease in red blood cells
• Hemoglobinuria and symptoms**{**xe "symptoms"**}** if hemolysis**{**xe "lysis"**}{**xe "hemolysis"**}** severe (overcomes the liver's ability to metabolize hemoglobin**{**xe "hemoglobin"**}** breakdown products)

G-6-PD{xe "G-6-PD"} Types. The gene for G-6-PD is located on the X chromosome(s). Severe deficiency is fully expressed in males and rare in females. Over 200 variants have been identified. In the U.S. military, the two types that are often encountered are G-6-PD $^{A-}$, found in 16% of Afro-American males, and the more rare G-6-PD^{Med}{xe "G-6-PD^{Med}"} found in Greeks, Sardinians, Sephardic Jews, Arabs, and other males of Mediterranean descent.

Table 5-2. Drugs and Chemicals that Should be Avoided by G-6-PD{xe "G-6-PD"} Deficient Individuals

Acetanilid	Primaquine
Furazolidone	Sulfacetamide
Methylene blue	Sulfamethoxazole (Gantanol^{R})
Nalidixic acid	Sulfanilamide
Naphthalene	Sulfapyridine
Niridazole (Ambilhar^{R})	Thiazolesulfone
Isobutyl nitrite	Toluidine blue
Nitrofurantoin (Furadantin^{R})	Trinitrotoluene (TNT)
Phenazopyridium (Pyridium^{R})	Urate oxidase
Phenylhydrazine	

As normal red blood cells age, the activity of G-6-PD**{**xe "G-6-PD"**}** decays slowly, reaching 50% of its original level in 60 days. Despite this loss, normal red blood cells retain enough activity to sufficiently protect red blood cells from oxidant**{**xe "oxidant"**}**s. G-6-PD decay is significantly pronounced in deficient individuals. G-6-PD^{A-}{xe "G-6-PD^{A-}"} declines to 50% of baseline activity in 13 days, while G-6-PD^{Med}{xe "G-6-PD^{Med}"} declines to 50% of baseline activity in 1-2 days. In G-6-PD $^{A-}$ deficiency, young red blood cells have normal enzyme activity, while older cells are grossly deficient. In G-6-PD^{Med} virtually all red blood cells are deficient. Thus, hemolysis**{**xe "lysis"**}{**xe "hemolysis"**}** is self limited in individuals with G-6-PD^{A-}, ending when older red blood cells are destroyed. In G-6-PD^{Med} hemolysis is much more severe, as all red blood cells are at risk (see Table 5-3).

Most cases of drug induced hemolytic reactions related to G-6-PD**{**xe "G-6-PD"**}** $^{A-}$ deficiency are probably sub-clinical. During the Vietnam War, only 20 persons were documented to have developed a severe drug reaction because of G-6-PD deficiency**{**xe "G-6-PD deficiency"**}**. At that time, chloroquine-primaquine**{**xe "Chloroquine-primaquine"**}{**xe "primaquine"**}** tablets were given weekly to service members as malaria prophylactic therapy, and routine G-6-PD testing was not done. As thousands of service members were required to take the weekly prophylaxis, 20 cases were much less than expected. It is probable that the reactions that occurred were due to G-6-PD^{Med}{xe "G-6-PD^{Med}"}, not G-6-PD^{A-}{xe "G-6-PD^{A-}"}.

Table 5-3. Clinical Comparison: G-6-PD{xe "G-6-PD"} A- and G-6-PDMed{xe "G-6-PDMed"}

	G-6-PD{xe "G-6-PD"} A-	G-6-PD{xe "G-6-PD"}MED
Frequency	Common in Afro-American populations	Common in Mediterranean populations
Degree of Hemolysis{xe "lysis"}	Moderate	Severe
Hemolysis{xe "lysis"} with: Drugs Infection	 Unusual Common	 Common Common
Need for transfusion{xe "transfusion"}s	No	Sometimes
Chronic Hemolysis{xe "lysis"}	No	No

Signs{xe "Signs"} and Symptoms of Hemolysis{xe "lysis"}. Signs and symptoms{xe "symptoms"} appear 1-3 days after initiation of drug therapy. Shortness of breath, rapid pulse, hemoglobin{xe "hemoglobin"}uria{xe "hemoglobinuria"} (brown or black urine), and fatigue are common clinical manifestations. In mild cases, shortness of breath, rapid pulse, and fatigue appear during or after physical exertion. A modest decline in hemoglobin (3-4 mg/dl) occurs without hemoglobinuria. Most of these cases are easily overlooked unless caregivers are alert.

If hemolysis{xe "lysis"}{xe "hemolysis"} is markedly severe, shortness of breath, rapid pulse, palpitations, and fatigue can present at rest. Some patients complain of abdominal or back pain{xe "back pain"}. Signs{xe "Signs"} include hemoglobin{xe "hemoglobin"}emia (pink to brown plasma), hemoglobinuria{xe "hemoglobinuria"}, and jaundice. Heinz bodies{xe "Heinz bodies"} can be seen if red blood cells are stained using methyl violet.

Laboratory Analysis{xe "lysis"}. Urine dipstick and hematocrit{xe "hematocrit"} are simple and useful screening tools that can be done in the field. Hemoglobin (blood), bilirubin (urobilinogen), and protein should be monitored when using urine dipsticks**{**xe "ticks"**}** to screen for hemolysis**{**xe "hemolysis"**}**. It is important to differentiate the “blood” identified by urine dipstick as free hemoglobin**{**xe "hemoglobin"**}** or as red blood cells (hematuria). Hemoglobin in urine is present when red blood cells are destroyed in the hemolytic process, while intact red blood cells are present due to another pathologic process. Hematocrit testing, if performed, should be compared to baseline values. If facilities are available, other useful laboratory tests include blood and plasma hemoglobin levels, plasma haptoglobin level, reticulocyte**{**xe "reticulocyte"**}** count, lactose dehydrogenase level, and identification of Heinz bodies**{**xe "Heinz bodies"**}**.

Primaquine Use in G-6-PD{xe "G-6-PD"} Deficient Personnel

G-6-PD{xe "G-6-PD"} Screening and Documentation. All Navy and Marine Corps personnel are tested for G-6-PD deficiency**{**xe "G-6-PD deficiency"**}**. Testing is qualitative, determining the presence of G-6-PD deficiency, but not the type or severity. Members who test positive must be informed of the deficiency, the signs and symptoms**{**xe "symptoms"**}** they may experience and why they may occur, and the risks of taking oxidant**{**xe "oxidant"**}** medications. They also should be advised to consult with their unit corpsman**{**xe "corpsman"**}** or medical officer if malaria medications are administered to them.

The results of G-6-PD**{**xe "G-6-PD"**}** screening must be recorded in individual medical records, along with an entry documenting individual counseling of their deficiency. Unit medical records should be checked periodically to ensure that G-6-PD and other important information such as immunization status, blood type, etc., are recorded. If the information is not available, testing should be repeated. Use of spreadsheet software and microcomputers is an excellent medium for maintenance of unit medical readiness data.

Current Navy policy prohibits primaquine**{**xe "primaquine"**}** prophylaxis of G-6-PD**{**xe "G-6-PD"**}** deficient service members. If, in the future, treatment of G-6-PD deficient personnel is authorized, testing for the specific type of deficiency is recommended. Once tested, such personnel should be informed of the type and details of their deficiency. If test information is not available as to an individual's specific type of deficiency when terminal primaquine prophylaxis**{**xe "terminal primaquine prophylaxis"**}** is sanctioned, the dosage regimen should be given based on demographic data. These data support the assumptions that G-6-PD deficiency**{**xe "G-6-PD deficiency"**}** in Afro-American personnel is the G-6-PD^{A-}**{**xe "G-6-PD^{A-}"**}** type, and personnel of European descent have the G-6-PD^{Med}**{**xe "G-6-PD^{Med}"**}** type.

Terminal Primaquine Prophylaxis/Treatment. Primaquine remains the only drug available for treatment of the relapsing types of malaria. It can be used safely in G-6-PD**{**xe "G-6-PD"**}** deficient personnel under close medical supervision. Doses must be given less often and over a longer period of time to avoid a serious hemolytic reaction. Ensuring treatment compliance**{**xe "compliance"**}** will be challenging, as the primaquine**{**xe "primaquine"**}** regimen consists of 24 doses over 8 weeks in G-6-PD^{A-}**{**xe "G-6-PD^{A-}"**}** deficient personnel, and 60 doses over 30 weeks in G-6-PD^{Med}**{**xe "G-6-PD^{Med}"**}** deficient personnel (see table 5-4).

Monitoring. If, in the future, primaquine prophylaxis of G-6-PD**{**xe "G-6-PD"**}** deficient personnel is authorized, monitoring of deficient members is recommended. G-6-PD deficient personnel taking primaquine**{**xe "primaquine"**}** should be advised to seek medical evaluation if any symptoms**{**xe "symptoms"**}** or change in urine color occur. A simple urine dipstick and/or hematocrit**{**xe "hematocrit"**}** performed 3 to 4 days after the initial dose and checked periodically would identify severe cases of hemolysis**{**xe "lysis"**}{**xe "hemolysis"**}**.

Therapy of Drug Reaction. If hemolysis**{**xe "lysis"**}{**xe "hemolysis"**}** occurs, particularly in G-6-PD**{**xe "G-6-PD"**}**$^{A-}$ deficient persons, transfusion**{**xe "transfusion"**}** is usually not required. Hemolytic episodes are usually self-limited, even if drug administration is continued. This is not the case with the more severe G-6-PD^{Med}**{**xe "G-6-PD^{Med}"**}** deficiency and drug treatment should be stopped. If the rate of hemolysis is rapid, transfusion of whole blood or packed cells may be useful. Good urine flow should be maintained in patients with hemoglobin**{**xe "hemoglobin"**}**uria**{**xe "hemoglobinuria"**}** to prevent kidney damage. Folic acid**{**xe "Folic acid"**}** may be beneficial as in other patients with increased bone marrow**{**xe "bone marrow"**}** activity (an increase in bone marrow activity is caused by red blood cell formation).

Table 5-4. Primaquine Treatment Regimens

G-6-PD**{**xe "G-6-PD"**}** Normal	1 tablet* per day x 14 days
G-6-PD**{**xe "G-6-PD"**}**$^{A-}$ Deficiency	3 tablets per week for 8 weeks
G-6-PD**{**xe "G-6-PD"**}**^{Med} Deficiency	2 tablets per week for 30 weeks

*1 tablet consists of 26.3 mg primaquine phosphate, 15 mg primaquine base.

CHAPTER SIX

MILITARY MALARIA CONTROL RESPONSIBILITIES

Throughout history, diseases and non-battle injuries (DNBI**{**xe "DNBI"**}**) have resulted in more casualties to the Navy/Marine Corps team than combat. Historically, malaria has been the most formidable disease to prevent. The resources expended in its treatment, and the personnel hours lost due to malaria significantly decrease force readiness, especially in combat situations.

