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Navy and Marine Corps Public Health Center Pocket Guide to MALARIA PREVENTION AND CONTROL



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Pocket Guide to
MALARIA PREVENTION AND CONTROL**

2011

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TABLE OF CONTENTS

INTRODUCTION	1
1. MALARIA: DISEASE, LIFE CYCLE, DISTRIBUTION	5
1.1 Disease	5
1.2 Life Cycle	5
1.2.1 Infective Stage.....	6
1.2.2 Primary Liver Stage.....	6
1.2.3 Dormant or Hypnozoite Liver Stage	6
1.2.4 Erythrocytic (Blood) Phase.....	7
1.2.5 Vector (Mosquito) Phase	8
1.2.6 Environmental Factors	10
1.3 Distribution	11
2. PREVENTION	13
2.1 Personal Protective Measures – Barrier Methods	14
2.1.1 Topical Repellents	15
2.1.2 Permethrin-Impregnated Uniform and Other Protective Clothing	17
2.1.3 Protective Netting	20
2.2 Chemoprophylaxis	21
2.2.1 Chemoprophylaxis: Before, During, After	22
2.2.2 Directly Observed Therapy (DOT)	23
2.2.3 Chemoprophylactic Regimens	24
2.3 Unit Protective Measures	25
2.3.1 Discipline and Training	25
2.3.2 Treatment of Clothing and Equipment with Permethrin.....	26
2.3.3 Location of Base Camp	27
2.3.4 Vector Control.....	29
3. DIAGNOSIS	30
3.1 Clinical Diagnosis	30
3.1.1 Signs and Symptoms – Uncomplicated Malaria.....	32
3.1.2 Signs and Symptoms – Severe Malaria	35

3.2	Diagnostic Study Findings	37
3.2.1	Blood	37
3.2.2	Urine.....	38
3.2.3	Chemistries	38
3.3	Parasitological Diagnosis.....	39
3.3.1	Microscopic Examination of Giemsa-Stained Blood Smears.....	40
3.3.2	Rapid Diagnostic Tests.....	41
3.3.3	Additional Malaria-Specific Tests.....	42
3.3.4	Timing of Screening.....	42
3.4	Pathophysiology and Clinical Presentation of Infections with Specific Malaria Species.....	43
3.4.1	Malaria Due to <i>P. falciparum</i> Infection	43
3.4.2	Malaria Due to <i>P. vivax</i> (or <i>P. ovale</i>) Infection.....	44
3.4.3	Malaria Due to <i>P. malariae</i> Infection.....	45
3.4.4	Malaria Due to <i>P. knowlesi</i> Infection	46
4.	TREATMENT	47
4.1	Specific Treatment Regimen	47
4.1.1	Plasmodium Species.....	47
4.1.2	Clinical Status of Patient	48
4.1.3	Drug Susceptibility.....	48
4.2	Uncomplicated Malaria	49
4.3	Presumptive Anti-Relapse Therapy (PART)	50
4.4	Severe/Complicated Malaria.....	50
5.	SPECIAL CIRCUMSTANCES.....	53
5.1	Occupational Impact of Malaria Chemoprophylaxis and Treatment.....	53
5.2	Glucose-6-Phosphate Dehydrogenase Deficiency.....	53
6.	MILITARY MALARIA CONTROL RESPONSIBILITIES	55
6.1	Unit Commanding Officers	56
6.2	Medical Department Responsibilities.....	56
6.2.1	Unit Medical Officers	57
6.2.2	Preventive Medicine Officers.....	57
6.2.3	Hospital Corpsmen.....	58
6.2.4	Preventive Medicine Technicians	58
6.2.5	Laboratory Personnel.....	58

6.2.6	Environmental Health Officers.....	59
6.2.7	Medical Entomologists	59
6.2.8	Other Preventive Medicine Units.....	60
6.3	Administrative Responsibilities	60
6.3.1	Medical Record Review and Documentation	60
6.3.2	Malaria Medical Event Reporting	61
6.3.3	Blood Donor Programs.....	62

APPENDIX 1: RESOURCES FOR PREVENTIVE MEDICINE

	GUIDANCE AND MEDICAL INTELLIGENCE.....	64
APPENDIX 2:	ANTIMALARIAL MEDICATIONS	69
APPENDIX 3:	LABORATORY DIAGNOSTIC TECHNIQUES	81
APPENDIX 4:	SUPPLIES AND TRAINING AIDS	94
APPENDIX 5:	GLOSSARY	97
ACRONYMS		101
INDEX.....		103

LIST OF FIGURES AND TABLES

Figure 1-1.	The Malaria Life Cycle	9
Figure 1-2.	The Distribution of <i>P. falciparum</i> and <i>P. vivax</i> by Country.....	12
Table 1-1.	Characteristics of the Four Principal Species of Human Malaria.....	10
Table 2-1.	WHO International Travel and Health Organization Guidelines for Chemoprophylaxis.....	24
Table 2-2.	Drugs Used for Malaria Prophylaxis	25
Table 3-1.	Features of Severe Malaria.....	32
Table 3-2.	Malaria Clinical Findings	35
Table 3-3.	Malaria Laboratory Findings	39
Table 4-1.	Manifestations of Complicated/Severe Malaria.....	52

INTRODUCTION

The threat to health and readiness of Sailors and Marines posed by malaria stimulated the creation of the first Malaria “Blue Book” in 1984. Prevention and treatment of malaria is becoming increasingly more complex due to the emergence of drug resistance, insecticide-resistant mosquito vectors, and large populations of infected people in many areas of the world. In 2010, the World Health Organization (WHO) estimated 225 million cases of malaria among 3.5 billion people at risk. They further estimated 780,000 deaths.

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 who serve in such operations requires thorough understanding of the prevention and treatment of malaria. This “Malaria Pocket Guide” includes information to help service personnel do the following four things:

- 1) Understand the transmission and life cycle of malaria parasites
- 2) Prevent malaria
- 3) Diagnose and treat malaria
- 4) Persuade commanders to enforce malaria preventive measures

Command Responsibility

Malaria control depends on directed discipline by those in command. In their role as advisors, medical personnel must identify threats and present countermeasures and their benefits so those in command can make effective decisions. In World War II, Lieutenant General Sir William 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 [antimalarial 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, doctors, regimental officers, staff officers, and 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 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 in Somalia developed malaria. The explanation for the outbreak is complex and involves a number of factors: the complex life cycle of malaria, lack of command support leading to poor execution of personal protective measures, and incomplete medical intelligence of the malaria threat. Available medical intelligence concluded that *Plasmodium falciparum* was the predominant malaria threat in Somalia. Task Force medical planners were influenced by the Army's policy of not performing Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency screening on its personnel. Without this screening, the risk of precipitating a hemolytic reaction from terminal primaquine prophylaxis had to be weighed

against the chance that *P. vivax* and *P. ovale* were present. Based on those factors, Task Force medical planners did not recommend terminal primaquine prophylaxis.

Unfortunately, *P. vivax* was endemic in 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 prophylaxis was instituted. Despite this precaution, another 45 soldiers developed malaria infections and had to be hospitalized and administered higher dosages of primaquine, which indicated that drug resistant strains were developing. It should be just as obvious that poor execution of personal protective measures allowed these soldiers to be bitten by infective mosquitoes.

During Operation Restore Hope, medical surveillance of Naval Forces revealed that half of all malaria and dengue cases were occurring in a single Marine battalion located in the Baardera area. Investigation of these outbreaks found that the Marine commander had not enforced recommended countermeasures. Fortunately, consequences were minimal. The ill Marines recovered, and the unit was not involved in any significant engagements in its weakened condition. 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.

In 2003, 80 of 225 members of a United States Marine Corps (USMC) Marine Expeditionary Unit (MEU) that went ashore on a peacekeeping mission in Liberia contracted malaria, for an overall attack rate of 36%. Not all components of the forces going ashore had the same experience, however. The quick reaction force of 115 Marines who spent ten continuous days ashore had 44 cases for an attack rate of 38%. A thorough investigation revealed a global failure of personal preventive measures (PPM) and chemoprophylaxis. The 2003 experience is a reliable predictor of future experience in the presence of similar failure.

The stand-up of the United States African Command (AFRICOM) has increased deployments in Africa, including many to highly malarious countries. A 2011 field training mission in West Africa of only two weeks duration resulted in 14% of the participating Naval personnel acquiring malaria, including one case that required intensive care unit admission. These infections followed the 2009 death of a Construction Battalion Sailor from *P. falciparum* malaria acquired in Liberia.

These examples demonstrate 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 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 to enforce personal protective measures is difficult. No vaccine is yet available, though *P. falciparum* malaria vaccines are being tested.

The necessary tools for successful prevention of malaria already exist. Medical personnel must successfully communicate the threat. After convincing commanders, medical personnel must teach, supervise, and practice personal protective measures. They must be able to diagnose and treat personnel stricken with malaria, as well. **It cannot be emphasized enough, as General Slim demonstrated, that success against malaria requires a unified effort enforced by commanders. Malaria prevention is not a medical program.**

1. MALARIA: DISEASE, LIFE CYCLE, DISTRIBUTION

1.1 Disease

Malaria is a parasitic mosquito-borne infection with both acute and chronic phases. It is caused by protozoa of the genus *Plasmodium*. There are over 150 species of the malaria parasite that infect many species of vertebrates. Each type of protozoa tends to remain within one type of host, such as bird or mammal. Four species infect and rely on humans to sustain malaria transmission: *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*. The protozoa are transmitted to humans by the bite of the female anopheline mosquitoes. Plasmodia also are transmitted to humans by direct inoculation of infected red blood cells via transfusion, needles, and congenitally. *Plasmodium knowlesi* has recently been described as a human pathogen. It is known that *P. knowlesi* differs from the four species of human malaria in that it is a zoonotic infection of long-tailed macaques in Southeast Asia.

The discussions and figures in this guide refer to the four recognized human malaria species. Common signs and symptoms of all species of human malaria are high fever, chills, headache, anemia, and splenomegaly. Most serious and fatal complications are caused by *P. falciparum*.

1.2 Life Cycle

The life cycle of the malaria parasite is complex (see Figure 1-1). Its developmental stages (with associated symptoms) vary according to the *Plasmodium* species involved (see Table 1-1). Developmental stages include the following: infective stage, primary liver stage, dormant or hypnozoite liver stage, erythrocytic (blood) phase, and

vector (mosquito) phase. Environmental factors should also be considered.

1.2.1 Infective Stage

During the infective stage, the plasmodia, in a form known as sporozoites, are injected from the salivary glands of infected mosquitoes while feeding. These sporozoites disappear from the blood of the person within 30 minutes. Many sporozoites are destroyed by white blood cells, but some enter liver cells where they proceed to the next developmental stage.

1.2.2 Primary Liver Stage

Sporozoites that enter liver cells multiply asexually in a process called exoerythrocytic schizogony. Thousands of merozoites form in the dividing schizonts, eventually displacing the nucleus of the liver cell. Since all these changes occur inside the liver cell, there is no inflammatory reaction in the liver. Eventually, the 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* species.

1.2.3 Dormant or Hypnozoite Liver Stage

All infections due to *P. falciparum* and *P. malariae* have a single exoerythrocytic form. All infected liver cells parasitized with *P. falciparum* and *P. malariae* rupture and release merozoites at about the same time. In contrast, *P. vivax* and *P. ovale* have two exoerythrocytic forms. The primary form develops, causes liver cell rupture, and releases merozoites just as described for

P. falciparum and *P. malariae*. The other form, which develops concurrently, is known as the hypnozoite. Sporozoites of *P. vivax* and *P. ovale* species differentiate into hypnozoites that remain dormant for weeks, months, or years. This means that these two species have a dormant form of the infection, and at some future time, these hypnozoites activate and undergo exoerythrocytic schizogony, forming a second wave of merozoites that invade the blood and cause a delayed case or a clinical relapse. Thus special preventive measures must be taken for *P. vivax* and *P. ovale* infections to prevent relapse; these measures are typically referred to as presumptive anti-relapse therapy (PART).

1.2.4 Erythrocytic (Blood) Phase

Merozoites that are released from the infected liver cells circulate freely in the bloodstream. They invade red blood cells (erythrocytes) where they develop into 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 red blood cells rupture, releasing mature merozoites. Symptoms associated with malaria occur at this point.

The mature merozoites then invade fresh erythrocytes and another generation of parasites develops in the same manner. This process occurs repeatedly during the course of infection and is called erythrocytic schizogony (in contrast to exoerythrocytic schizogony described above). The periodicity of this development cycle differs according to the species of parasite, varying from

48 hours in *P. vivax*, *P. ovale*, and *P. falciparum* malaria to 72 hours in *P. malariae* infections. This is what gives the characteristic periodic nature to the classic malaria fever in the host. In the early stages of infection, there is no characteristic periodicity as groups of parasites develop at different times. Initial febrile episodes are inconsistent. Later, the erythrocytic schizogony development cycle becomes synchronized, and the febrile paroxysms become more consistent. The different types of clinical malaria may be referred to as “tertian” (or three-day) or “quartan” (or four-day) malaria in older literature. These febrile paroxysms rarely occur in non-immune military personnel, who typically present with debilitating illness long before synchronization. Therefore, the absence of periodicity cannot be relied upon to rule out malaria in febrile patients or in patients returning from malaria-endemic locations. Some merozoites differentiate into sexual forms (female macrogametocytes, male microgametocytes) and develop in invaded red blood cells.

1.2.5 Vector (Mosquito) Phase

Anopheles mosquitoes feeding on infected hosts ingest the sexual forms along with the blood meal. The infection of the mosquito is therefore passive and is coincidental with taking a blood meal from an infected human. The female macrogametocytes and male microgametocytes mature in the mosquito’s stomach and combine, forming a zygote that undergoes mitosis. The products of mitosis are ookinetes, which force themselves between epithelial cells to the outer surface of the stomach where they form into small spheres called oocysts. The oocysts enlarge

as the nucleus divides and eventually rupture, releasing thousands of motile sporozoites into the body cavity. The sporozoites migrate to the salivary glands, making the female mosquito infective. The vector phase of the life cycle, called sporogony, is complete in 8 to 35 days depending on species and environmental conditions.

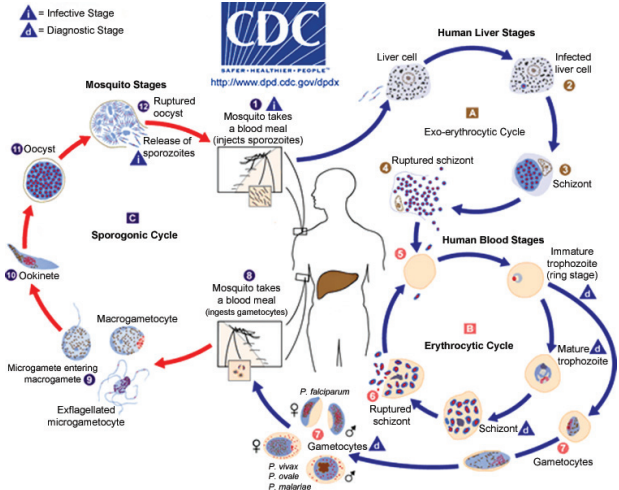


Figure 1-1. The Malaria Life Cycle

Table 1-1. Characteristics of the Four Principal Species of Human Malaria¹

	<i>P. falciparum</i>	<i>P. vivax</i>	<i>P. ovale</i>	<i>P. malariae</i>
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 cycle (days)	5.5–7	6–8	9	12–16
Number of merozoites per liver cell	40,000	10,000	15,000	2,000
Erythrocytic cycle (hours)	48	42–48	49–50	72
Red blood cell preference	Younger cells, but can invade cells of all ages	Reticulocytes	Reticulocytes	Senescent cells
Relapses	No	Yes	Yes	No
Fever periodicity (hours)	None	48	48	72
Febrile 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	++++	+	-	-

¹ There is insufficient information on the characteristics of *P. knowlesi* infections to include in this table at this time.

1.2.6 Environmental Factors

Anopheles mosquitoes are essential for development, multiplication, and spread of plasmodia. Therefore, service personnel traveling to any area harboring anopheline mosquitoes may be at risk for malaria transmission. Specific environmental conditions favoring anopheline mosquito vector and parasite development include temperatures between 20 and 30°C (68 and

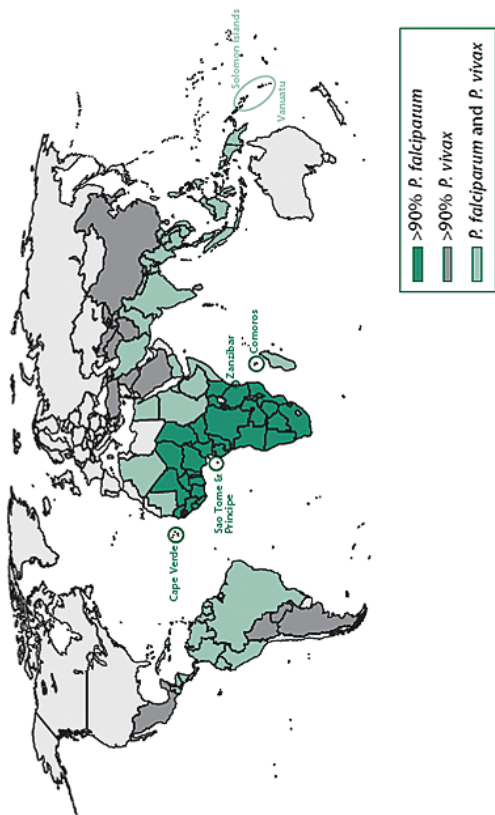
86°F) and a mean relative humidity of 60%. The sporogony phase requires temperatures between 16 and 33°C (61 and 91°F). High relative humidity increases mosquito life-span, thereby increasing the probability of mosquitoes becoming infective. Areas with high rainfall have increased malaria incidence because 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. Transmission rarely occurs above 2000–2500 meters.

The minimum temperatures for mosquito development are between 8 and 10°C (46 and 57°F). The minimum temperatures for parasite development are between 14 and 19°C (57 and 66°F) with *P. vivax* surviving at lower temperatures than *P. falciparum*. Therefore, malaria transmission can and does occur in temperate zones at non-tropical temperatures. Warmer temperatures shorten the time required for parasite development within the mosquito host, the number of blood meals taken by the same female, and the frequency of eggs laid. Anopheline mosquitoes can also live inside buildings, thus malaria transmission may occur at ambient temperatures less than 20°C (68°F).

1.3 Distribution

The worldwide distribution of malaria (*P. falciparum* and *P. vivax*) is illustrated by Figure 1-2. This is a general representation and not intended for threat assessment or countermeasure planning. Detailed country-specific information can be obtained from the National Center for Medical Intelligence (<https://www.intelink.gov/ncmi/index.php#>) in the section labeled Baseline Infectious Disease

Figure 1-2. The Distribution of *P. falciparum* and *P. vivax* by Country²



² Printed with the permission of Feachem, R.G.A. and The Malaria Elimination Group (2009). Shrinking the Malaria Map: A Guide on Malaria Elimination for Policy Makers. San Francisco: The Global Health Group, Global Health Sciences, University of California, San Francisco.

Risk Assessment, and from the Navy Environmental and Preventive Medicine Unit (NEPMU) responsible for a particular geographic area. (Further medical intelligence can be obtained from the agencies listed in Appendix 1.)

2. PREVENTION

Four tactics prevent disease in the field and during combat operations. These tactics may be successfully employed against any disease threat and are the basic strategy of military disease and injury prevention. They are as follows:

- 1) Determination of disease and injury threats in the area of operation before deployment.
- 2) Identification or development, and employment, of countermeasures to reduce threats to an acceptable level before deployment.
- 3) Education of personnel regarding threats and training in correct use of countermeasures, and continuous reinforcement of this training during deployment.
- 4) Enforcement of countermeasures by the command.

There are three types of countermeasures that can prevent malaria: **Personal Protective Measures, Chemoprophylaxis, and Unit Protective Measures.** None of the recommended interventions is 100% effective. Even in combination and when efficiently and consistently applied, malaria infection may still occur in high incidence areas or on prolonged deployments. Medical personnel must seek information to answer the six questions outlined below and determine which countermeasures to employ; they must also make recommendations for the same to commanders.

- 1) What type(s) of malaria is (are) present?
- 2) What are the known antimalarial susceptibilities of the *Plasmodium* species present in that location?
- 3) Which countermeasures will be effective in the area and within the operational context the unit will encounter?
- 4) How will the unit obtain the necessary supplies, personnel, and equipment?
- 5) Do unit personnel know how to apply the countermeasures chosen? Will they apply them? What training is needed?

- 6) Does the chain of command understand its role and accountability in enforcing the countermeasures?

Primary sources of information regarding malaria and malaria species are the National Center for Medical Intelligence (NCMI) and the NEPMU responsible for that area of the world. The NCMI produces the Medical Environmental Disease Intelligence and Countermeasures (MEDIC), a compendium of unclassified NCMI medical intelligence, reference documents, and operational material configured to function in environments that lack access to the unclassified NCMI website. The files can be downloaded to a hard drive or portable electronic media such as a CD or DVD. The NCMI also provides Infectious Disease Risk Assessments on its website and can be contacted directly for specific questions relevant to a unit's anticipated malaria exposure.