Prevention of DNBI**{**xe "DNBI"**}** is arguably the most important mission of military medicine. Success is achieved only when line commanders**{**xe "commanders"**}** are convinced that principles of preventive medicine are an essential element in force protection**{**xe "force protection"**}**. As Field Marshal Slim**{**xe "Slim"**}** maintained (see Introduction), the countermeasures**{**xe "countermeasures"**}** necessary to prevent malaria must be enforced by line commanders. Medical personnel must understand and practice the following three basic principles of Force Protection:

1) Threat assessment.
2) Countermeasure selection and implementation.
3) Reassessment of threats**{**xe "threats"**}** and countermeasures**{**xe "countermeasures"**}** guided by outcome measurement and analysis.**{**xe "lysis"**}**

After careful analysis of the deployment situation, appropriate countermeasure recommendations to commanders can be made. Then, with command support, countermeasure training and coordination can be instituted throughout the chain of command.

Medical Surveillance. Medical personnel must actively track unit illnesses and injuries. A single case of malaria may constitute an outbreak and signals a breakdown in preventive measures. Cases must be investigated and analyzed by unit medical personnel. Recommendations to correct the problem should be made immediately to the unit commander and followed by the institution of corrective measures.

This chapter will outline the application of the second and third principles to control malaria and other DNBIs by the chain of command. In general, malaria control is achieved through **Personal Protective Measures, Mosquito Control, {xe "Personal Protective Measures"}and Chemoprophylaxis{xe "Chemoprophylaxis"}.** In military situations, personal protective measures and chemoprophylaxis are simple, effective, and successful. Mosquito control may be less suitable in contingency settings but can be particularly useful in long-term or humanitarian operations. Consult the cognizant medical entomologist. To prevent malaria, strong line involvement and enforcement is essential. Medical personnel must work closely with line commanders and staff to implement measures to prevent malaria.

I. Line Commander Responsibilities

CINCs and JTF Commanders. These commanders**{**xe "commanders"**}** exercise authority over all assigned and attached forces in their area of operations. The decisions they make regarding medical guidance, assignment of medical tasks, and the joint medical concept of the operation are based on the advice received from CINC or Joint Task Force Surgeons. Prior to the operation, detailed medical guidance is published in Annex Q**{**xe "Annex Q"**}** of the operation order. The malaria risk is characterized, and required countermeasures**{**xe "countermeasures"**}** selected are included in that document. Annex Q is prepared by the CINC or JTF Surgeon staff, endorsed by the CINC or JTF commander.

This process reveals the impact that medical advice has on military operations. Line commanders**{**xe "commanders"**}** need their medical officers to supply accurate, clear advice to enable them to make decisions to keep their forces ready. Jonathan Letterman**{**xe "Letterman"**}**, the Medical Director for the Army of the Potomac during the Civil War, clearly defines that role in the following quote:

> “A corps of medical officers**{**xe "medical officers"**}** was not established solely for the purpose of attending the sick and wounded...the labors of medical officers covers a more extended field. The leading idea, which should be constantly kept in view, is to strengthen the hands of the Commanding General by keeping his army in the most vigorous health, thus rendering it, in

> the highest degree, efficient for enduring fatigue and for fighting. In this view, the duties of the corps are of vital importance to the success of an army, and commanders**{**xe "commanders"**}** seldom appreciate the full affect of their proper fulfillment."

Fleet and Force Commanders. These service commands are responsible for training and equipping units in their service, and maintaining their operational readiness. In prevention of DNBI**{**xe "DNBI"**}** (malaria control), their function is to provide all supplies necessary for implementation of countermeasures**{**xe "countermeasures"**}**, as well as to ensure that all personnel are trained to employ personal protective measures**{**xe "Personal Protective Measures"**}**. An example of this is First Marine Expeditionary Force's readiness policy requiring every Marine deploying as part of a Marine Expeditionary Unit**{**xe "Marine Expeditionary Unit"**}** (MEU) to have three sets of utility uniforms pretreated with permethrin.

Unit Commanding Officers{xe "Commanding Officers"}. The success of malaria control depends on the enforcement of personal protective measures**{**xe "personal protective measures"**}** by Commanding Officers (COs). Part of the responsibility of enforcing personal protective measures is ensuring that personnel are adequately trained and can employ them. Commanding Officers ultimately decide how chemoprophylaxis is administered, whether before a meal, by separate departments, or by employment of directly observed therapy (DOT**{**xe "DOT"**}**). Finally, they must provide a surveillance**{**xe "surveillance"**}** report as directed in the Navy reportable disease instruction**{**xe "Disease Alert Report"**}**. Accurate surveillance data and analysis**{**xe "lysis"**}** yield accurate reassessment of threats**{**xe "threats"**}** and countermeasures**{**xe "countermeasures"**}**.

II. Medical Department Responsibilities

DNBI**{**xe "DNBI"**}** and malaria control efforts depend on medical department personnel. They provide the expertise to: 1) perform medical surveillance**{**xe "surveillance"**}**; 2) educate, train, and supervise the employment of personal protective measures**{**xe "Personal Protective Measures"**}** and chemoprophylactic regimens**{**xe "Chemoprophylactic regimens"**}**; 3) diagnose and treat malaria, and other diseases and injuries; and 4) perform vector{xe "vector"} surveillance and control. Superior medical departments train their personnel to demonstrate and instruct other service members in the use of field hygiene and personal protective measures{xe "personal protective measures"}. In addition, they instruct corpsmen as well as medical officers to be familiar with the various chemoprophylaxis and treatment regimens, and the alternate treatments required for G-6-PD{xe "G-6-PD"} deficient individuals, pregnant service members, and persons who have had adverse reactions from anti-malarial drugs.

Medical personnel also must understand the threat in order to counter it. Essential sources of medical intelligence{xe "medical intelligence"} are the Armed Forces Medical Intelligence Center{xe "Armed Forces Medical Intelligence Center"}, and Navy Environmental and Preventive Medicine Units. Appendix 1 describes in detail these and other resources from which medical intelligence, threat assessments, and other information can be obtained.

Senior Medical Officers. Force and Fleet medical officers{xe "medical officers"} have two priorities:

1) Advising force commanders of DNBI{xe "DNBI"} threats, including malaria, and recommending appropriate countermeasures{xe "countermeasures"}.
2) Preparing medical department personnel to counter identified threats{xe "threats"}.

Advising force commanders{xe "commanders"} of the appropriate countermeasures{xe "countermeasures"} to employ requires medical commanders to characterize the DNBI{xe "DNBI"} threat. By combining medical intelligence{xe "medical intelligence"} on the area of operation with an understanding of mission operations, plans, and objectives, the risks to the force can be judged. Countermeasures are then recommended to reduce risks and ensure mission accomplishment. This is a synergistic process; countermeasures prevent illness and injury, increasing force readiness.

Part of the process of recommending countermeasures{xe "countermeasures"} is estimating the resources needed to employ them. This includes identifying and directing necessary training, along with identifying and procuring necessary supplies needed to implement recommended countermeasures. This information needs to be passed on as expeditiously as possible to the personnel responsible for action.

Unit Medical Officers. Unit medical officers, including Independent Duty Corpsmen, are essential in prevention of DNBI**{**xe "DNBI"**}** and malaria. They advise their CO on all medical matters. Enforcement of personal protective measures**{**xe "personal protective measures"**}** and method of administration of chemoprophylaxis depend on the advice given the CO by the Unit medical officer. By doing continuous surveillance**{**xe "surveillance"**}** of malaria incidence rates, other DNBI rates, and proper employment of personal protective measures, Unit medical officers**{**xe "medical officers"**}** can monitor the success of countermeasures**{**xe "countermeasures"**}**, and reassess the threats**{**xe "threats"**}**. Unit medical officers**{**xe "medical officers"**}** must also train and supervise the unit's corpsmen**{**xe "corpsman"**}** to ensure optimal medical care is delivered.

Flight Surgeons. Flight surgeon**{**xe "Flight surgeon"**}** responsibility is the same as that of Unit medical officers**{**xe "medical officers"**}**, with special attention to the effects of malarial chemoprophylaxis medications on flight personnel. Continuous or periodic monitoring of flight personnel on medication may be required to ensure safety. Flight personnel under treatment for malaria cannot fly until completion of treatment and evaluation by a flight surgeon. It is important to note that chemoprophylaxis with mefloquine**{**xe "mefloquine"**}** is not authorized for use in flight personnel.

Preventive Medicine Officer{xe "Preventive Medicine Officer"}s. The General Preventive Medicine Officer (PMO) serves as a source of information for all levels of the chain of command. Currently PMOs serve on all Marine Expeditionary Force staffs, and requests have been made to place PMOs on the staffs of the geographic CINCs. Knowledge of the general duties of all medical department personnel involved in malaria control (Medical Entomologists, Environmental Health Officers**{**xe "Environmental Health Officers"**}**, Preventive Medicine Technicians**{**xe "Preventive Medicine Technicians"**}**) allows them to consult and coordinate the provision of any needed training, supplies, or control measures with units in the field or in garrison. PMOs will usually deploy to the area of operation with a deployable lab, a resource able to aid in disease diagnosis and vector**{**xe "vector"**}** identification and surveillance**{**xe "surveillance"**}**.

One of their primary duties is to coordinate or assist in any illness or outbreak investigation. All surveillance**{**xe "surveillance"**}** data are monitored and analyzed by PMOs, forwarded to all unit and military treatment facility medical departments, and to commanders, along with pertinent recommendations. Current malaria prevalence, incidence, and any pattern of drug resistance**{**xe "drug resistance"**}** in an operational area are included in these reports. (Reports are not limited to malaria statistics).

Hospital Corpsmen. The training and support of hospital corpsmen is of paramount importance to force readiness and must be emphasized at every level in the chain of command. Hospital corpsmen are the first line of defense in malaria and DNBI**{**xe "DNBI"**}** prevention. Unit corpsmen**{**xe "corpsman"**}** perform most of the personal protective measures**{**xe "Personal Protective Measures"**}** training given to unit personnel. They live among them in the field and monitor the daily employment of countermeasures**{**xe "countermeasures"**}**. They supervise administration of chemoprophylaxis**{**xe "Chemoprophylaxis"**}**, and are often the first to initiate the diagnosis and care of any malaria cases.

Preventive Medicine Technicians{xe "Preventive Medicine Technicians"} (PMTs). These are specially trained hospital corpsman, and are directly involved in all aspects of malaria and DNBI**{**xe "DNBI"**}** control. They provide training in personal protective measures**{**xe "Personal Protective Measures"**}** to hospital corpsmen**{**xe "corpsman"**}** and unit personnel. They also perform field vector**{**xe "vector"**}** surveillance**{**xe "surveillance"**}**, collect epidemiological data, and will supervise or conduct field sanitation and vector control measures if needed. They serve along side PMOs, and are excellent resources for preventive medicine information in the field.

Laboratory Personnel{xe "Laboratory Personnel"}. Laboratory personnel assigned to deployable labs, fleet hospitals, Marine Medical Battalions, or any other unit that deploys to malaria endemic areas must be able to perform thick and thin peripheral blood smears**{**xe "blood smears"**}** and differentiate between the four plasmodia species that cause malaria in humans. They should be able to teach this diagnostic technique to interested medical personnel.

An important responsibility is sending prepared duplicate blood smear slides to the Navy Environmental and Preventive Medicine Unit assigned to monitor the area of operation. Such samples enable update of the area threat assessment and diagnosis confirmation. The slides should be both stained and unstained, and accompanied by identifying information and the clinical history of the case.

Environmental Health Officers (EHOs){xe "Environmental Health Officers"}. Environmental Health Officers are often assigned to deployable labs, preventive medicine units, Marine Force Service Support Groups, Marine Divisions, Marine Air Wings, and Joint Task Forces. They assist in collection of epidemiological and entomological data, and evaluate the environmental conditions that affect malaria control. **{**xe "vector"**}**They also have a primary role in the training and supervision of PMTs**{**xe "Preventive Medicine Technicians"**}**.

Medical Entomologists. Medical entomologists**{**xe "entomologists"**}** obtain the most current mosquito information and recommend applicable methods of vector**{**xe "vector"**}** control. They supervise adult and larval mosquito surveys, pesticide application, and train personnel in identification and control measures. They are assigned to Marine Force Service Support Groups to:

1) Recommend and ensure that personal protective measures**{**xe "Personal Protective Measures"**}** are employed.
2) Select optimum locations for bivouacs and base camps.
3) Recommend safe times for training and field exercises.

Preventive Medicine teams can deploy EHOs, Medical Entomologists, Epidemiologists, Laboratory Technicians, and Industrial Health Officers. These teams can provide varied and useful services to deployed forces.

III. Administrative Responsibilities{xe "Administrative Responsibilities"}

Medical Records. Medical records of Navy/Marine Corps service members are required to include:

G-6-PD**{**xe "G-6-PD"**}** Screening Results: A result, either deficient or normal, must be entered on a Standard Form 600 (SF

600). If deficient, this information must be highlighted on the Problem Summary List (NAVMED 6150/20). In addition, the "Sensitivities" block in the "Alert box" on the cover of their medical treatment record must be checked. Other health care beneficiaries, including civilian technical experts, should be offered this screening test if traveling to endemic areas.

Chemoprophylaxis{xe "Chemoprophylaxis"}. The date prophylaxis began and ended, drug type, and dosage should be entered on a SF 600. If terminal primaquine prophylaxis is given, entry of the same information is required.

All personnel required to take chemoprophylaxis must be informed of the reason for taking the medication, common side effects{xe "side effects"} of the drug, and when to take the medication. It should also be communicated clearly that taking prophylactic medication does not guarantee malaria prevention.

Service members should be advised to seek medical evaluation if they suffer drug side effects{xe "side effects"} or have symptoms{xe "symptoms"} of malaria. This information is usually presented at the unit level. When this information is presented, personal protective measures may be demonstrated,{xe "Personal Protective Measures"} and DEET{xe "DEET"}, permethrin, netting, and other necessary items may be issued.

Medical Event Reports{xe "Disease Alert Report"}. Medical Event Reports (MERs) are required, by instruction, on any member diagnosed with malaria. The report should be generated using the Naval Disease Reporting System software package which can be downloaded from the NEHC homepage (http://www-nehc.med.navy.mil/main.htm). If the software is unavailable, a message can be generated. The MERs are then sent to the Navy Environmental and Preventive Medicine Unit assigned to monitor the area of operation. The message should also "info" all military treatment facilities in the area, the nearest Navy Disease Vector Ecology and Control Center, and the Navy Environmental Health Center (NEHC){xe "Naval Health Environmental Center (NEHC)"}. The information is important to monitor and update both the malaria threat and presence of drug-resistant malaria in the area of operation.

The following is the minimum information included in the MER:

1) Patient travel history 3 months prior to diagnosis.

2) Type and duration of chemoprophylaxis or treatment medications taken, if applicable.
3) Interpretation (diagnosis) of blood smears**{**xe "blood smears"**}** performed on the patient.
4) Date that blood smears**{**xe "blood smears"**}** were sent to a Navy Environmental and Preventive Medicine Unit for confirmation.

Medical Treatment Facilities. The staff of Military Treatment Facilities that may receive malaria patients should be familiarized with treatment. Commanders should arrange training from available sources such as the Internal Medicine or Infectious Disease department, or the nearest Navy Environmental and Preventive Medicine Unit. A general in-service training session that includes the following topics is recommended:

1) Diagnosis, treatment and monitoring.
2) Common complications of severe falciparum malaria**{**xe "falciparum malaria"**}** infections.
3) The physiology of terminal primaquine**{**xe "primaquine"**}** prophylaxis**{**xe "terminal primaquine prophylaxis"**}** and G-6-PD**{**xe "G-6-PD"**}** deficiency.
4) Monitoring blood parasite concentration with peripheral blood smears**{**xe "blood smears"**}** for treatment response.

Another important aspect in the care of malaria patients is to send a timed and dated peripheral blood smear upon transfer, so the receiving facility can compare it with their initial blood smear, and confirm the diagnosis.

Medical Board{xe "Medical Board"} Evaluations. Service members who develop severe malaria complicated**{**xe "complicated"**}** by a severe hemolytic reaction characterized by hemoglobinuria together with the diagnosis of “blackwater fever**{**xe "blackwater fever"**}{**xe "fever"**}**” and/or renal failure are required to be evaluated for fitness for further duty by a Medical Board. A Medical Board is also required on personnel who develop a similar severe hemolytic reaction as a result of taking malaria chemoprophylactic**{**xe "chemoprophylactic"**}** drugs. The complication of cerebral malaria does not require evaluation by a Medical Board unless permanent neurologic**{**xe "neurologic"**}** disability has occurred.

Blood Donor Programs. Blood donation programs are subject to the guidance of BUMED P-5120, "Standards for Blood Bank**{**xe "Blood Bank"**}** and Transfusion Services." The directive is applicable to both military and civilian blood banks and requires that individuals treated for malaria wait three years from the date of completion of therapy to donate blood. Individuals who took malaria chemoprophylactic**{**xe "chemoprophylactic"**}** drugs while in endemic areas must also wait three years from completion of chemoprophylaxis to donate blood. The reason for the waiting period is to prevent donated blood from being contaminated by malaria parasites**{**xe "parasites"**}**, not drugs.

Individuals who visited a malaria-endemic area without taking chemoprophylactic**{**xe "chemoprophylactic"**}** drugs and remained asymptomatic are required to wait six months before being eligible to donate blood. Persons placed on chemoprophylactic therapy in readiness, but who did not travel into a malaria endemic area, do not have a required waiting period to donate blood.

APPENDIX ONE

INFORMATION & INTELLIGENCE SOURCES; CONSULTANTS

Introduction. Resources listed in this appendix for malaria and DNBI prevention are divided into two general sections, Medical Information and Medical Intelligence. Directions on how to acquire information, references, or software are included along with points of contact and Internet/E-mail addresses. Some of the Medical Intelligence products listed are classified and require a security clearance for access.

I. MEDICAL INFORMATION

1. Military Sources

A. General Policy and Guidance

Bureau of Medicine and Surgery, Division of Public Health
(MED-33) 2300 E Street NW, Washington, DC 20372-5300
Phone: (202) 762-3495; DSN: 294-3495; FAX: (202) 762-3490

Navy Environmental Health Center, Preventive Medicine Directorate
620 John Paul Jones Circle, Suite 1100
Portsmouth, Virginia, 23708-
Phone: (757) 953-0700; DSN: 377-0700
FAX: (757) 953-0685
E-mail: epi@nehc.med.navy.mil.

B. Navy Environmental & Preventive Medicine Units

(NEPMUs), four world-wide:

Navy Environmental & Preventive Medicine Unit 2
Epidemiology Department,
1887 Powhatan St
Norfolk, VA 23511-3394
Phone: (757) 444-7671; DSN 564-7671
Fax: (757) 444-1191; DSN 564-1191
E-mail: admin-nepmu2-nor@mar.med.navy.mil

Navy Environmental & Preventive Medicine Unit 5
Epidemiology Department,
3235 Albacore Alley
San Diego, CA 92136-5199
Phone: (619) 556-7070; DSN 526-7070
Fax: (619) 556-7071; DSN 526-7071;
E-mail: nepmu5@nepmu5.med.navy.mil

Navy Environmental & Preventive Medicine Unit 6
Epidemiology Department,
1215 North Road
Pearl Harbor, HI 96860
Phone: (808) 473-0555; DSN 315-0555
Fax: (808) 473-2754; DSN 315-2754
E-mail: nepmu6@nepmu6.med.navy.mil

NEPMUs Publications and Services available:

* Pre-deployment medical briefings.
* Courses on malaria, hepatitis, field sanitation, etc.
* Consultation with representative of Epidemiology Department.
* PPM – Entomologist.

C. Navy Disease Vector Ecology and Control Center

Navy Entomology Center of Excellence (NECE)
Naval Air Station, Jacksonville,
P.O. Box 43, Bldg 937
Jacksonville, FL 32212-0043
Commercial: (904) 542-2424 or CDO (904) 229-9988
DSN: 942-2424
E-mail: mei@nece.med.navy.mil
NECE Publications and services available:

* "VECTRAPS," or vector reports, descriptions of disease vectors and control measures worldwide.
* Information on pesticide usage and resistance and personal protective measures.

D. Navy Infectious Diseases Consultants

National Naval Medical Center, Infectious Diseases Division
8901 Wisconsin Ave, Bethesda, MD 20889-5600
DSN: 295-4237, Phone: (301) 295-4237, Fax: -2831

Naval Medical Center, Infectious Diseases Division
620 John Paul Jones Circle, Portsmouth, VA 23708
Phone: (757) 953-5179, Fax: -7674

Naval Medical Center, Infectious Diseases Division,
34800 Bob Wilson Drive Suite 201, San Diego, CA 92134-1201
DSN: 522-7475, Phone: (619) 532-7475, Fax: -7478/8798

E. Naval Medical Research Units

U.S. Naval Medical Research Institute No. 3
PSC 452, Box 5000 FPO AE 09835-0007
(Cairo, Egypt)
Phone: ask overseas operator for Cairo, 820727

U.S. Naval Medical Research Institute No. 2
Box 3, APO AP 96520 (Jakarta, Indonesia)
Phone: ask overseas operator for Jakarta, 414-507
co@narmu2.med.navy.mil

U.S. Naval Medical Research Institute Detachment
American embassy Unit 3800, APO AA 34031-0008 (Lima, Peru)
Phone: ask overseas operator for Lima, 52-1560, 9662
Within U.S.: 011-51-14-52-1562, 9662

F. Preventive Medicine Recommendations for Specific Operations

Available from the JTF or CINC Surgeon's office, Fleet or Force Surgeon's office, or the Navy Environmental and Preventive Medicine Unit assigned to the area of operation. If involved in the planning phase for a regularly recurring exercise, contact the cognizant NEPMU to obtain recommendations for specific operation.

G. Armed Forces Medical Intelligence Center. See Medical Intelligence section for description of AFMIC products including the Medical Enviro nmental Disease Intelligence and Countermeasures CD-ROM ("MEDIC").