2.1 Personal Protective Measures – Barrier Methods

These measures prevent mosquitoes from biting and thus potentially transmitting malaria. **Personal protective measures are effective against a wide range of disease vectors, not solely for prevention of malaria.** In many military operations, they will be the only means of protection against biting arthropods. Personal protective measures 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 is that their effectiveness is dependent on service member adherence. Persuasion by medical personnel and enforcement by non-commissioned officers (NCOs) and commanders are necessary to ensure continuous and proper application. Medical personnel must circulate among units—teaching, examining, and improving personal protective measure practice—and report their findings to those in charge.

Commanders and NCOs must ensure compliance and lead by personal example. Personal protective measures include proper application of repellents, the use of impregnated uniforms and/or other protective clothing, and the use of protective netting.

2.1.1 Topical Repellents

Successful use of repellents requires that individuals wear uniforms treated with permethrin and apply and maintain a topical insect repellent to exposed skin. The active ingredients of all topical insect repellents listed in this guide are registered by the Environmental Protection Agency (EPA) and have been reviewed by the Centers for Disease Control and Prevention (CDC).

Topical repellents are natural or synthetic compounds that repel 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 in 1910, continued with the discovery of dimethyl phthalate during WW II, and led to the development of diethyl toluamide, or DEET, in 1957. The efficacy and safety of DEET has been thoroughly established. Although other topical repellents have been registered by the EPA, DEET remains the gold-standard to which other topical repellents are compared because of its long and safe history.

The duration of a repellent's effectiveness decreases with activity, heat, and humidity. Although it is true that many *Anopheles* mosquitoes inhabit warm tropical environments, topical repellents available to the military are designed to remain effective for up to 12 hours,

even in a harsh environment, making frequent reapplication unnecessary. Users should check the product label to determine how often reapplication is required. Contrary to public opinion, Avon Skin So Soft® and flea collars are not effective repellents. In fact, wearing flea collars can cause serious localized skin reactions and should never be tried.

DEET. Ultrathon® Insect/Arthropod Repellent Lotion (NSN 6840-01 -284-3982) is a 33% DEET lotion developed to last 12 hours. It has a low odor and is less damaging to plastics than previous formulations. It is applied in the same manner as skin lotion; neglected skin is not protected. This product is the most effective and longest-lasting formulation available.

Ultra30® (NSN 6840-01-584-8393), also referred to as Lipo-Deet, is a 30% DEET lotion designed to last 12 hours. This was added to the military standard stock system in 2010. Some users say this product is less greasy than other DEET formulations.

Various other personal application DEET products are available through the military standard stock system. Cutter Repellent Stick® (NSN 6840-00-142-8965) is a 30% DEET formulation that comes in a 1-oz 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). When making separate applications of sunscreen and insect repellent products, apply sunscreen first, followed by repellent.

Picaridin/Icaridin. Picaridin is considered to be a reasonable alternative to DEET. Two 15% picaridin products are available through the federal stock system—Cutter Spray BT® (NSN 6840-01-541-9380) and Cutter Spray Aerosol® (NSN 6840-01-541-9424). These are odorless and have a clean feel. Some formulations are long-lasting.

Lemon Eucalyptus Oil. The active ingredient in lemon eucalyptus oil, methyl ester menthane diol (PMD), has been shown to have equal repellency and longevity as DEET. Moreover, it has been shown to prevent malaria in clinical trials. At the time of this writing, there are no products containing PMD that available in the federal stock system.

2.1.2 Permethrin-Impregnated Uniform and Other Protective Clothing

Permethrin impregnants are compounds that are longer-lasting than topical repellents and cannot be applied to skin. Permethrin is an impregnant for fabric only, and it is used by the military to treat tents, bed nets, 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 such as ticks, and flying insects such as mosquitoes and biting flies.

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 are available.

Recently, each service has issued unique camouflage uniforms with digital patterns. The differences in the fabric and add-on treatments, such as permanent press or fire retardant, complicate the issue of fabric treatment. The most important point to remember is that camouflage uniforms must be treated with permethrin when troops are in malaria-endemic areas.

Uniforms may be factory-treated, or treatments may be applied after their receipt. Marine Corps Combat Utility Uniforms are factory-treated with permethrin. Quality assurance of this application has shown that permethrin binds to the fabric and provides high levels of bite protection up to 50 washings. Factory-treated uniforms have a label on the inside of the garment that indicates the garment has been treated and how long the treatment will last. Preventive medicine personnel must look for the presence of labeling to determine if a garment from any service is factory-treated before applying permethrin to a particular uniform.

After-purchase treatment methods have not changed. The original application methods were applied to tricolor Battle Dress Uniforms, which were worn by all three services in the 1990s. The currently issued Navy Working Uniform (NWU) and the Air Force's Airman Battle Uniform (ABU) are not treated at the factory and should be treated according to one of the methods below if

the garments are to be worn in areas endemic for vector-borne disease.

There are several available military stock supplies for impregnated/protective clothing.

Permanone Aerosol Spray. 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, nonirritating, and can last through three to five washings or 6 weeks. It is applied the same way as spray paint (slow sweeping motion, 6–8 inches from object) until the surface of the fabric appears moistened, then it is allowed to dry for 2 hours before wearing. It should not be applied to caps, socks, or undergarments, or while clothing is being worn.

Individual Dynamic Absorption (IDA) Kit.

Individual Dynamic Absorption (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 on the cotton tricolor camouflage uniforms (old-style non-digital uniform). At the time of this writing, data are not available to determine how long this treatment lasts on the NWU.

Insect Repellent, Clothing Application. Insect Repellent, clothing application, 40% permethrin, liquid (2-gal sprayer) (NSN 6840-01-334-2666) is commonly used to treat large numbers of uniforms at one time. Treatment is accomplished

by spreading the uniform over a large area and spraying with 8 ounces (one bottle) of concentrate diluted in 2 gallons of water. Two gallons of finished spray will treat eight uniforms. Treatment lasts through about 50 washings on the cotton tricolor camouflage uniforms (old-style non-digital uniform). At the time of this writing, data are not available to determine how long this treatment lasts on the NWU.

2.1.3 Protective Netting

The available military stock supplies include several types of netting, including a jacket, head net, and bed nets and poles. More information on these products and personal protective measures 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).

Insect Repellent Mesh Parka (DEET jacket).

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

Insect Head Net. 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.

Mosquito Bed Nets and Poles. Mosquito 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 should be established for each unit to coach, inspect, and advise on the application of personal protective measures, including bed net use. Also available are self-contained pop-up bed nets that are pretreated with permethrin. They are available in green (NSN: 3740-01-516-4415) and coyote brown (NSN: 3740-01-518-7310).

2.2 Chemoprophylaxis

This section presents drug regimens recommended by the CDC for the prevention of malaria. These recommendations may change between revisions of this field guide and therefore should be confirmed with the NEPMU responsible for the relevant area of responsibility and/or through the CDC website at <http://cdc.gov> before selecting an agent for a unit or individual. Choice among the many regimens is determined by several factors:

- 1) Known or suspected drug resistance in specific locations
- 2) Species of malaria in the endemic area (*P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*)
- 3) Length of time to be spent in the endemic area
- 4) Any adverse reaction to the antimalarial drug of choice,

or restriction by job (e.g., mefloquine is not authorized for prophylaxis in aviators and divers)

- 5) Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency and other medical contraindications

Other factors may be pertinent (e.g., young age, pregnancy, etc.) if other contingency operations are anticipated.

2.2.1 Chemoprophylaxis: Before, During, After

One of the least-appreciated aspects of malaria chemoprophylaxis is the requirement for taking the drug before, during, and after exposure to malaria, regardless of subtype. All malaria species have bloodstream and liver stages. Disease symptoms only occur during the blood phase. *Plasmodium vivax* and *P. ovale* parasites can stay dormant in the liver for long periods (up to several years) and then can enter the bloodstream, causing symptoms well after exposure. Because of this period of dormancy, individuals who may have been exposed to *P. vivax* and *P. ovale* infections need an additional medication when they leave an endemic malaria region to eradicate the hypnozoites in the liver. This post-exposure treatment is called presumptive anti-relapse therapy (PART) (formerly known as terminal prophylaxis), and is required only for exposure to *P. vivax* and *P. ovale*.

Unit personnel must be screened before malaria chemoprophylaxis is initiated. Personnel who have had prior adverse drug reactions or have risk factors (e.g., G6PD deficiency, pregnancy, etc.) and those in certain occupations (e.g., personnel on flight status and divers) need to be identified and provided an appropriate regimen.

Determining when to begin chemoprophylaxis depends on the medication being prescribed. Chemoprophylaxis may need to begin before travel to endemic areas to allow adequate blood levels to develop, depending on the choice of medication. The lead time for beginning chemoprophylaxis is also useful to monitor personnel for drug reactions. Most prophylactic antimalarials are suppressive blood schizontocides and must be continued for 4 weeks after leaving an endemic area to ensure adequate suppressive whole blood concentrations of the drug at the time exoerythrocytic merozoites enter the bloodstream. The combination medication atovaquone/proguanil hydrochloride (Malarone®) is an exception to the rule, requiring only 7 days of post-exposure continuation because it is active against primary liver stages as well as the erythrocytic stages of the parasites.

2.2.2 Directly Observed Therapy (DOT)

Directly Observed Therapy (DOT) is the only way leadership can ensure that members take their medications as indicated (daily or weekly). As lack of adherence to chemoprophylaxis regimens has been cited as a primary causative factor in multiple malaria outbreaks in the past, DOT is recommended whenever practicable and for any chemoprophylaxis regimen. It is a method proven by the WHO and other public health authorities for the chain of command to ensure service members take all their medication correctly and completely. In DOT, a trained person (chain-of-command authority) monitors the service member taking each dose of malaria chemoprophylaxis (either daily or weekly, depending on the medicine prescribed), actually watching the service member swallow

each dose. Chain-of-command support is crucial to ensuring effective implementation of DOT.

2.2.3 Chemoprophylactic Regimens

Below, in Table 2-1, are WHO International Travel and Health Organization guidelines for selecting a chemoprophylactic regimen. Table 2-2 provides a matrix of medications used for malaria prophylaxis under varying circumstances. More complete information on medications used for prophylaxis and treatment may be found in Appendix 2.