2. Internet Homepages and Other Computer Related Sources:

NEHC Web page: http://www-nehc.med.navy.mil/
CDC: http://www.cdc.gov/travel/

American Society of Tropical Medicine and Hygiene (ASTMH): http://www.ASTMH.org/

PROMED: Intended to be an increasingly sensitive aid for detection of outbreaks worldwide: http://www.fas.org/promed/

National Library of Medicine: http://www.ncbi.nlm.nih.gov/PubMed

3. Textbooks and Publications

A) Medical Products for Supporting Military Readiness: Vaccines & Drugs ("The GO Book"), 2005, U.S. Army Medical Research & Materiel Command: Secretary of the General Staff, USA-MC, Fort Detrick, Maryland, (301) 619-7549, DSN: 343-7549

B) Pocket Book of Infectious Disease Therapy, Bartlett JG, Williams & Wilkins, 2004

C) Control of Communicable Diseases Manual, Chin, ed., American Public Health Association, 17th Edition, 2000

D) Hunter's Tropical Medicine, Strickland, ed., Saunders, 8th Edition, 2004

E) Principles and Practice of Infectious Diseases, Mandell et. al., Churchill Livingstone, 6th Edition, 2004

F) Manson's Tropical Diseases, Cook, ed., Saunders, 21st Edition, 2003

G) Wilderness Medicine, Auerbach, 4tn Edition, Mosby, 2001

H) The Sanford Guide to Antimicrobial Therapy, Sanford, Antimicrobial Therapy, Inc., yearly

II. MEDICAL INTELLIGENCE

A. AFMIC. The primary source of medical intelligence products is the Armed Forces Medical Intelligence Center (AFMIC), a division of the Defense Intelligence Agency, located at Fort Detrick, Maryland. Described are the medical intelligence products AFMIC provides:

- ***Medical Environmental Disease Intelligence and Countermeasures CD-ROM ("MEDIC").*** "MEDIC" provides worldwide disease and environmental health risks hyperlinked to Joint Service approved country-specific countermeasure recommendations and other pertinent military medical references. Also included in "MEDIC" are military and civilian health care delivery capabilities, operational information, arthropod vector information, an expanded poisonous snake section on some countries, an expanded section on poisonous and injurious plants, and significant portions of Control of Communicable Diseases Manual (included by permission from the American Public Health Association).

- ***Infectious Disease Risk Assessment, (IDRA) and Environmental Health Risk Assessment, (EHRA).*** Infectious Disease and Environmental Health Risk Assessments are unclassified risk assessments on individual countries without countermeasure recommendations. They are available in three media: by message, via the AFMIC bulletin board system (BBS), and on the "MEDIC" CD-ROM. The most current assessments are available through the BBS, and each month some countries are updated through a cyclic update process. Assessments are oriented for and available only to operational U.S. military personnel. IDRAs and EHRAs were formerly known as the Disease and Environmental Alert Reports (DEARs).

- **Disease Occurrence Worldwide (DOWW).** Classified and unclassified supplements to IDRAs and EHRAs. The DOWW is a monthly compilation of reports on disease outbreaks which serve as late-breaking updates to the IDRA. DOWW is published as an unclassified message with a classified supplement if necessary.

- **AFMIC Wire.** A bi-weekly message serving as an update of infectious disease and environmental risks worldwide. AFMIC's version of Headline News, it is a current intelligence document, which presents analysis of new information of potential tactical interest. In addition to the scheduled wire, "Special Wires" may be produced periodically on topics of interest to deploying units.

- **Medical Capability Studies (MEDCAP).** Information on foreign country assets and medical infrastructure. It evaluates the ability of a country to support its armed forces in peace and war, and the suitability of facilities in the country to support U.S. operations. These studies are produced on countries of tactical significance, usually those with power projection capability.

- **Health Services Assessment (HSA).** Health Service Assessments are comprehensive evaluations of a country's health infrastructure, and may be considered a short form of the MEDCAP. HSA evaluates a country in less detail, and is designed to provide an overview of a country's civilian and military/health care systems to support operational planning.

- **Urban Area Medical Capabilities Study.** The Urban Study was recently redesigned to meet the needs of United States Special Operations Command (USSOCOM). It includes a map of the urban area, general health information, and locations, descriptions, and photographs of key medical treatment facilities.

- **AFMIC Bulletin Board System (BBS).** The BBS is an automated on-line system for the dissemination of unclassified medical intelligence products. This system is designed to provide timely, user friendly access to finished AFMIC products. All textual components of the "MEDIC" are available on the BBS. The BBS System Operator may be reached at (301) 619-2686 or DSN 343-2686. The BBS may be accessed by dialing: (301) 619-3625 or 2000 or DSN 343-3625 or 2000.

- **Request for Information (RFIs).** An RFI is a way to ask AFMIC for answers to questions not found in published studies, usually requiring AFMIC to assemble specific information. The RFI system is designed to respond to requests for specific information on countries or areas worldwide, 24 hours per day, 7 days per week. RFIs should be directed to AFMIC through unit intelligence sections by way of the Community On-line Intelligence System for End-Users and Managers (COLISEUM) or by contacting AFMIC Operations at their 24 hour contact number, (301) 619-7574 or DSN 343-7574. Their phones are secure via STU-III through the TS-SCI level.

Procedures for obtaining the AFMIC wire, the DOWW, the IDRA, and the EHRA. AFMIC produces the AFMICWire under Address Indicator Group (AIG) 6623 for CONUS plus Alaska & Hawaii, and under AIG 12630 for OCONUS not including Alaska & Hawaii. The DOWW, IDRA, and EHRA are transmitted under AIG 12243 for CONUS plus Alaska & Hawaii and AIG 11829 for OCONUS not including Alaska & Hawaii. To be added to distribution for any of the AFMIC message products, please send name, organization, mailing address, routing indicator, plain language address, DSN and commercial telephone numbers, and a brief justification to: **AFMIC, ATTN: MA-1, Frederick, MD 21702-5004** or **DIRAFMIC FT DETRICK MD//MA-1.** AFMIC can be reached at (301) 619-3837 or DSN 343-3837 for information.

Procedures for receiving hardcopy AFMIC productsand other intelligence products. Hardcopy publications produced by AFMIC are disseminated by the Defense Intelligence Agency through the Defense Intelligence Dissemination System (DIDS). An organization receives products based on requirements registered by the organization's Intelligence Office (IN) in a Statement of Intelligence Interest (SII). Largely, the SII is maintained by the IN or Security Office. Once a document is published by AFMIC, it is automatically mailed to the organization's IN or Security Office for distribution within the organization. Once an organization has an SII registered distribution for AFMIC hardcopy products, but is not receiving some publications, its IN can modify the SII by adding the desired Intelligence Function Codes (IFCs) and country codes for those publications. If an organization does not have an SII registered with DIA, follow the procedures as outlined in DIA Regulation No. 59-1, dated 12 June 1995, "DoD Intelligence Dissemination Program."

B. CIA World Factbook. The CIA World Factbook is an unclassified publication that provides general political and economic data on all countries of the world. It is updated annually and available as a hardcopy publication or through the Internet CIA home page. There is also a classified supplement that provides information on military, security, and intelligence forces worldwide.

C. Military Capabilities Study (MCS). The MCS is designed to serve as a ready reference document for national, operational, and tactical planners and consumers. Each study presents a compilation of intelligence on forces and resources that contribute to the military security of each country, and on the political and economic factors affecting the country's military capabilities.

D. Intelink. This is the classified Internet system, and functions in the same manner as NetscapeR or Internet ExchangeR, and documents can be easily downloaded and printed. Within the intelligence community it is rapidly becoming the preferred method of dissemination of information. The ultimate goal is to have INTELINK available to all battalion level and higher intelligence sections. National level intelligence organizations, including each of the Unified Command Joint Intelligence Centers and AFMIC have home pages on INTELINK. All AFMIC products, and most recent intelligence publications, may be found there.

E. Internet Sites. There are a number of unclassified sources available. The Central Intelligence Agency has a home page where users may access the World Factbook. The State Department home page contains State Department country fact sheets, embassy information, and travel advisories. Other commercial databases are available which address travel medicine. Take time to find and bookmark useful resources.

F. Joint Worldwide Intelligence Communication System (JWICS). This secure telecommunications system links sites throughout the intelligence and operations communities, and allows secure teleconferencing. In support of time sensitive or complex requirements, it may be possible to arrange a teleconference between medical planners and AFMIC analysts. To arrange a conference, contact the unit intelligence officer to determine if a JWICS site exists and is available, then work with the local site manager and AFMIC Operations on specifics.

APPENDIX TWO

MOSQUITO VECTORS AND IDENTIFICATION

Introduction. Human malaria is transmitted only by mosquitoes belonging to the genus *Anopheles*{xe "Anopheles"}. Currently 422 species of *Anopheles* mosquitoes have been identified throughout the world, 70 of which transmit malaria. Of the 70 species that transmit malaria, only 40 are of major significance.

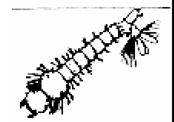
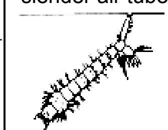
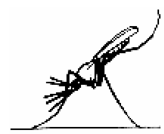
Anopheles{xe "Anopheles"} mosquitoes are most frequently found in tropical regions, but are also found in temperate climates and in the Arctic during summer (see Appendix Table 2.1). As a rule, they are not found at elevations above 2000-2500 meters (6500-8200 ft).

Mosquito Life Cycle. Development time from egg to adult depends on species and temperature, ranging from 7 days at an average temperature of 31^{O}C, to 20 days at an average temperature of 20^{O}C. Life span is species specific, and is affected by temperature, humidity{xe "humidity"}, and presence of natural enemies. When the temperature is over 35^{O}C or the humidity is less than 50%, longevity is greatly reduced. Average life span of a female mosquito under favorable conditions is 10-14 days, with some able to live as long as 3-4 weeks.

Eggs. Females lay their first batch of eggs{xe "eggs"} 3-6 days after they emerge from the pupal stage. Anopheline eggs are laid singly on the type of water preferred by the particular species. They are blackish, 0.5 mm long, and have tiny air-filled floats that let them drift on the water surface. Eggs hatch 2-3 days after being laid.

Larvae. *Anopheles*{xe "Anopheles"} mosquito larvae{xe "larvae"} have unique characteristics. They lack the prominent air tube or siphon found in other mosquito species larvae. They float horizontally on the surface of the water, and turn their heads 180^{O} to feed. They move in sudden jerks, and sink below the surface if disturbed. After molting three times, they develop into pupae{xe "pupae"}.

Appendix Figure 2-1: Differences between *Anopheles*{xe "Anopheles"}, *Aedes*, and *Culex* mosquitoes at various stages of development.

	Anophelines	**Culicines**	
	Anopheles{xe "Anopheles"}	*Aedes*	*Culex*
Eggs	 with floats, laid singly on water	 no floats, laid singly on dry/ damp surface	 no floats, laid in rafts on water
Larva	no air tube  rest parallel to water surface, head rotated 180° when feeding	one tuft on short stout air tube  rest at angle to surface, head not rotated	several tufts on slender air tube  rest at angle to surface, head not rotated
Adult	 resting position	 resting position	 resting position

Pupae. Mosquito pupae are comma-shaped. There are two separate body regions: the cephalothorax (the head and thorax combined), and the abdomen (tail section). They do not feed, but come to the water surface to breathe through short paired respiratory trumpets. The pupal stage lasts 2-4 days, after which an adult mosquito emerges.

Adults. In order for eggs to develop, female mosquitoes require at least one, sometimes two blood meals. Male mosquitoes do not take a blood meal. Adult mosquitoes typically fly and bite within a two-three kilometer radius of breeding areas but strong winds have carried them as far as 30km. Peak biting time is between 1900-2100 hours for some species while other species such as *A. gambiae* are late feeders, biting between 2400-0300 hours. Control methods should be targeted to coincide with peak biting times when possible. The resting posture of adult mosquitoes differs by species (see Appendix Figure 2-1).

Appendix Table 2-1. *Anopheles*{xe "Anopheles"} species of importance in transmission{xe "transmission"} of human malaria.

Region	Description	Major Vectors
North America	From Great Lakes to southern Mexico	*A. freeborni* *A. quadrimaculatus* *A. hermsi*
Central America	Southern Mexico, Caribbean islands, fringe of South American coast	*A. albimanus* *A. argyritarsis* *A. pseudopunctipennis* *A. aquasalis* *A. darlingi*
South America	South American continent	*A. pseudopunctipennis* *A. punctimacula* *A. albimanus* *A. albitaris* *A. aquasalis* *A. darlingi* *A. nuneztovari*

North Eurasia	Europe and west Asia, Arctic south excluding Mediterranean coast	*A. atroparvus*

Appendix Table 2-1, continued. *Anopheles*{xe "Anopheles"} species of importance in transmission{xe "transmission"} of human malaria.

Region	Description	Major Vectors
Mediterranean	South coast of Europe, North coast of Africa	*A. atroparvus* *A. labranchiae* *A. sacharovi* *A. superpictus*
Africa-Arabia	Saharan Africa, North Arabian peninsula	*A. pharoensis* *A. sergentii* *A. labranchiae* *A. multicolor* *A. stephensi*
Sub-Saharan Africa	South Arabian peninsula, Ethiopia, Somalia**{**xe "Somalia"**}**, tropical Africa, Madagascar	*A. funestus* *A. arabiensis* *A. gambiae* *A. melas* *A. merus*
India-Iran	Northwest of the Persian Gulf, Indian subcontinent	*A. culicifacies* *A. fluviatilis* *A. pulcherrimus* *A. sacharovi*
Indochina	Indochinese peninsula	*A. dirus* *A. maculatus* *A. fluviatilis* *A. minimus* *A. sundaicus*
Malaysia	Indonesia, Malaysian peninsula, Philippines, Timor	*A. campestris* *A. donaldi* *A. letifer* *A. aconitus* *A. balabacensis* *A. dirus* *A. flavirostris* *A. leucosphyrus* *A. maculatus* *A. sundaicus* *A. barbirostris*

		A. punctulatus

Appendix Table 2-1, continued. *Anopheles*{xe "Anopheles"} species of importance in transmission{xe "transmission"} of human malaria.

Region	Description	Major Vectors
China	Korea, Taiwan, Japan, and the Coast of mainland China	*A. anthropophagus* *A. sinensis*
Australia-Pacific	Northern Australia, Papua New Guinea, islands west of 175^0 east latitude	*A. farauti type 1* *A. farauti type 2* *A. koliensis* *A. punctulatus*

APPENDIX THREE

LABORATORY DIAGNOSTIC TECHNIQUES

Introduction. Despite development of serological techniques, conclusive diagnosis of malaria continues to be made through microscopic examination of peripheral blood smears**{**xe "blood smears"**}**. This is the only method that can differentiate among the four species of plasmodia that cause human malaria.

Thick{xe "Thick"} Smears. Red blood cells are hemolyzed in thick smears**{**xe "thick smears"**}**; leukocytes and any malaria parasites**{**xe "parasites"**}** present are the detectable elements. The hemolysis**{**xe "lysis"**}{**xe "hemolysis"**}** and slow drying that occur in thick smear preparation cause distortion of plasmodia morphology, making differentiation of species difficult. Thick smears are used to detect infection, and estimate parasite concentration.

Thin Smears. Thin smears are fixed with methanol, preventing hemolysis**{**xe "lysis"**}{**xe "hemolysis"**}**. Red blood cells are intact, and any Plasmodia present are less likely to be distorted, and remain within erythrocytes**{**xe "erythrocytes"**}**. Identification of specific species is usually done using thin smears**{**xe "thin smears"**}** after detection of parasites**{**xe "parasites"**}** on the thick smears**{**xe "thick smears"**}**.

Navy Environmental & Preventive Medicine Units offer training classes on preparation of thick and thin smears**{**xe "thin smears"**}** and microscopic examination for diagnosis of malaria. This appendix summarizes thick and thin blood smear preparation for field reference.

Drawing Blood

- Anytime malaria is suspected.
- Repeat if smears are negative.
- Maximum frequency: once per hour.

Obtaining Blood

- Fresh blood is required from either fingerstick or venous phlebotomy

- Follow universal precautions (gloves, hand washing, proper handling and disposal of sharp instruments and other materials contaminated with blood)

- Fingerstick Method:
  1) Clean end of finger with disinfectant solution.
  2) Wipe fingertip with sterile material (remove remaining disinfectant that may interfere with diagnostic process).
  3) Pierce fingertip with sterile lancet.
  4) Allow blood to flow freely, do not squeeze finger.

- For venous blood obtained in a vacutainer, use a pipette to apply a drop of blood to slide(s) for thick and thin smears**{**xe "thin smears"**}**

Slide Preparation (see Appendix Figure 3-1)

Thick{xe "Thick"} Smear

5) Wipe away first drop of blood at fingerstick site. Then touch a clean microscope slide near one end to the next blood drop that forms.
6) Spread drop of blood with corner of another slide to make an area about 1 cm in diameter.

- This is the thick smear. Correct thickness is attained when newsprint is barely legible through the smear.

Thin Smear

7) Touch a new drop of blood (smaller than the first) with the edge of a clean slide.
8) Bring the edge of the slide with the new drop of blood to the surface of the first slide. Place it at the far end, and wait until the blood spreads along the whole edge.
9) Holding the slide at an angle of 45^0, push it forward with a rapid, gentle movement.

- For preparation of separate slides for thick and thin smears**{**xe "thin smears"**}**, use a second slide in step 4.
- Dry the smears. Air dry, allowing 10 minutes for the thin smear and 30 minutes for the thick smear.
- Mark slide with patient identification and date and time of collection. This can be done using a pencil on the thin smear after it has dried.

Fixing Thin Smears

- After drying, only thin smears**{**xe "thin smears"**}** are fixed. Fixing is done using methanol in one of two ways:

10) Dip thin smear into methanol for 5 seconds.

11) Dab thin smear with methanol-soaked cotton ball.

- Do not fix the thick smear. Even exposure**{**xe "exposure"**}** of the thick smear to methanol fumes will prevent hemolysis**{**xe "lysis"**}{**xe "hemolysis"**}** and make it unreadable. If using the one slide method, prevent exposure of the thick smear to methanol or methanol fumes by carefully dipping or dabbing the slide, and gently blowing the fumes away from the thick smear area.

Staining Slides

Giemsa**{**xe "Giemsa"**}** stain is available in the military supply system, and this staining method is presented. Preparation of Giemsa staining solution is done with buffered water and Giemsa concentrate. Do not shake the Giemsa concentrate as this will cause suspension of particulate matter in the stain resulting in artifacts on final slides. Formation of artifacts renders slides difficult to interpret. Do not confuse “Giemsa-like” stain with true Giemsa. “Giemsa-like stain” should not be used.

Preparation of Giemsa{xe "Giemsa"} staining solution

1) Prepare buffered water solution, pH 7.2:
   - Mix capful of buffering salts into 1000 ml of distilled water.
   - Check pH. Titrate with sodium hydroxide (NaOH) solution until pH is 7.2.
     (pH is critical. Incorrect pH will inhibit the appearance of Shuffner’s dots)

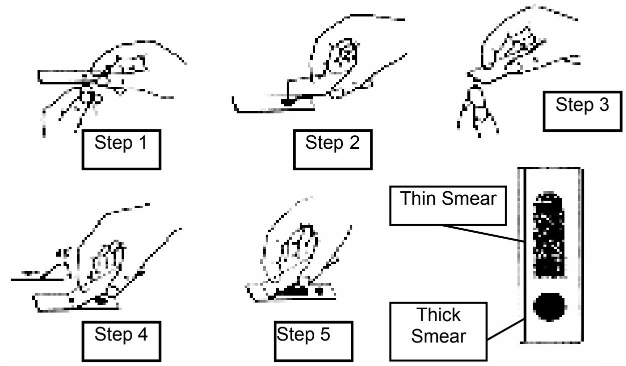
2) Prepare Giemsa**{**xe "Giemsa"**}** staining solution by mixing:
   - 1 part unshaken Giemsa**{**xe "Giemsa"**}** stain concentrate.
   - 9 parts buffered water.

Slide Staining with prepared Giemsa{xe "Giemsa"} solution

- Place slides flat in a staining rack or other suitable surface.

- Cover with 1-2 ml of Giemsa**{**xe "Giemsa"**}** solution. Commercially available Giemsa stain may be used straight as long as it is properly pH'd.
- Let stand for 10 minutes.
- Gently rinse by "floating" excess stain off slide with buffered water; be careful not to wash the blood smear away.

Appendix Figure 3-1. Thick{xe "Thick"} and Thin Blood Smear Preparation.



- Rinse until no more stain is seen in solution.
- Dry smear side down, making sure that smear does not touch the slide rack or other surface used for drying.

Slide Preparation Pointers

- Clean microscope slides before use. Blood will spread cleanly, stain will adhere properly, and no artifacts will impede diagnosis.
- Do not fix slides with a heat source. If overexposed to heat, parasites**{**xe "parasites"**}** are destroyed, and cannot be seen microscopically.
- Parasites stain best at pH of 7.2. Check stain pH for optimal staining.
- Filter the Giemsa**{**xe "Giemsa"**}** stain. Removal of particles and residue will make slides much easier to interpret.

Microscopic Examination of Thick{xe "Thick"} and Thin Blood Smears

Training and experience are essential for accurate reading. Slides should be examined for at least 20 minutes before being judged to be free of malaria parasites**{**xe "parasites"**}**. Parasites are often not readily apparent, and quick visual scans are insufficient for diagnostic purposes. Appendix Table 3-1 shows selected microscopic characteristics of human malaria species.

Part of the diagnostic process is estimation of the extent of infection. Two methods are presented to estimate the parasite concentration or parasitemia**{**xe "parasitemia"**}**. One requires the use of thick smears**{**xe "thick smears"**}**, and is called the Absolute Numbers Method**{**xe "Absolute Numbers Method"**}**. The other requires the use of thin smears**{**xe "thin smears"**}**, and is called the Percent Method.