Table 2-1. WHO International Travel and Health Organization Guidelines for Chemoprophylaxis

Malaria Risk	Type of Prevention
Very limited risk of malaria transmission	Mosquito bite prevention only
Risk of <i>P. vivax</i> malaria only; or fully chloroquine-sensitive <i>P. falciparum</i>	Mosquito bite prevention and chloroquine chemoprophylaxis and PART with primaquine
Risk of <i>P. vivax</i> , <i>P. ovale</i> , and <i>P. falciparum</i> malaria transmission, combined with emerging chloroquine resistance	Mosquito bite prevention and mefloquine, atovaquone-proguanil, or doxycycline chemoprophylaxis and PART with primaquine
(1) High risk of <i>P. falciparum</i> malaria, in combination with reported antimalarial drug resistance; or (2) Moderate/low risk of <i>P. falciparum</i> malaria, in combination with reported high levels of drug resistance; or (3) <i>P. malariae</i> and <i>P. knowlesi</i> do not have persistent liver forms and are usually in <i>P. falciparum</i> dominant areas – PART is not needed.	Mosquito bite prevention and mefloquine, atovaquone-proguanil, or doxycycline (select according to reported resistance pattern)

Table 2-2. Drugs Used for Malaria Prophylaxis*

Drug	Usage	Adult Dosage
Atovaquone/proguanil (Malarone®)	Prophylaxis in all areas	250 mg/100 mg (adult tablet) once/day
Chloroquine phosphate (Aralen®)	Prophylaxis in areas with chloroquine-sensitive malaria	300 mg base (500 mg salt) once/wk
Doxycycline (many brand and generic names)	Prophylaxis in all areas	100 mg/daily
Mefloquine	Prophylaxis in areas with mefloquine-sensitive malaria	228 mg base (250 mg salt) once/week
Primaquine phosphate (PART)	Used for presumptive anti-relapse therapy to decrease the risk for relapses of <i>P. vivax</i> and <i>P. ovale</i>	15 mg base (26.3 mg salt) once/day for 14 days after departure from malarious area

*All are oral doses.

2.3 Unit Protective Measures

Unit protective measures for malaria consist of the following:

- 1) Discipline and training
- 2) Treatment of clothing and equipment with permethrin
- 3) Location of base camp
- 4) Vector control

2.3.1 Discipline and Training

Avoiding malaria, other diseases, and non-battle injuries is a team effort that must be visibly supported by command authority. Medical personnel must be prepared to decisively advise those in command of such threats and their

countermeasures, train personnel in the use of protective measures, and monitor their application and effectiveness. Disciplined and correct use of the personal protective measures as thus far presented is very effective in preventing malaria and other arthropod-borne diseases.

2.3.2 Treatment of Clothing and Equipment with Permethrin

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. There is information regarding treating the myriad of new camouflage uniforms that have been recently issued by the three services in previous sections of this chapter.

Tents should be treated while erected, and uniforms and miscellaneous items while spread on the ground. Treated uniforms are ready to wear when dry; do not treat underwear or caps. Date of treatment should be marked on items. 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.

Uniform treatments are effective 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.)

2.3.3 Location of Base Camp

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

The following factors affect the risk of exposure:

- 1) Presence of mosquito breeding sites
- 2) Direction of prevailing winds
- 3) Proximity of settlements with malaria-infected inhabitants
- 4) Length of time unit will be present in area
- 5) Exposure during peak biting times

Breeding areas vary depending on the specific species of anopheline mosquito responsible for malaria transmission. Sunlit streams, shaded lagoons, rice fields, and marshes are all breeding habitats for different species of anopheline mosquitoes. Campsite selection close to possible 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 anopheline mosquitoes is unavoidable, camp where the prevailing winds will blow the mosquitoes away from camp.

A host population of infected humans is necessary to infect mosquitoes. If possible, locate base camps distant enough from settlements with infected inhabitants so as to be beyond normal flight range (2–3 kilometers) of the anopheline vector.

Duration of deployment in the area is also important for planning permanent mosquito control measures. If the military presence may be prolonged, establishment of a long-term base camp 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. Improvement projects that impound water should be screened by entomologists and preventive medicine personnel to prevent the creation of mosquito breeding areas.

Another unit protective measure to consider when operating in endemic areas is reducing troop exposure during peak biting times (dusk till dawn for most anophelines). Examples include the following:

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

2.3.4 Vector Control

Vector control includes two stages: surveillance and control. First, mosquito surveillance and analysis of collected data are performed. The analysis leads to the choice of control measures most applicable to area and situation.

Preventive medicine teams deployed in contingency situations are prepared to survey campsites for mosquitoes and other disease vectors, determine vector breeding areas, and establish programs to control them. These teams are experienced at implementing sanitation and other public health measures and are 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.

Medical entomologists supervise the two-stage process; first, they determine mosquito species, their abundance, and breeding sites. Second, they recommend a control plan, including specific control methods and their evaluation. Details of these procedures are beyond the scope of this guide.

3. DIAGNOSIS

Untreated malaria can be a rapidly progressive and fatal disease. Early diagnosis followed by expedient, appropriate treatment saves lives. A detailed travel history should be obtained in any febrile patient without an obvious source of infection, and malaria should be considered in those who have traveled to malaria-endemic areas. Clinical diagnosis may be challenging—early signs and symptoms of malaria are nonspecific, and the disease can masquerade as all manner of illness. Malaria patients have been initially misdiagnosed as having viral illness, gastroenteritis, flu, or even heat exhaustion. Even in malaria-endemic areas, malaria may not be considered because it shares signs and symptoms with other tropical illnesses such as typhoid fever, dengue fever, and bacterial meningitis. *Therefore, diagnosis of malaria requires heightened clinical suspicion and diligent screening.*

3.1 Clinical Diagnosis

Clinical suspicion of malaria is primarily based on the presence or history of fever in a patient who may have been exposed to the disease. The signs and symptoms of malaria are nonspecific, and infected patients may not exhibit symptoms for several weeks after exposure. Initial presentation is rare after one month but inadequately treated patients with *P. vivax* or *P. ovale* may relapse after longer periods due to the dormant hypnozoite stage (liver infestation). Diagnosis based on clinical features alone has low specificity and will lead to treatment of individuals who do not have malaria. *However, in an operational setting, the risks of empiric treatment are generally far lower than the potentially deadly risk of failing to treat malaria.* Nevertheless, always consider other possible causes of fever and the need for alternative or additional treatment.

Malaria infections are often classified as either “uncomplicated” or “severe.” The distinction is important as treatment and

evacuation strategies may differ for each. The WHO defines “uncomplicated malaria” as symptomatic malaria without signs of severity or evidence of vital organ dysfunction. Uncomplicated malaria may, however, progress to severe malaria within hours, especially in *P. falciparum* infection. “Severe malaria” is a medical emergency. It is typically associated with infection with *P. falciparum* and includes signs of severity and/or vital organ dysfunction. Severe *P. vivax* mono-infections have been increasingly reported over the last decade, so patients with proven *P. vivax* may be treated as benign but should be monitored closely for complications that might necessitate elevation of the level of care. The WHO defines severe malaria as the presence of one or more of the features listed in Table 3-1 in a patient with *P. falciparum* parasitemia and no other obvious cause of symptoms.

Table 3-1. Features of Severe Malaria

Clinical Features
• Impaired consciousness or coma
• Prostration (i.e., generalized weakness so that the patient is unable to walk or sit up without assistance)
• Failure to feed
• Multiple convulsions (>2 episodes within 24 h)
• Deep breathing, respiratory distress (acidotic breathing)
• Circulatory collapse/shock, SBP<70 mmHg in adults
• Clinical jaundice or evidence of other vital organ dysfunction
• Hemoglobinuria
• Abnormal spontaneous bleeding
• Pulmonary edema
Laboratory Findings
• Hypoglycemia (blood glucose <40mg/dl)
• Metabolic acidosis
• Hemoglobinuria
• Hyperparasitemia (>2% or 100,000/ μ l in low intensity transmission areas or >5% or 250,000/ μ l in areas of high stable malaria transmission intensity)
• Hyperlactatemia
• Renal impairment

3.1.1 Signs and Symptoms – Uncomplicated Malaria

Patients may present with a variety of symptoms depending on the stage of infection and the infecting species (Table 3-2). Fever is virtually always present in non-immune military personnel, and fever plus any other symptom might be malaria if exposure occurred. Other common complaints include mild to moderate malaise, fatigue, muscle aches, back pain, headache, dizziness, loss of

appetite, nausea, vomiting, abdominal pain, and diarrhea. Dry 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.

Clinical signs and symptoms of malaria occur shortly before or at the time of red blood cell lysis. Chills or rigor, followed by high fever, occur in a cyclical pattern in infections due to *P. vivax*, *P. ovale*, and *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 that are infected intermittently and have developed partial immunity.

The malaria 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 *P. falciparum* infections often present with a constant fever. The classic paroxysm typically has three stages and is preceded in some patients by an initial period of nonspecific symptoms. Those symptoms include fatigue, muscle aches, loss of appetite, headache, and a slight fever of 2–3 days' duration. A paroxysm begins with the "cold" or "chilling" stage lasting 15 minutes to several hours during which the patient feels cold and has shaking 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°C (104°F) or higher. There is minimal sweating and the patient is at risk of febrile seizures or hyperthermic brain damage. Clinical signs and symptoms include tachycardia, hypotension, cough, headache, backache, nausea, abdominal pain, vomiting, diarrhea, and altered consciousness. Within 2–6 hours, the patient enters the third “sweating” stage of the paroxysm with generalized sweating, resolution of fever, and marked exhaustion, usually giving way to sleep. Paroxysms occur in regular intervals but take several days to emerge. Therefore, the absence of paroxysms cannot be relied upon to rule out malaria in febrile patients returning from or residing in malaria-endemic locations.

Physical examination usually demonstrates an increased temperature, tachycardia, orthostatic hypotension, and warm flushed skin. The 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. Mental confusion and cyanosis are sometimes encountered. Most patients with *P. falciparum* malaria complain of loss of appetite and nausea.

Table 3-2. Malaria Clinical Findings

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

3.1.2 Signs and Symptoms – Severe Malaria

In addition to the above general signs and symptoms, patients with severe malaria may present with or develop the following manifestations: cerebral malaria, severe anemia, acute kidney injury, or respiratory distress.