Absolute Numbers Method{xe "Absolute Numbers Method"} (thick smear)

This method is based on the assumption that 8000 leukocytes (white blood cells) are found in a ml of blood. By counting the number of parasites**{**xe "parasites"**}** seen in same visual fields needed to count either 200 or 500 leukocytes, the parasite concentration per ml can be estimated. Perform the following steps to estimate parasite concentration:

1) Examine the equivalent of 0.25 ml of blood (100 visual fields using a 7X ocular lens and a 100X oil-immersion objective lens) to determine if an infection exists.
2) In a systematic manner of scanning visual fields, identify 200 leukocytes, while counting the number of malarial parasites**{**xe "parasites"**}** in those same visual fields.
3) If after 200 leukocytes have been identified and less than 9 malarial parasites**{**xe "parasites"**}** have been counted, continue the process until 500 leukocytes have been identified.
4) If after 200 leukocytes have been identified and 10 or more parasites**{**xe "parasites"**}** have been counted, record the number of parasites counted per 200 leukocytes.

Appendix Table 3-1. Selected microscopic characteristics

Species	Stages found in circulating Blood	Appearance of Red Blood Cells

		Size	Stippling
Plasmodium{ xe "Plasmodium "} falciparum	Trophozoites Gametocytes	Normal	Maurer's dots or clefts infrequently seen
Plasmodium{xe "Plasmodium" } vivax	All: Schizonts Trophozoites Gametocytes	Enlarged, Maximum size may be 1.5-2 times normal	Schuffner's dots may be present
Plasmodium{xe "Plasmodium" } ovale	All: Schizonts Trophozoites Gametocytes	Enlarged, Maximum size may be 1.25-1.5 times normal	Schuffner's dots may be present
Plasmodium{xe "Plasmodium" } malariae	All: Schizonts Trophozoites Gametocytes	Normal	Ziemann's dots rarely seen

5) Once 500 leukocytes have been identified, record the number of parasites{xe "parasites"} counted.
6) Convert the parasite count per leukocytes identified into parasite concentration per ml with one of the following formulas:

<u>Number of parasites{xe "parasites"} x 8000</u> = parasites per ml
Number of leukocytes counted

or

if 200 leukocytes were counted:
Number of parasites{xe "parasites"} counted x 40 = parasites per ml

or

if 500 leukocytes were counted:
Number of parasites{xe "parasites"} counted x 16 = parasites per ml

Appendix Table 3-1. Selected microscopic characteristics (con't)

Appearance of Parasites {xe "merozoites"}		
Cytoplasm	**Pigment**	**No. of merozoites**

Double dots in rings common, rings small and delicate	Black Coarse and conspicuous in gametocytes	6-32 Avg. = 10-24
Ameboid trophs light blue, has irregular “spread out” appearance in troph stage	Golden-brown, inconspicuous	12-24 Avg. = 16
Rounded, compact trophs, dark to medium blue, usually dense; Chromatin is large	Dark brown, conspicuous	6-14 Avg. = 8
Rounded, compact trophs, dark blue with dense cytoplasm; band form trophs occasionally seen	Dark brown, coarse, conspicuous	6-12 Avg. = 8 “Rosette” occasionally seen

7) All parasite species and forms are tabulated together. This includes both sexual (gametocytes) and asexual (trophozoites**{**xe "trophozoites"**}**, merozoites**{**xe "merozoites"**}**) forms.

Percent Method (thin smear){xe "Percent Method (thin smear)"}.

This method estimates the percentage of red blood cells infected with malarial parasites**{**xe "parasites"**}**. It is based on the number of red blood cells found parasitized on a thin smear, and is executed in the following manner:

1) Locate an area in the thin smear where red blood cells are close together but not touching.
2) Scan in a systematic method (use the microscope stage control to scan one “row” at a time).
3) Count the total number of red blood cells in each row. At the same time, tabulate the number of red blood cells parasitized.
4) Count a total of 300-500 red blood cells.
5) Divide the number parasitized by the total number counted and multiply the result by 100 to obtain a percentage estimate of red blood cells parasitized:

<u>Red Blood Cells parasitized X 100</u> = Percent of Red Blood

Total Red Blood Cells counted Cells parasitized

6) If occasional parasites**{**xe "parasites"**}** are seen when scanning the smear, but none are identified during the process of counting 300-500 red blood cells, a percentage value of less than 1% of red blood cells parasitized is assigned.
7) An estimate of less than 1% of red blood cells parasitized does not need to be refined, since no clinical predictive value is gained. It is values of 2-3% or above that are of clinical concern.

Future Diagnostic Techniques

There are new, easy to perform serum serology**{**xe "serum serology"**}** techniques for malaria diagnosis being developed. Two such methods, now approved by the FDA (*ParaSight^{R}F***{**xe "ParaSight^{R}F"**}**, Becton Dickinson, Sparks, MD; ICT**{**xe "CT"**}** Malaria P.f^{R}{xe "ICT Malaria P.f^{R}"}, ICT Diagnostics, Sydney, Australia), are designed for easy performance in field situations, and require no laboratory experience and little training. Both tools detect *P. falciparum***{***xe "P. falciparum"***}** serologically using enzyme linked immunosorbent assay (ELISA**{**xe "ELISA"**}**), with results in 10 minutes. Clinical trials show these methods detect *P. falciparum* infections at parasite blood concentration of greater than 40 parasites**{**xe "parasites"**}** per microliter (>40 parasites/μl).

APPENDIX FOUR

ANTIMALARIAL MEDICATIONS

Antimalarial drugs are divided into 4 classifications corresponding to their action on the different plasmodium life cycle**{**xe "life cycle"**}** stages in human host**{**xe "host"**}**s (see Table 5-1). The 4 classes are listed below:

1) Blood schizonticides attack plasmodia in red blood cells preventing or terminating the clinical attack.
2) Tissue schizonticides attack the exoerythrocytic forms in the liver. .
3) Gametocytocidal drugs**{**xe "Gametocidal drugs"**}** attack the gametocyte stage in red blood cells.
4) Hypnozoiticidal drugs**{**xe "Hypnozoitocidal drugs"**}** kill dormant*{xe "dormant"} P. vivax*{xe "P. vivax"} or *P. ovale{xe "P. ovale"}* hypnozoites**{**xe "hypnozoites"**}** in liver cells.

All common drugs used worldwide for treatment of malaria are discussed in this chapter. As with treatment of tuberculosis, multi-drug treatment regimens are becoming necessary as drug-resistant strains emerge. The status, availability, effectiveness, dosage, and side effects**{**xe "side effects"**}** of each are presented. Drugs are listed by generic name in alphabetical order.

Table 5-1. Antimalarial Drugs classified by action on *Plasmodia* Life Cycle Stages

Drug Class	Drugs
Blood Schizontocide	Chloroquine, Quinine, Quinidine**{**xe "Quinidine"**}**, Mefloquine, Tetracyclines, tovaquone **{**xe "Atovaquone"**}**
Tissue Schizontocide	Primaquine, Proguanil**{**xe "Proguanil"**}**
Gametocidal	Primaquine
Hypnozoitocidal	Primaquine

An important avenue of treatment is nasogastric**{**xe "nasogastric"**}** administration of oral anti-malarial medications. If intravenous treatment in severe malaria patients is not possible, oral anti-malarial medications pulverized, mixed with water, and delivered via nasogastric tube are absorbed well and effectively. Dosage for nasogastric treatment is the same as the oral dose.

Atovaquone/proguanil (Malarone^{R}){xe "Atovaquone"}

Description: (atovaquone{xe "Atovaquone"} 250 mg + proguanil 100mg)/tablet{xe "Proguanil"}.
Product: An antiprotozoal agent that is a synthetic derivative of hydroxynaphthoquinone, and may exert its effect by selectively inhibiting electron transport in mitochondria.
Effectiveness: Recent trials have shown that a 3 day course of 1000 mg of atovaquone and 400 mg of proguanil had a cure rate of 87% for chloroquine{xe "chloroquine"}-resistant falciparum malaria{xe "falciparum malaria"}.

Dose & Administration:
For prophylaxis: One tablet per day, starting 1-2 days before entering malaria risk area. Continue one tablet daily while in and for 7 days after leaving the malaria risk area.
For treatment: 4 tablets (1000 mg/400mg) per day for 3 days.

Contraindications:
Children 12 pounds (5 kilograms)
Pregnant women
Women breast feeding infants < 25 pounds(11 Kilograms)
Patients with severe renal impairment
Patients with allergies to atovaquone or proguanil
*Atovaquone/proguanil{xe "Atovaquone"} should be administered with food.

Side Effects: Atovaquone/proguanil{xe "Atovaquone"} is well tolerated. Common side effects{xe "side effects"} listed in order of occurrence are rash, nausea{xe "nausea"}, diarrhea{xe "diarrhea"}, headache{xe "headache"}, fever{xe "fever"}, and vomiting{xe "vomiting"}.

Chloroquine Phosphate

Description: 500 mg (300 mg base) tablet.
Product: A 4-aminoquinoline compound, chloroquine{xe "chloroquine"} is a blood schizonticide active against *P.{xe "Plasmodium"} vivax, P. malariae{xe "P. malariae"},* and *P.*

ovale{xe "P. ovale"}. It has limited activity against most *P. falciparum*{xe "P. falciparum"} infections.

Effectiveness: Chloroquine phosphate is indicated for chemoprophylaxis and for acute attacks of malaria due to Plasmodium{xe "Plasmodium"} vivax, *P. malariae{xe "P. malariae"}, P. ovale*{xe "P. ovale"}, and susceptible strains of P. falciparum{xe "P. falciparum"}. It does not prevent relapse{xe "relapse"} in patients with *P. vivax{xe "P. vivax"}* and *P. ovale* infections, because it does not eliminate persistent liver stage parasites{xe "parasites"}. Primaquine must be given to achieve radical cure{xe "radical cure"} (elimination of dormant{xe "dormant"} hypnozoites{xe "hypnozoites"} in liver cells). Because of the increasing frequency of parasite resistance to chloroquine{xe "chloroquine"}, its use as a prophylactic is limited to Mexico, Central America, and limited areas of the Middle East.

Dose & Administration:

For prophylaxis: One 500 mg tablet weekly beginning 2 weeks prior to arrival in the endemic area. Continue weekly dosing while in and for 4 additional weeks after leaving high risk area..

For treatment: An initial dose of two 500 mg tablets followed by one 500 mg tablet at 6, 24, and 48 hours after initial dose for a total of five tablets (2,500 mg).

Contraindications: Patients allergic to chloroquine

Side Effects: The most frequently observed side effects{xe "side effects"} are gastrointestinal{xe "gastrointestinal"} and include anorexia, nausea{xe "nausea"}, vomiting{xe "vomiting"}, diarrhea{xe "diarrhea"}, and abdominal cramps. Mild and transient headache{xe "headache"}, tinnitus, and deafness have been reported. Ocular reactions including blurred vision, and reversible interference with visual accommodation or focusing of vision may also occur. Long-term or high-dosage therapy may result in irreversible retinal damage.

Chloroquine may cause hemolysis{xe "lysis"}{xe "hemolysis"} when administered to patients with G-6-PD{xe "G-6-PD"} deficiency, but reactions are not as severe as those seen with primaquine. G-6-PD deficient service members taking chloroquine{xe "chloroquine"} prophylaxis should be informed of side effects{xe "side effects"} and advised to seek medical evaluation if they occur. For severe reactions, an alternate prophylactic regimen should be provided.

Doxycycline Hyclate

Description: Available as 100mg tablets
Product: A widely used antibiotic useful as an anti-malarial primarily for prevention of *P. falciparum*{xe "P. falciparum"} infections.

Effectiveness: Doxycycline is indicated for the prophylaxis of malaria due to *P.{xe "Plasmodium"} falciparum;* it is less effective against *P. vivax{xe "P. vivax"}* infections. It is effective against asexual, erythrocytic forms of *P. falciparum*{xe "P. falciparum"}, but not gametocytes of the sexual stage. It is also indicated for treatment of resistant strains of falciparum malaria{xe "falciparum malaria"}.

Dose & Administration:

For prophylaxis: One tablet daily beginning 1-2 days prior to entering endemic areas. Continue daily during stay in the area, and continue daily for 4 weeks after departure.

For treatment: Doxycycline (100 mg twice daily for 7 days) or tetracyline (250 mg four times daily for 7 days) given as part of a multi-drug regimen is effective in areas with drug resistant{xe "drug resistant"} strains of falciparum malaria{xe "falciparum malaria"}. Most often used with mefloquine{xe "mefloquine"}.

Side Effects: Most frequently observed side effects{xe "side effects"} include nausea{xe "nausea"} and epigastric distress; less frequent are incidents of diarrhea{xe "diarrhea"} and vomiting{xe "vomiting"}. Stomach and esophageal ulceration has been reported. The frequency and severity of gastrointestinal{xe "gastrointestinal"} side effects may be reduced by taking doxycycline{xe "doxycycline"} with meals. Absorption of this drug is impaired by antacids containing aluminum, calcium, magnesium, iron, or bismuth subsalicylate. Monilial vaginitis and increased sensitivity to sun exposure{xe "exposure"} are also common side effects.

Mefloquine HCl (Lariam^{R})

Description: Available as 250 mg tablets.

Product: An anti-malarial drug effective against *P. falciparum* and *P. vivax*{xe "P. vivax"} infections.

Effectiveness: Mefloquine HCl provides improved prophylaxis against chloroquine{xe "chloroquine"}-resistant strains of *P. falciparum*{xe "P. falciparum"} and *P. vivax*{xe "P. vivax"}. However, *P. falciparum* strains resistant to mefloquine{xe "mefloquine"} have been reported.

Dose & Administration: For prophylaxis: One 250 mg tablet weekly, beginning 2 weeks prior to departure to endemic areas, and continued for 4 additional weeks after departure.

For treatment: Five 250 mg tablets (15-25 mg/kg) given as a single oral dose. The drug should be taken with at least 8 ounces of water with meals or a snack.

Contrindications:

Pregnant women

Children < 8 years of age

Persons allergic to doxycycline or other tetracyclines

Side Effects: The most frequently observed side effect is vomiting{xe "vomiting"}, (3% incidence). It has also been associated with the occurrence of neurologic{xe "neurologic"} and psychiatric events{xe "psychiatric events"} after both prophylactic and therapeutic use. Minor neurologic events include dizziness{xe "dizziness"}, vertigo, headache{xe "headache"}, decrease in sleep, visual, and auditory disturbances. Serious adverse events such as seizures{xe "seizures"}, disorientation, and toxic encephalopathy have been reported after therapeutic doses in patients with predisposing medical history (epilepsy, alcohol and drug abuse, or psychiatric disorder). Neurologic side effects{xe "side effects"} have an incidence of less than 1%.

Primaquine Phosphate

Description: Available as 52.6 mg (30 mg base) tablet

Product: An anti-malarial drug for elimination of persistent *P.{xe "Plasmodium"} vivax* and *P. ovale*{xe "P. ovale"} liver stage parasites{xe "parasites"} (hypnozoites{xe "hypnozoites"}).

Effectiveness: Primaquine phosphate is indicated for cure and prevention of relapse{xe "relapse"} of *P.{xe "Plasmodium"} vivax* and *P. ovale*{xe "P. ovale"} malaria.

Dose & Administration:

An option for prophylaxis in special circumstances. Call Malaria Hotline (770-488-7788) for additional information.

For treatment and terminal prophylaxis: Two tablets daily for 14 days in individuals who are not G-6-PD**{**xe "G-6-PD"**}** deficient. The primaquine regimen must overlap at least one dose of chloroquine.**{**xe "chloroquine"**}** Therefore, primaquine**{**xe "primaquine"**}** must be started no later than 1 week before the last dose of chloroquine. Current Navy guidance directs that G-6-PD**{**xe "G-6-PD"**}** deficient individuals are not to be given primaquine**{**xe "primaquine"**}**. Do not use on pregnant females or persons allergic to primaquine.

Side Effects: The most frequently observed side effects**{**xe "side effects"**}** include abdominal discomfort, nausea**{**xe "nausea"**}**, headache**{**xe "headache"**}**, interference with visual accommodation, and pruritus. Methemoglobin**{**xe "hemoglobin"**}**emia is common, but rarely necessitates interruption of therapy. Leukopenia and agranulocytosis occur rarely. Do not use during pregnancy**{**xe "pregnancy"**}**. If used for treatment in G-6-PD**{**xe "G-6-PD"**}** individuals, caution service members of possible side effects. If side effects occur, advise members to seek medical evaluation and treatment.

Quinidine{xe "Quinidine"} Gluconate

Description: 80 mg/ml (55mg base /ml) intravenous solution available in 10 ml vials as quinidine**{**xe "Quinidine"**}** gluconate.

Product: Quinidine**{**xe "Quinidine"**}** is a cinchona alkaloid, the dextrostereoisomer of quinine**{**xe "quinine"**}**. Used to treat cardiac arrhythmia**{**xe "arrhythmia"**}**, it is now the drug of choice for intravenous treatment of chloroquine**{**xe "chloroquine"**}**-resistant falciparum malaria**{**xe "falciparum malaria"**}** as intravenous quinine is no longer available in the U.S.

Effectiveness: Very effective and safe for intravenous treatment of severe malaria. No reports of resistance in any strains of Plasmodia.

Dose & Administration:

For prophylaxis: Not indicated.

For treatment: Loading dose of 10 mg/kg (6.2 mg base/kg) given over 1-2 hours, followed by 0.02mg salt/kg/min (0.0125mg base/kg/min) continuous infusion for at least 24 hours. Alternative regimen is 24 mg salt/kg (15 base mg/kg) loading dose IV infused over 4 hours, followed by 12 mg salt/ kg (7.5 mg base/kg) infused over 4 hours every 8 hours, starting 8 hours after loading dose. It is strongly recommended that consults with a cardiologist and a physician having experience treating severe malaria be made. Intravenous quinidine**{**xe "quinidine"**}** can safely be administered by monitoring EKG, blood pressure, and infusion speed; quinidine blood levels should be kept between 3-7 mg/L if monitored. Life-threatening arrhythmia**{**xe "arrhythmia"**}**s are rare with proper doses, but infusion should be stopped temporarily if the EKG shows prolongation of the QRS interval by >50%, or if the QT interval is prolonged >50% of the preceding R-R interval. Hypotension may occur if infusion is too rapid. Loading dose is not indicated if patient started quinine**{**xe "quinine"**}**, quinidine, or mefloquine**{**xe "mefloquine"**}** treatment within the preceding 24 hours.

Side Effects: Quinidine**{**xe "Quinidine"**}** is toxic to the heart if given too quickly or in too high a dose. EKG changes including prolonged QT**{**xe "QT"**}** intervals are common, but life threatening arrhythmia**{**xe "arrhythmia"**}**s are rare if proper dosages are used. Most side effects**{**xe "side effects"**}** are gastrointestinal**{**xe "gastrointestinal"**}** in nature and include nausea**{**xe "nausea"**}**, vomiting**{**xe "vomiting"**}**, abdominal pain**{**xe "abdominal pain"**}**, diarrhea**{**xe "diarrhea"**}**, and rarely, esophagitis**{**xe "esophagitis"**}**. Symptoms of mild to moderate cinchonism**{**xe "cinchonism"**}** (ringing in the ears, headache**{**xe "headache"**}**, nausea, and impaired vision) may appear in sensitive patients after one dose of the drug. Less frequent side effects include urticaria**{**xe "urticaria"**}**, skin flushing with intense itching, and hypersensitivity**{**xe "hypersensitivity"**}** reactions of angioedema, acute asthmatic episode, and liver toxicity.

Quinine (Quinamm^{R})

Description: Available as 130, 200, 260, 300, and 325 mg capsules, and 260 and 325 mg tablets

Product: The first successful compound for treatment of malaria, it has been available for three centuries. With the introduction of chloroquine**{**xe "chloroquine"**}**, the use of quinine**{**xe "quinine"**}** fell dramatically, but the widespread emergence of chloroquine-resistant P. falciparum has increased its use. The intravenous form was last available in the U.S. in 1991.

Effectiveness: Acts rapidly against asexual erythrocytic stages of all four Plasmodium**{**xe "Plasmodium"**}** species that infect humans. There is resistance reported in the rural, northern mountainous area of Thailand and West Africa. Quinine should be used as part of a multi-drug regimen in those areas.

Dose & Administration:
For prophylaxis: Not indicated.
For treatment: Adults: 650 mg 3 times a day for 7 days. Plus doxycycline or tetracycline or clindamycin for 7 days.

Side Effects: Quinine has the poorest therapeutic-to-toxic ratio of all of the anti-malarial drugs. Side effects are collectively known as cinchonism**{**xe "cinchonism"**}** and include ringing in the ears, decreased hearing, headache**{**xe "headache"**}**, nausea**{**xe "nausea"**}**, vomiting,**{**xe "vomiting"**}** and mild visual disturbances. These side effects**{**xe "side effects"**}** are all dose related and reversible. Less common side effects include urticaria**{**xe "urticaria"**}**, angioedema of the face, itching, agranulocytosis, hepatitis, and hypoglycemia**{**xe "hypoglycemia"**}** in patients with high P. falciparum**{**xe "P. falciparum"**}** parasitemia**{**xe "parasitemia"**}**.

APPENDIX FIVE

SUPPLIES AND TRAINING AIDS

Following is an extensive list of useful items available through the Federal Supply System for personal protection, chemoprophylaxis, and treatment of malaria. Special circumstances (i.e., new drug development, new patterns of drug resistant plasmodia, significant product improvement, items required due to unique deployment or geographical contingencies) may necessitate purchase of civilian products. The nearest Navy Environmental and Preventive Medicine Unit or Navy Disease Vector Ecology and Control Center are excellent and knowledgeable sources of advice regarding such situations.