Cerebral Malaria. This feature is almost always caused by *P. falciparum* infection. Cerebral malaria is NOT an infectious cerebritis. Manifestations of cerebral malaria are thought to be caused by microvascular obstruction that prevents the exchange of glucose and oxygen at the capillary level, causing hypoglycemia, lactic acidosis, and high-grade fever. These effects impair brain function yet cause little tissue damage in most cases, as rapid and full recovery follows prompt treatment. Although any neurological deficit is possible with cerebral malaria, one or more of three primary signs are generally present: 1) impaired consciousness; 2) generalized, prolonged, or recurrent grand mal seizures unresponsive to correction of hypoglycemia or hyperpyrexia; and 3) coma, usually preceded by a severe headache, that persists for 24–72 hours,

during which the patient is initially rousable and then unrousable. Neurologic examination may be unremarkable or have findings that include contracted or unequal pupils, a Babinski sign, and absent or exaggerated deep tendon reflexes. High fever, 41 to 42°C (106 to 108°F), with hot, dry skin as seen in heat stroke can occur. Ten to twelve percent of patients surviving cerebral malaria have persistent neurologic abnormalities.

Severe Anemia. The anemia associated with malaria is multifactorial and is usually associated with *P. falciparum* infection. *Plasmodium falciparum* parasites can infect red blood cells of all ages, which theoretically would allow infection of all circulating red blood cells. (*P. vivax* and *P. ovale* require young red blood cells [reticulocytes] and *P. malariae* requires mature blood cells for infection.) Severe anemia is defined as a hematocrit of less than 21%, and clinical manifestations may include dark brown or red urine (hemoglobinuria), decrease in urine production, and jaundice. (Note: Another cause of hemolysis and hemoglobinuria in patients with malaria who are being treated is the destruction of G6PD-deficient red blood cells by oxidant antimalarial drugs such as primaquine.)

Acute Kidney Injury. Renal complications are seen in one-third of adult patients with severe falciparum malaria. Oliguric renal failure is most common and may be due to hypotension/circulatory collapse, hemoglobin-induced acute tubular necrosis, or a combination of both. Failure of urine production is a poor prognostic sign but may be reversible, although supportive dialysis is often required. Careful fluid management is critical, specifically in determining whether the

patient's apparent renal compromise is pre-renal or primarily intra-renal. If hemodynamics improve after a small fluid bolus (200–250 mL) with little change in pulmonary capillary wedge pressure (PCWP), continue the fluid bolus. If a marked increase in heart rate occurs with an increase in PCWP and little improvement in hemodynamics, the risk of pulmonary edema with little impact on renal perfusion is high and cardiac inotropes should be administered instead.

Respiratory Distress. Patients with malaria may develop metabolic acidosis and associated respiratory distress due to compensation. Often fatal acute pulmonary edema can develop rapidly and is associated with excessive intravenous fluid therapy. A conscious patient may feel more short of breath when lying down (orthopnea). Fast, labored respiration, a non-productive cough, and moist rales and rhonchi are usually present. Signs of malarial hyperpneic syndrome include alar flaring, chest retraction (intercostal or subcostal), use of accessory muscles for respiration, or abnormally deep breathing. A rapidly progressive acute respiratory distress syndrome (ARDS) may ensue.

3.2 Diagnostic Study Findings

Abnormal laboratory findings reflect the severity of hemolysis (Table 3-3). Far-forward deployed medical personnel will likely not have all or even some of the necessary testing equipment.

3.2.1 Blood

A normocytic, normochromic anemia with leukopenia and thrombocytopenia is sometimes present on initial screening but is almost always

present following medication therapy with the resultant clearing of parasitemia. Massive *P. falciparum* infections cause acute decreases in hemoglobin and hematocrit and cause an increase in reticulocyte count. Malaria does not cause eosinophilia.

3.2.2 Urine

Trace to moderate protein, urobilinogen, and conjugated bilirubin may be found on urinalysis. In severe *P. falciparum* infections, massive hemolysis combined with circulating immune complexes produces acute renal insufficiency or failure (“blackwater fever”) with laboratory findings of hemoglobinuria, proteinuria, and an elevated serum creatinine.

3.2.3 Chemistries

Renal insufficiency may produce an elevated serum creatinine. Fever and 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 impairment may occur, though hyperbilirubinemia normally results from hemolysis. Abnormalities in liver function tests, including increased ALT, AST, and prolonged prothrombin time, sometimes occur, causing diagnostic confusion with viral hepatitis. Serum albumin is usually decreased. Hypoglycemia is commonly seen in *P. falciparum* infections and pregnancy and is due to the 75-fold increase in glucose consumption by parasitized red blood cells. If a patient deteriorates during convalescence, especially with deterioration in

neurologic function, hypoglycemia should be considered as a possible cause.

Table 3-3. 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 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

3.3 Parasitological Diagnosis

Whenever practicable, all febrile patients who may possibly have been exposed to malaria should be tested for the disease. This includes personnel who took malaria chemoprophylaxis medication while deployed to endemic areas. *While laboratory confirmation of the diagnosis of malaria is desirable, empiric treatment should not be delayed if clinical suspicion of the disease is high.*

The two main methods of parasitological diagnosis are light microscopy and rapid diagnostic tests (RDTs). Both require diligent quality assurance and attention to detail. Light microscopy allows identification of specific malaria species and degree of infection but requires specialized equipment and a well-trained reader. The RDTs may be useful in certain settings when microscopy is not immediately available, but results must be interpreted

carefully. *While a positive RDT can confirm a diagnosis of malaria, a negative RDT does NOT necessarily rule out malaria.* If a patient is clinically suspected of having the disease but has a negative RDT result, treatment should not be withheld since prompt treatment saves lives.

3.3.1 Microscopic Examination of Giemsa-Stained Blood Smears

The reference standard and confirmatory test of choice for malaria diagnosis is microscopic examination of thick and thin blood smears. Thick smear examination detects the presence of plasmodia but is not useful for species identification; thin smear examination identifies the specific infecting *Plasmodium* species. Thick and thin smears can be prepared on the same microscope slide.

Whole blood samples and additional slides should be prepared and submitted to preventive medicine specialists at supporting organizations (e.g., a NEPMU) for further testing. These samples can be analyzed later to help identify the specific species of malaria and detect resistance to antimalarials. Appendix 3 describes methods for preparing, staining, and reviewing thick and thin smears and provides a specimen shipping protocol developed by the Walter Reed Army Institute of Research.

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

3.3.2 Rapid Diagnostic Tests

The RDTs are immunochromatographic tests that detect malaria antigens in blood, and some may be able to differentiate between certain species of malaria. BinaxNOW® Malaria is the only RDT currently (2011) approved by the Food and Drug Administration (FDA) for use in the United States. In certain settings, RDTs may be useful if results are properly interpreted. A positive RDT provides useful information in confirming a diagnosis of malaria. A negative RDT result does NOT rule out malaria and should not be used to determine therapy. A negative result could be due to any number of factors, including failure of the test due to equipment/reagent degradation, procedural error, levels of parasitemia below the test's threshold for detection, or an infecting species not reliably detectable by the test. If expert microscopy is not available, as is frequently the case in military deployment settings, serial repeat testing with an RDT will increase diagnostic sensitivity of the test as parasite density increases. A fortuitous feature of the RDT is that if an initial result is a false negative due to parasitemia below detection threshold, serial testing will eventually produce a true positive result as the parasitemia detection threshold will be reached before parasitemia becomes life-threatening. Thus, serial testing should be continued every 12 or even every 8 hours until the following occurs: 1) malaria is diagnosed, 2) another diagnosis is found, or 3) the patient recovers. If the patient becomes progressively more ill and RDTs continue to be negative, empiric antimalarial therapy can be administered to cover the possibility that the RDT has been degraded.

3.3.3 Additional Malaria-Specific Tests

Other laboratory methods may detect and help identify malaria infections, but these are typically not useful in initial diagnosis of acutely ill patients due to the time and specialized equipment required, and they are not likely to be available in close proximity to military field operations. Polymerase chain reaction (PCR) testing can detect parasite nucleic acids and may be useful for confirming the infecting malarial species. The PCR assays can be performed on whole blood kept at room temperature for extended periods or on dried blood on slides as well as filter paper, stored with a desiccant.

3.3.4 Timing of Screening

Symptoms often precede detectable parasitemia by 1–2 days. The majority of patients do not exhibit significant parasitemia at the time of initial fever. Therefore, specimen collection should occur several times a day (frequency is more important than timing) until a diagnosis of malaria is made or ruled out. Thin smear diagnosis for causative species is crucial, as *P. falciparum* infections are life-threatening and require specific treatment. After diagnosis, blood smears should continue to be monitored for response to therapy. Decreasing parasite count (density) signifies favorable response to therapy; frequency of testing depends on therapeutic response and severity of illness. Seriously ill patients should be tested (using blood smears) 2–3 times daily until they significantly improve, then daily until the parasite level is zero. For most *Plasmodium* species, an early increase in the asexual parasite density is common but should

fall below the pre-treatment level by day two, to 25% of the pre-treatment density by day three, and to zero by day four.

Early diagnosis and treatment is lifesaving; *P. 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, empirically treat for *P. falciparum* infection 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.

3.4 Pathophysiology and Clinical Presentation of Infections with Specific Malaria Species

The pathogenesis, disease progression, and prognosis of malaria vary with the infecting organism. *Plasmodium falciparum* malaria is more severe and qualitatively different from the other plasmodia that infect humans and is the only type that causes microvascular disease. Other distinctions are discussed below.

3.4.1 Malaria Due to *P. falciparum* Infection

Plasmodium falciparum malaria is a microvascular disease with a substantial metabolic element that damages tissue in the following manner: *P. falciparum* parasites mature in red blood cells causing knobs to form on their surface, in effect making them “sticky”. This stickiness causes parasitized red blood cells to adhere to endothelial cells lining capillaries and postcapillary venules of brain, 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 and produce lactate, resulting in acidemia and release of 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 due to the edema, leading to organ damage and death. In some cases, diagnosis of *P. falciparum* infection is difficult because no parasites are seen on peripheral blood smears, as they are sequestered in the host's microvasculature.

3.4.2 Malaria Due to *P. vivax* (or *P. ovale*) Infection

Infections due to *P. vivax* and *P. ovale* are virtually the same. *Plasmodium vivax* or *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°C (104°F), and symptoms during this stage have been described as worse than *P. falciparum* malaria. Physical findings usually include an enlarged, tender spleen and a palpable liver present by the second week of infection. Deaths have been reported due to rupture of an enlarged spleen.

Plasmodium vivax and *P. ovale* form a dormant stage in liver cells called hypnozoites. These parasites activate and cause delayed infections or relapses. A relapse usually occurs 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* or *P. ovale* is endemic in the area of exposure, presumptive anti-relapse therapy with primaquine must be given to prevent illness.

Disease caused by *P. vivax* and *P. ovale* is less severe than *P. falciparum* malaria. The parasitemia is less than that due to *P. falciparum* because *P. vivax* and *P. ovale* infect only young red blood cells (unlike *P. falciparum* which can infect red blood cells of all ages). Fewer red blood cells are hemolyzed, and their loss stimulates replacement. This increases the number of young red blood cells (reticulocytes), which are susceptible to infection, leading to parasitemia levels greater than 1 to 2% in *P. vivax* or *P. ovale* infections.

3.4.3 Malaria Due to *P. malariae* Infection

Plasmodium 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 are usually mild. Patients may have several febrile paroxysms before parasites are seen in the peripheral blood. *Plasmodium malariae*, like *P. falciparum*, does not have a hypnozoite stage; therefore, relapses do not occur in infections with this species.

Recrudescence can be seen with *P. malariae* infections many years after an untreated initial infection.

3.4.4 Malaria Due to *P. knowlesi* Infection

Plasmodium knowlesi has recently gained recognition as an emerging zoonosis in Southeast Asia that causes human infections. Clinically, patients infected with *P. knowlesi* often present with symptoms similar to those of *P. falciparum*, while microscopically the parasite may be easily confused with *P. malariae*. This disconnect between clinical picture and microscopic appearance, coupled with exposure to *P. knowlesi* endemic locations, should raise suspicion for infection with *P. knowlesi*.

4. TREATMENT

Treatment should be initiated as soon as possible once the diagnosis of malaria is made and should be instituted presumptively based on strong clinical suspicion if a delay in laboratory diagnosis is anticipated. 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.

Specific treatment regimen—type(s) of drug and route of administration—depends on (a) infecting *Plasmodium* species; (b) clinical status of patient, including co-morbidities, drug allergies, and other medications; and (c) drug susceptibility of parasites. Consultation with a physician trained and experienced with treatment of malaria or specialists at supporting public health organizations should be sought if a patient is suspected to have malaria.

4.1 Specific Treatment Regimen

4.1.1 Plasmodium Species

The first step is determining the species. *Plasmodium falciparum* and *P. knowlesi* can rapidly progress to severe illness and death, whereas *P. vivax*, *P. ovale*, and *P. malariae* usually cause less severe illness. Patients with *P. vivax* and *P. ovale* need treatment for the hypnozoites that lie dormant in the liver and cause relapsing infection. *Plasmodium falciparum* and *P. vivax* species have different drug-resistance patterns in various areas of the world. If the diagnosis of malaria is suspected and cannot be confirmed, or if the diagnosis of malaria is confirmed but species determination is not possible, antimalarial

treatment effective against *P. falciparum* must be initiated immediately.

4.1.2 Clinical Status of Patient

Patients are generally categorized into uncomplicated and severe malaria. Patients with uncomplicated malaria can be treated with oral antimalarials. Patients with severe malaria must be treated aggressively and with parenteral antimalarial medications. Patients who have one or more of the following clinical criteria are considered to have a severe malaria infection: impaired consciousness/coma, severe normocytic anemia (hemoglobin < 7), renal failure, ARDS, hypotension, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of > 5%. Any patient with severe malaria should be considered a candidate for emergency evacuation to definitive treatment facilities.

4.1.3 Drug Susceptibility

Determining the area where the patient acquired the malaria infection yields information on potential parasite drug resistance. Chloroquine-resistant strains of *P. falciparum* are present in nearly all malarious areas. The CDC maintains current information on countries with drug resistant malaria on its malaria webpage at http://www.cdc.gov/malaria/travelers/country_table/p.html.

4.2 Uncomplicated Malaria

In the past, chloroquine was the mainstay antimalarial of choice for uncomplicated malaria of all types. Because of widespread drug resistance, chloroquine is no longer the drug of choice for treatment (if delivered outside of fixed MTFs) of uncomplicated *P. falciparum* malaria in Naval Forces personnel. Chloroquine continues to play a major role in the treatment of uncomplicated non-falciparum malaria when the provider is certain that the infection was acquired in an area where chloroquine-resistant *P. falciparum* or *P. vivax* has NOT been reported. Chloroquine treatment is as follows:

- Chloroquine: initial dose of 600 mg base (= 1,000 mg salt) followed by 300 mg base (= 500 mg salt) at 6, 24, and 48 hours after the initial dose for a total dose of 1,500 mg base (=2,500 mg salt)

In the event of *P. falciparum* or unknown species malaria, treatment choices include the following:

- Artemether 20 mg-lumefantrine 120 mg: 1 po initially, followed at 8 hours by a second dose, then 1 po bid x 2 days (6 tabs total)
- Atovaquone 250 mg-proguanil 100 mg: 4 tabs po qd x 3 days (12 tabs total)
- Mefloquine: 684 mg base (=750 mg salt) po initially, followed by 456 mg base (=500 mg salt) after 6–12 hours, for a total of 1130 mg base (=1250 mg salt)
- Quinine sulfate plus doxycycline, tetracycline, or clindamycin
- Quinine sulfate: 542 mg base (=650 mg salt) pot id x 3 days (Note: Continue for 7 days for infections acquired in Southeast Asia)
 - Doxycycline: 100 mg po bid x 7 days
 - Tetracycline: 250 mg po qid x 7 days
 - Clindamycin: 20 mg base/kg/day po divided tid x 7 days

In the event of known *P. vivax* malaria in a chloroquine-resistant area, any of the treatment regimens for *P. falciparum* or unknown species malaria listed above may be used. (Note: Clindamycin is not indicated as an adjunct to quinine sulfate for *P. vivax* malaria.) Primaquine phosphate must be added to any of these regimens to eradicate *P. vivax* hypnozoites.

Additional information on prophylaxis and treatment medications may be found in Appendix 2.

4.3 Presumptive Anti-Relapse Therapy (PART)

In addition to requiring blood phase treatment, infections with *P. vivax* and *P. ovale* can relapse due to hypnozoites that remain dormant in the liver and need to be treated with a 14-day course of primaquine phosphate, 15 mg (base) by mouth daily for 14 days.

Because primaquine can cause hemolytic anemia in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency, personnel must be screened for G6PD deficiency prior to starting primaquine treatment. Screening is qualitative, determining the presence of G6PD deficiency but not the type or severity. Primaquine can be used safely in G6PD-deficient persons under close medical supervision. Consult an expert in infectious disease and/or hematology before treating a G6PD-deficient person with primaquine.

4.4 Severe/Complicated Malaria

Severe/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. Patients

presenting with any of the clinical manifestations listed in Table 4-1 should be treated for complicated malaria. Patients diagnosed with, or suspected of having, severe malaria require aggressive treatment with parenteral antimalarial therapy, preferably in an intensive care unit. If there is clinical evidence of severe malaria but the blood smear is reported as *P. vivax*, *P. ovale*, or *P. malariae*, the patient should still be treated for *P. falciparum* malaria because of the possibility of a mixed infection or misdiagnosis. It is strongly advised that consultation with a cardiologist and a physician with experience in treating malaria be obtained when treating a patient with severe malaria.

Patients with severe malaria should be treated with intravenous quinidine plus doxycycline, tetracycline, or clindamycin. Intravenous quinidine is a potent blood schizonticide, and therapeutic plasma concentrations can be quickly and safely achieved by administration of a loading dose. Intravenous quinidine will be an intervention likely administered only in a medical treatment facility (MTF) setting by a qualified provider. The use of intravenous quinidine is beyond the scope of this pocket guide.

A parenteral alternative, developed by the Walter Reed Army Institute of Research and available in the United States from the CDC under an IND, is intravenous artesunate followed by one of the following: atovaquone-proguanil, doxycycline (clindamycin in pregnant women), or mefloquine. Non-FDA approved parenteral artemisinin derivatives such as artemether may be available from host nation healthcare facilities.

Table 4-1. Manifestations of Complicated/Severe Malaria

Major Signs	Description
Coma	Failure to localize or abnormal response to painful stimuli; coma persisting for >30 min after generalized convulsion
Seizures	More than two generalized convulsions in 24 hours
Severe anemia (normochromic, normocytic)	Hematocrit rapidly falling to <15%, or hemoglobin <7 g/dl
Severe bleeding abnormalities	Significant bleeding from gums, nose, GI tract, and/or evidence of disseminated intravascular coagulation
Pulmonary edema/ acute respiratory distress syndrome	Shortness of breath, fast labored respiration, rales
Renal failure	Urine output <400 ml/24 hrs; 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/G6PD)
Hyperparasitemia	> 5% of RBC infected with malaria parasites
Hypoglycemia	Glucose <40mg/dl (<2.2 mmol/l)
Hypotension/shock	Systolic BP <80; core to skin temperature >10°C difference
Acid base disturbances	Arterial pH <7.25 or plasma bicarbonate <15 mmol/l

5. SPECIAL CIRCUMSTANCES

5.1 Occupational Impact of Malaria Chemoprophylaxis and Treatment

In general, the first-line medications used for chemoprophylaxis and treatment of malaria are safe for all personnel regardless of military occupation. With uncomplicated malaria, especially with few symptoms, return to work may be accomplished while therapy continues. There are certain military positions which require, at a minimum, special attention. These include flight or diving status. These personnel should be closely monitored during prophylaxis and treatment in that adverse effects could seriously hazard operations. In specific, primaquine is safe for use in personnel on flight status, as are chloroquine and doxycycline. Personnel are prohibited from using mefloquine while in an active flight or diving status.

5.2 Glucose-6-Phosphate Dehydrogenase Deficiency

Navy and Marine Corps military personnel are required to have been tested for G6PD deficiency and to have the results of this test permanently documented in their health records and on deployable health records. Because the level of deficiency remains constant over time, repeat testing is not needed. However, the results of the test (or testing if no results have been documented) is required before issuing a prescription for primaquine phosphate for presumptive anti-relapse therapy. If a G6PD-deficient person has had a significant, prolonged exposure to malarial parasites that have a liver stage (for example, *P. vivax* or *P. ovale*) and it is determined that primaquine treatment or prophylaxis is needed, the medication should be administered only under the direct care of the treating physician. Chloroquine may also cause hemolytic anemia in G6PD-deficient patients,

although this is unlikely when it is given in therapeutic doses. The drug should be administered with caution to patients having G6PD deficiency.

6. MILITARY MALARIA CONTROL RESPONSIBILITIES

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

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

- 1) Threat assessment
- 2) Countermeasure selection and implementation
- 3) Reassessment of threats and countermeasures guided by outcome measurement and analysis

Threat assessment is covered in other chapters of this guide. This chapter will outline the application of the second and third principles by the chain of command to control malaria. Most, if not all, of these principles apply to other DNIBs. To prevent malaria, strong line involvement and enforcement is essential. Medical personnel must work closely with line commanders and their staff to implement measures to prevent malaria. In general, malaria prevention and control is achieved through personal protective measures, mosquito control, and chemoprophylaxis. 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. The decision to recommend and/or implement mosquito control measures should be made in consultation with a cognizant medical entomologist.