Personal Protection Supplies

NSN ITEM

6840-00-753-4963 Insect repellent, clothing and personal, 75 percent DEET, 2 ounces

6840-01-067-4634 Insecticide, D-phenothrin, 2 percent aerosol formulation

6840-01-278-1336 Insect repellent, clothing, Permethrin aerosol, 6 ounce can

6840-01-284-3982 Insect repellent, personal, 33 percent DEET, 2 ounces

7210-01-010-2052 Insect Bar (netting), cot type

7210-00-267-5641 Poles, insect bar (for suspending insect bar)

8415-01-035-0846 Parka, fabric mesh, insect repellent (DEET jacket) – size small

8514-01-035-0847 Parka, fabric mesh, insect repellent (DEETjacket) – size medium

8514-01-035-0848 Parka, fabric mesh, insect repellent (DEET jacket) – size large

8415-00-935-3130 Head net, insect

Antimalarial Drugs

6506-01-384-9199 Atovaquone

6505-01-491-9430 Atovaquone +Proguanil

6505-00-117-6147 Tetracyclines

6505-00-117-6450 Chloroquine phosphate tablets, 0.5 gm, 500's

6505-00-913-7905 Chloroquine/Primaquine phosphate tablets, individually sealed, 150's

6505-01-348-2465 Primaquine phosphate tablets, 1000's

6505-01-132-0257 Pyrimethamine-sulfadoxine (FansidarR) tablets, 25's

6505-00-957-9532 Quinine sulfate, 325 mg capsules, 100's

6505-01-095-4175 Doxycycline, 100 mg tablets, 50's

6505-01-078-3717 Chloroquine hydrochloride, injection

6505-00-864-6298 Quinidine gluconate, injection

6505-01-315-1275 Mefloquine hydrochloride, tablets, 25's (use this stock number after previous stock number is depleted)

Training Aids

1. Bench Aids for the Diagnosis of Malaria, 2nd Edition. A set of twelve plastic laminated A4 size, available from World Health Organization Publications Center USA, 49 Sheridan Avenue, Albany, NY 12210. (518) 436-9686. Cost is less than $36.00, which includes shipping and handling.

APPENDIX SIX

GLOSSARY

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

Anorexia – lack of appetite, lack of desire or interest in food.

Arthralgia – pain or aching of the joints.

Chemoprophylaxis – method of disease prevention by taking specific medications. Malaria chemoprophylaxis requires drugs to be taken before, during, and after exposure. Very effective, but not absolute because of drug resistance and poor compliance. Chemoprophylaxisis also called "suppressive treatment."

Cinchonism – side effects from quinine or quinidine, reversible with lower dosages or termination of the drugs. Effects include tinnitus, headache, nausea, diarrhea, altered auditory acuity, and blurred vision. The term derives from cinchona bark, the natural source of quinine.

Clinical cure – elimination of malaria symptoms, sometimes without eliminating all parasites. See "radical cure" and "suppressive cure."

Coma – decreased state of consciousness from which a person cannot be aroused. See "Glasgow coma scale," Table 4-3 in Chapter 4, page 42.

Cure – see "clinical cure," "radical cure ," and "suppressive cure."

Cyanosis, cyanotic – physical sign where the skin appears blue, caused by lack of oxygen.

Delirious – mental state characterized by confusion and agitation. Delusions and hallucinations may also be present.

D.O.T. (directly observed therapy) – most effective method of ensuring drug compliance, where drug administration is observed by an appointed authority.

Dyspnea – shallow, labored breathing.

Eosinophilia – an increased number of eosinophils, a type of white blood cell. Greater than normal numbers of eosinophils are often associated with parasitic infections, but not malaria.

Erythrocyte – a red blood cell.

Erythrocytic Stage – The malaria parasite's life cycle when infecting and developing within red blood cells.

Exoerythrocytic Stage – stage in plasmodia life cycle when developing in liver cells (hepatocytes).

Fever Paroxysm – see "paroxysm."

Fluid Overload – A condition in which an excessive amount of IV fluids (crystalloids, blood products) has been administered. In severe episodes causes pulmonary edema.

Fluid Resuscitation – Administration of IV fluids to correct a loss or decrease in blood volume. The loss may be actual, relative, or both. Actual loss of blood volume is due to hemorrhage, sweating, or

Diarrhea – Relative loss of blood volume occurs when the vascular system dilates, increasing total volume. Fluid resuscitation is done with a variety of IV fluids, such as normal saline, lactated ringers, dextrose solutions, and blood products.

Flush – capillary dilation causing skin to appear reddish in color.

Gametocyte – sexual stage of malaria parasites which form in red blood cells. Macrogametocytes (female) and microgametocytes (male) form in individual erythrocytes, are ingested by female mosquitoes, and unite in the mosq uito's stomach. Characteristic diagnostic features of *P. falciparum* gametocytes include their crescent or banana shape, and their overshadowing of the morphology of infected red blood cells.

Hematemesis – vomiting of blood which may be either acute and bright red; or old and clotted appearing as coffee grounds.

Hematochezia – passing blood rectally; blood may appear bright red, or dark red-black, and is usually foul smelling and sticky.

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%.

Hemoglobin – the protein in red blood cells which carries oxygen. Normal range of hemoglobin values: Males – 13.6 - 17.2 g/dl; Females – 12.0 – 15.0 g/dl (136-173 g/L and 120-150 g/L).

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

Hepatocytes – liver cells.

Hepatomegaly – enlarged liver. An unusual physical finding in malaria.

Hyperpyrexia – high fever greater than 105º F (40.5º C).

Hyperthermic – elevated temperature.

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 hypnozoites. Primaquine is the only available drug active against hypnozoites.

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

Hyponatremia – serum sodium less than the normal lower limit, which is 135-147 mEq/L (135-147 mmol/L in SI reference units). Serum sodium levels approaching 120 and below constitute severe

Hyponatremia – A medical emergency. Hyponatremia can be seen in malaria, and is indicative of complicated malaria.

Hypotension – see "orthostatic hypotension."

Icterus – yellow discoloration of the eyes due to an elevated bilirubin. Faint discoloration is seen when bilirubin blood levels rise to 2.5-3.0 mg/dl (43-51 mmol/L in SI reference units). Often identified as scleral icterus, because the sclera or "whites" of the eyes
turn yellow.

Immunity – the body's ability to control or lessen a malaria attack with antibodies and other protective reactions developed in response to previous malaria attacks. Semi-immune individuals live in malaria endemic areas and are repeatedly infected. Immunity developed does not prevent or cure malaria attacks, but controls the attack, minimizing symptoms. Such individuals typically have low blood levels of malaria parasites.

Incubation Period – time period beginning when malaria parasites are injected by a mosquito bite, ending when symptoms develop. Incubation periods range from 7 to 40 days, depending on species.

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

Leukocytosis – total white blood cell count greater than 11,000 per cubic millimeter. Leukocytosis refers specifically to elevation in the number of polymorphonuclear leukocytes, which make up the majority of white blood cells.

Leukopenia – total white blood cell count of less than 5,000 per cubic millimeter. Leukopenia refers specifically to a reduction in the number of polymorphonuclear leukocytes, which make up the majority of white blood cells.

Lymphadenopathy – enlarged lymph nodes, which can be detected by physical examination. Lymphadenopathy is not a usual physical finding in malaria.

Malaise – subjective feeling of being sick, ill, or not healthy. The feeling is generalized, varying from mild to severe in intensity. It may be the lone clinical manifestation of malaria, or may accompany other signs and symptoms.

Merozoite – the end product of the asexual reproductive stage (schizogony) of the malaria parasite life cycle. Merozoite maturation takes place in erythrocytes or hepatocytes. Schizogony in erythrocytes ends in their rupture, releasing merozoites which infect other red blood cells. Schizogony in liver cells culminates in their rupture and merozoite release, which infect red blood cells. In *P. vivax* and *P. ovale* infections, released merozoites can also infect other liver cells and develop into hypnozoites.

Myalgia – muscle pain or ache.

Obtunded – mental state in which reaction to stimuli is dulled or blunted, such as persons with severe alcohol intoxication.

Oliguria – decrease of urine production.

Oocyst – cysts located in the outer stomach wall of mosquitoes, where sporozoite development takes place. When mature, the oocysts rupture and release sporozoites. Sporozoites subsequently migrate to salivary glands, and get injected into the host when mosquitoes feed.

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-headedness, dizziness, or increased pulse. Orthostatic hypotension is a common finding in patients with malaria infections.

Parasitemia – level of malaria parasites in blood. If no fever or other symptoms except for an enlarged spleen accompany finding of malaria parasites in blood, the condition is referred to as "asymptomatic parasitemia."

Paroxysm – a sudden attack or increase in intensity of a symptom, usually occurring in intervals. Malaria is classically described as producing fever paroxysms; sudden severe temperature elevations accompanied by profuse sweating. However, fever paroxysms are rarely exhibited in the majority of malaria cases in non-immune persons, while semi-immune local inhabitants are more likely to have them. Therefore, diagnosis should not be based on this finding in U.S. military personnel.

Petechiae – small red or purple skin macules, usually 1-3 mm in diameter. They are manifestations of small subcutaneous bleeds and seen in minor trauma, when the platelet count is very low, or in clotting defects. They are also caused by immune complex deposits in the skin.

Petechial Rash – grouping of petechiae.

Presumptive treatment – administration of anti -malarial drugs in suspected cases before results of laboratory tests are available to confirm diagnosis.

Prophylaxis – see "chemoprophylaxis."

Prostration – a state characterized by an extreme loss of strength.

Pulmonary Edema – accumulation of fluid in lung alveoli due to leakage, resulting in difficulty breathing. It is generally due to breakdown of stability of membranes lining alveolar spaces and/or fluid overload.

QT Interval – measured from the beginning of the QRS to the end of the T wave, it represents total duration of ventricular systole. As a rule of thumb, it should be less than 50% of the preceding R-R interval. A prolonged QT interval indicates delayed repolarization of ventricular myocardium. Development of serious ventricular tachyarrhythmias (R on T phenomenon), syncope, and sudden death are possible under this condition.

Radical Treatment – treatment intended to achieve cure of P. vivax or P. ovale malaria. Requires primaquine treatment, which destroys latent exoerythrocytic stage parasites (hypnozoites).

Radical Cure – complete elimination of malaria parasites from the body, specifically hypnozoites.

Rales – crackling sounds heard at end inspiration during lung auscultation. An abnormal physical finding.

RBC – red blood cell.

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 red blood cells from malaria parasites (hypnozoites) that persisted in liver cells (hepatocytes).

Relapse – a repeat attack of malaria.

Resuscitation – see “fluid resuscitation.”

Rigor – severe chill, characterized by shaking of the body.

Sallow – pale, reddish -yellow in color.

Schizogony – asexual reproductive stage of malaria parasites. In red blood cells, schizogony entails development of a single trophozoite into numerous merozoites. A similar process happens in infected liver cells.

Scleral Icterus – see “icterus.” **Splenomegaly** – an enlarged spleen. A common finding in malaria patients that sometimes can be detected by physical examination.

Sporozoite – stage of malaria parasites injected into the bloodstream by biting infective mosquitoes. Sporozoites infect liver cells, disappearing from bloodstream within 30 minutes.

Stuporous – mental state characterized by lack of awareness of one's surroundings.

Suppressive Treatment – treatment intended to prevent clinical symptoms or parasitemia through destruction of parasites in red blood cells. It does not prevent or eliminate malaria infection as parasites may persist in the liver and produce a relapse after drug therapy is stopped. Suppressive treatment is also called "chemoprophylaxis."

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.

Tinnitus – ringing sound in the ears, a common side effect of quinine treatment.

Treatment – see "presumptive treatment," "radical treatment," and "suppressive treatment."

Trophozoite – early developmental stage of blood schizont.

Urticaria – hives. Numerous swellings in skin, ranging from many localized lesions a few mm to a few cm in diameter, to large blotchy irregular swellings.

Vasodilation – increase in diameter of small vessels of the vascular system. Net result is often a decrease in blood pressure, which may be significant.

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