6.1 Unit Commanding Officers

The success of malaria control depends on the enforcement of personal protective measures at the unit level. Part of the responsibility of enforcing personal protective measures is discharged by ensuring that personnel are adequately trained and equipped to employ them. Unit commanding officers ultimately decide how chemoprophylaxis is administered (e.g., whether before a meal, by separate departments, or by employment of DOT). Finally, they must report malaria cases, as discussed below under Medical Event Reporting and directed by BUMEDINST 6220.12 (series) Medical Surveillance and Notifiable Events Reporting. Accurate surveillance data and analysis yield accurate reassessment of threats and countermeasures.

6.2 Medical Department Responsibilities

Malaria prevention and control efforts depend on medical department personnel. These personnel provide the expertise to 1) conduct medical surveillance; 2) educate, train, and supervise personnel in the employment of personal protective measures and chemoprophylaxis regimens; 3) diagnose and treat malaria; and 4) perform 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. In addition, they instruct corpsmen as well as medical officers to be familiar with the various chemoprophylaxis and treatment regimens.

Medical personnel also must understand the threat in order to counter it. Essential sources of medical intelligence are the NCMI and NEPMU. Appendix 1 describes in detail these and other resources from which

medical intelligence, threat assessments, and other force health protection (FHP) information can be obtained.

6.2.1 Unit Medical Officers

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

6.2.2 Preventive Medicine Officers

The General Preventive Medicine Officer (PMO) serves as a source of information for all levels of the chain of command. Knowledge of the general duties of all medical department personnel involved in malaria control (Medical Entomologists, Environmental Health Officers, and Preventive Medicine Technicians) allows PMOs to consult and coordinate the provision of any needed training, supplies, or control measures with units in the field or in garrison.

6.2.3 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 prevention. Unit corpsmen perform most of the personal protective measures training given to unit personnel. They live with their units in the field and monitor the daily employment of countermeasures. They supervise administration of chemoprophylaxis and are often the first to initiate the diagnosis and care of any malaria cases.

6.2.4 Preventive Medicine Technicians

Preventive Medicine Technicians (PMTs) are specially trained hospital corpsmen who are directly involved in all aspects of malaria control and other DNBI collection/reporting. The PMTs are excellent field resources for preventive medicine information. They provide training in personal protective measures to hospital corpsmen and unit personnel. They also perform field vector surveillance, collect epidemiological data, and will supervise or conduct field sanitation and vector control measures if needed. They serve alongside PMOs.

6.2.5 Laboratory Personnel

Laboratory personnel assigned to deployable units must be able to perform thick and thin peripheral blood smears and identify plasmodia species that cause malaria in humans.

Laboratory personnel, where assigned, are responsible for handling, packaging, and sending prepared duplicate blood smear slides to the cognizant NEPMU (or other service preventive medicine unit, if designated) that is responsible for monitoring the area of operation. Such samples enable an update of the area threat assessment and diagnosis confirmation.

6.2.6 Environmental Health Officers

Environmental Health Officers (EHOs) are often assigned to deployable labs, preventive medicine units, hospital ships, Marine Logistics 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. They also have a primary role in the training and supervision of PMTs.

6.2.7 Medical Entomologists

Medical entomologists obtain the most current mosquito information and recommend applicable methods of vector control. They supervise adult and larval mosquito surveys, apply pesticides, and train personnel in identification and control measures. They are assigned to Marine Logistics Groups and other operational units to do the following:

- 1) Recommend and ensure that personal protective measures are employed
- 2) Select optimum locations for bivouacs and base camps
- 3) Recommend safe times for training and field exercises

6.2.8 Other Preventive Medicine Units

Preventive medicine teams can deploy EHOs, Medical Entomologists, PMOs and Laboratory Technicians. If a Navy Forward Deployable Preventive Medicine Unit (FDPMU) is in the theater, this Unit may be capable of specialized laboratory and vector control services.

6.3 Administrative Responsibilities

Administrative responsibilities include medical record review and documentation, malaria medical event reporting, and blood donor program monitoring.

6.3.1 Medical Record Review and Documentation

Medical records of Navy/Marine Corps service members are required to include G6PD screening results and chemoprophylaxis.

G6PD 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 the service member's medical treatment record must be checked.

Chemoprophylaxis. The date prophylaxis began and ended, drug type, and dosage should be entered on a SF 600. If PART 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 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 or have symptoms of malaria. This information is usually presented at the unit level. When this information is presented, personal protective measures may be demonstrated, and DEET, permethrin, netting, and other necessary items may be issued.

6.3.2 Malaria Medical Event Reporting

All Navy Medical Department personnel who diagnose a patient with a **suspected or confirmed** case of malaria shall report the case within 24 hours of diagnosis as directed by BUMEDINST 6220.12 (Series). Those with NIPRnet access shall report all suspect or confirmed cases and outbreaks via the Disease Reporting System internet (DRSi). The DRSi account access can be requested through the NDRS Helpdesk at NMCPhCPTS-DRSi@med.navy.mil, COMM: 757-953-0954, DSN: 377-0954). Alternative reporting methods are outlined in BUMED INST 6220.12 (Series). Outbreaks or clusters of suspect or confirmed malaria require submission of an outbreak medical event report (MER).

A confirmed case of malaria is defined as a person with a laboratory-confirmed malaria infection by one or more of the following methods:

- 1) Demonstration of malaria parasites in blood film, or
- 2) Positive result on Binax Now® test.

In addition to patient demographics listed in BUMED INST 6220.12 (Series), the following additional information is required to be provided with each malaria MER:

- 1) Relevant travel and/or deployment history,
- 2) Details of related chemoprophylaxis compliance, and
- 3) Details of all related laboratory tests and findings to include species when known.

Additional information concerning reporting can be obtained at the NMCPHC Medical Event Reporting page (http://www-nehc.med.navy.mil/Preventive_Medicine/reportingtools.aspx) or through the NDRS helpdesk (NMCPHCPTS-DRSi@med.navy.mil), COMM: 757-953-0954, DSN: 377-0954).

6.3.3 Blood Donor Programs

Blood donation programs are subject to the guidance of BUMED P-5120 (Series), "Standards for 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 chemoprophylaxis 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, not drugs.

Individuals who visited a malaria-endemic area without taking chemoprophylaxis and who have remained asymptomatic are required to wait six

months before being eligible to donate blood. Personnel placed on chemoprophylaxis in readiness, but who did not travel into a malaria-endemic area, do not have a required waiting period to donate blood.

APPENDIX 1: RESOURCES FOR PREVENTIVE MEDICINE GUIDANCE AND MEDICAL INTELLIGENCE

Resources listed in this appendix for malaria prevention are divided into two general sections: Navy preventive medicine guidance 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.

1.1 Navy Preventive Medicine Guidance

1.1.1 General Policy and Guidance

Navy and Marine Corps Public Health Center
620 John Paul Jones Circle, Suite 1100
Portsmouth, Virginia, 23708-2103
Phone: (757) 953-0700; DSN: 377-0700
FAX: (757) 953-0685
E-mail: NMCPHCPTS-ThreatAssessment@med.navy.mil

1.1.2 Navy Environmental & Preventive Medicine Units (NEPMUs)

Navy Environmental & Preventive Medicine Unit 2
1285 West D Street Norfolk, VA 23511-3394
Phone: (757) 953-6600; DSN 564-xxxx
Fax: (757) 953-7212/7213; DSN 377-7212/7213
E-mail: nepmu2norfolkthreatassessment@med.navy.mil

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

Navy Environmental & Preventive Medicine Unit 6
385 South Ave, Bldg. 618
JBPHH, HI 96860
Phone: (808) 471-0237; DSN (315) 471-0237
Fax: (808) 471-0157
E-mail: NEPMU6threatassessment@med.navy.mil

1.1.3 NEPMU Publications and Services

- Pre-deployment medical briefings
- Courses on malaria diagnosis and prevention
- Consultation with epidemiologists, microbiologists, and entomologists

1.1.4 Navy Entomology Center of Excellence (NECE)

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: NECE-OPSDept@med.navy.mil

1.1.5 NECE Publications and Services

- Vector Risk Assessment Profiles (VECTRAPS), or vector reports, descriptions of disease vectors and control measures worldwide
- Information on pesticide usage and resistance and personal protective measures

1.1.6 Navy Infectious Diseases Consultants

Walter Reed National Military Medical Center,
Infectious Diseases Division
8901 Rockville Pike
Bethesda, MD 20889-5600
DSN: 295-6400/4237,
Phone: (301) 295-6400/4237, Fax: -2831

Naval Medical Center Portsmouth
Infectious Diseases Division
620 John Paul Jones Circle
Portsmouth, VA 23708
DSN: 314-5179, Phone: (757) 953-5179,
Fax: -7674

Naval Medical Center San Diego
Infectious Diseases Division
34800 Bob Wilson Drive Suite 201
San Diego, CA 92134-1201
DSN: 522-7475/6194,
Phone: (619) 532-7475/6194, Fax: -7478

1.1.7 Preventive Medicine Recommendations for Specific Operations

Available from the Joint or Subordinate Component Surgeon's office, Fleet or Force Surgeon's office, or the NEPMU 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.

1.2 Medical Intelligence

The primary source of medical intelligence products is the National Center for Medical Intelligence (NCMI), a division of the Defense Intelligence Agency, located at Fort Detrick, Maryland. Described below are the medical intelligence products NCMI provides.

1.2.1 Medical Environmental Disease Intelligence and Countermeasures (MEDIC) CD-ROM

The MEDIC provides worldwide disease and environmental health risks. Also included in MEDIC are military and civilian healthcare delivery capabilities, operational information, arthropod vector information, an expanded poisonous snake section on some countries, and an expanded section on poisonous and injurious plants. It also includes significant portions of the Control of Communicable Disease Manual (included by permission from the American Public Health Association).

1.2.2 Infectious Disease Risk Assessment (IDRA) and Environmental Health Risk Assessment (EHRA)

Infectious Disease Risk Assessments (IDRAs) and Environmental Health Risk Assessments (EHRAs) are unclassified risk assessments on individual countries without countermeasure recommendations. The Navy/Marine Corps Intranet's (NMCI's) baseline IDRA (now in a

DIR format) assesses the overall country's risk of infectious diseases, contains a dynamically updated summary table, and incorporates all mandatory analytic tradecraft elements.

1.2.3 NCMI Contact Information

AFMICOPS@afmic.detrick.army.mil

1.2.4 NCMI Web Address (Note: This is https)

<https://www.intelink.gov/ncmi/index.php>

1.3 Internet Homepages and Other Computer-Related Sources

CDC: <http://www.cdc.gov/travel/>

APPENDIX 2: ANTIMALARIAL MEDICATIONS

Antimalarial medications are divided into four classifications corresponding to their actions on the different plasmodium life cycle stages in human hosts (see Table A2-1). The four classes are as follows:

- 1) Blood schizontocides attack plasmodia in red blood cells preventing or terminating the clinical attack.
- 2) Tissue schizontocides attack the exoerythrocytic forms in the liver.
- 3) Gametocytocidal drugs attack the gametocyte stage in red blood cells.
- 4) Hypnozoitocidal drugs kill dormant *P. vivax* or *P. ovale* hypnozoites in liver cells.

All common drugs used for treatment of malaria are discussed in this appendix. 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 of each medication are presented. Drugs are listed by generic name in alphabetical order.

Table A2-1. Antimalarial Drugs Classified by Action on Plasmodia Life Cycle Stages

Class	Drugs
Blood Schizontocide	Chloroquine, Quinine, Quinidine, Mefloquine, Tetracyclines, Atovaquone, Artemether, Lumefantrine
Tissue Schizontocide	Primaquine, Proguanil
Gametocide	Primaquine
Hypnozoitocide	Primaquine

An important avenue of treatment is nasogastric administration of oral antimalarial medications. If intravenous treatment in severe malaria patients is not possible, oral antimalarial medications pulverized, mixed with water, and delivered via nasogastric tube are absorbed well and effectively. Dosage for nasogastric treatment is the same as for the oral route.

1.1 Artemether+Lumefantrine (Coartem®)

Description: Combination tablet containing artemether 20 mg and lumefantrine 120 mg.

Product: Both of the two antimalarial active ingredients, artemether, an artemisinin derivative, and lumefantrine, are blood schizontocides.

Effectiveness: Clinical studies have demonstrated the efficacy (96% in non-immune adults) of a 6-dose regimen for the treatment of acute, uncomplicated malaria caused by *P. falciparum*.

Dose and Administration:

Prophylaxis: Not indicated.

Treatment: Six tablets taken orally over 3 days for a total of 6 doses: an initial dose, second dose after 8 hours, and then twice daily (morning and evening) for the following two days. Tablets should be taken with food.

Baseline Labs/Monitor: None.

Contraindications/Precautions: Contraindicated in patients hypersensitive to artemether or lumefantrine. Avoid use in patients with known QT prolongation, those with hypokalemia or hypomagnesemia, and those taking other drugs that prolong the QT interval.

Side Effects: The most common adverse reactions in adults (>30%) are headache, anorexia, dizziness, asthenia, arthralgia and myalgia.

1.2 Atovaquone+Proguanil (Malarone®)

Description: Combination tablet containing atovaquone 250 mg + proguanil 100 mg.

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 atovaquone and 400 mg of proguanil had a cure rate of 87% for chloroquine-resistant falciparum malaria.

Dose and Administration:

Prophylaxis: One tablet (250 mg/100 mg) taken orally, daily. Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas. Take with food or a milky drink.

Treatment: Four tablets (1000 mg/400 mg) taken orally per day for 3 days.

Baseline Labs/Monitor: None.

Contraindications/Precautions: Contraindicated in persons hypersensitive to either primary medication. Not recommended for women who are pregnant or lactating.

Side Effects: Well tolerated. Common effects include rash, nausea, diarrhea, headache, fever, and vomiting.

1.3 Chloroquine Phosphate

Description: 500 mg (300 mg base) tablet.

Product: A 4-aminoquinoline compound, chloroquine is a blood schizontocide active against *P. vivax*, *P. malariae*, and *P. ovale*. It has limited activity against most *P. falciparum* infections.

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

Dose and Administration:

Prophylaxis: One 500 mg tablet weekly beginning 2 weeks prior to arrival in the endemic area. Continue weekly dosing (on the same day of the week) while in and for 4 additional weeks after leaving high-risk area. (Note: If 2-week lead time is not possible, use a 3-day loading dose: 250mg daily for 3 days, then resume weekly dosing.)

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).

Baseline Labs/Monitor: Check G6PD status before starting.

Contraindications/Precautions: Not recommended for women who are pregnant or lactating, or for people with psoriasis, retinal/visual changes, or liver problems. Use caution if G6PD deficient.

Side Effects: The most frequent side effects include anorexia, nausea, vomiting, diarrhea, and abdominal cramping. Mild, transient headache, tinnitus, and deafness have been reported. Ocular reactions include blurred vision and reversible interference with visual accommodation or focusing. Long-term or high-dosage therapy may result in irreversible retinal damage. Chloroquine may cause hemolysis when administered to patients with G6PD deficiency, but reactions are not as severe as those seen with primaquine. Any G6PD-deficient service members needing chloroquine prophylaxis should be informed of side effects and advised to seek medical evaluation if they occur. For severe reactions, an alternate prophylactic regimen should be provided.

1.4 Doxycycline (many brand and generic names)

Description: 100 mg tablets.

Product: A widely used antibiotic useful as an antimalarial primarily for the prevention of *P. falciparum* infections.

Effectiveness: Doxycycline is indicated for the prophylaxis of malaria due to *P. falciparum*. It is less effective against *P. vivax* infections. It is effective against asexual, erythrocytic forms of *P. falciparum*, but not gametocytes of the sexual stage. It is also indicated for the treatment of resistant strains of falciparum malaria as part of a multi-drug regimen.

Dose and Administration:

Prophylaxis: 100 mg taken orally, daily. Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 4 weeks after leaving such areas. Do not take before going to bed.

Treatment: One tablet twice daily for 7 days (tetracycline, 250 mg four times daily may be substituted) as part of a multi-drug regimen is effective in areas with drug resistant strains of *falciparum* malaria. Most often used with mefloquine.

Baseline Labs/Monitor: BUN/Cr, CBC, LFTs if prolonged treatment.

Contraindications/Precautions: Persons with an allergy to tetracyclines, during pregnancy, and in infants and children <8 years of age.

Side Effects: Gastrointestinal (GI) symptoms are a common side effect of doxycycline that often leads to low compliance. Doxycycline monohydrate has fewer GI side effects than doxycycline hyclate. Side effects may be lessened if taken with a meal, but food and milk products can reduce absorption up to 20 percent. Antacids containing aluminum, calcium, magnesium, iron, or bismuth subsalicylate also interfere with absorption. Other side effects include photosensitivity, candidiasis, and headache. The sunburn reaction can be prevented by avoiding prolonged exposure to sunshine or by using a sunscreen.

1.5 Mefloquine (Lariam®)

Description: 250 mg tablets.

Product: An antimalarial drug effective against *P. falciparum* and *P. vivax* infections.

Effectiveness: Mefloquine HCL provides prophylaxis against chloroquine-resistant strains of *P. falciparum* and *P. vivax*. However, *P. falciparum* strains resistant to mefloquine have been reported.

Dose and Administration:

Prophylaxis: 228 mg base (250 mg salt) taken orally, once/week. Begin at least 2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas.

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.

Baseline Labs/Monitor: Liver function tests (LFTs), ophthalmological exams if long-term use.

Contraindications/Precautions: Contraindicated in persons allergic to mefloquine or related compounds (e.g., quinine, quinidine) and in persons with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in persons with psychiatric disturbances or a previous history of depression. Not recommended for persons with cardiac conduction abnormalities. Personnel on flight status and divers are prohibited from using mefloquine.

Side Effects: Rare serious adverse reactions (e.g., psychoses, seizures) at prophylactic doses; these reactions are more frequent with the higher doses used for treatment. Other more-severe neuropsychiatric disorders occasionally reported during post-marketing surveillance. Other side effects include GI disturbance, headache, insomnia, abnormal dreams, visual disturbances, depression, anxiety disorder, and dizziness.

1.6 Primaquine Phosphate

Description: 52.6 mg (30 mg base) tablet.

Product: Used for elimination of persistent *P. vivax* and *P. ovale* liver stage parasites. The drug eradicates hypnozoites that may remain dormant after treatment with other agents and can cause delayed attacks and relapse.

Effectiveness: Primaquine phosphate is indicated to prevent relapse of *P. vivax* and *P. ovale* malaria.

Dose and Administration:

Prophylaxis: Not indicated.

Treatment: When chloroquine, doxycycline, or mefloquine is used for primary prophylaxis, take 15 mg (base) orally, once/day for 14 days after departure from the malarious area. The sensitivity of *P. vivax* strains to hypnozoite eradication by primaquine varies among geographic regions. Treatment failures following the 15 mg (base) standard therapy have been demonstrated for the less-sensitive *P. vivax* strains found in New Guinea and other parts of the Pacific region. Heavier individuals (>80 kg) may be at increased risk for relapse

following the standard 15 mg (base) therapy. The CDC recommends 30 mg (base) primaquine for PART. Since the FDA-approved primaquine product label specifies 15 mg (base), the CDC's recommendation constitutes off-label use, an option individual providers can elect for their patients. However, DoD regulations prohibit off-label use of FDA-approved pharmaceuticals for FHP activities such as unit-level PART.

When atovaquone/proguanil is used for prophylaxis, primaquine may be taken during the final 7 days of atovaquone/proguanil, and then for an additional 7 days. It is preferable that primaquine be given concurrently with the primary prophylaxis medication. However, if that is not feasible, the primaquine course should still be administered after the primary prophylaxis medication has been completed.

Baseline Labs/Monitor: Glucose-6-phosphate dehydrogenase; a documented G6PD status in the medical record is required before starting primaquine. See Chapter 5 for details on G6PD deficiency and recommendations. Consult with the cognizant NEPMU or other authorities for further recommendations or questions as needed for PART.

Contraindications/Precautions: Contraindicated in persons with G6PD deficiency. Also contraindicated during pregnancy (even if a pregnant woman is G6PD normal, the fetus may not be) and lactation unless the infant being breastfed has a documented normal G6PD level.

Side Effects: Most common is GI upset. Severe side effects if G6PD deficient also has methemoglobinemia

1.7 Quinidine Gluconate

Description: 80 mg/ml (55 mg base/ml) intravenous solution available in 10 ml vials.

Product: Quinidine is a cinchona alkaloid, the dextrostereoisomer of quinine. It is used to treat cardiac arrhythmias. It is now the drug of choice for intravenous treatment of chloroquine-resistant *P. 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 plasmodia strains.

Dose and Administration:

Prophylaxis: Not indicated.

Treatment: Loading dose of 10 mg/kg (6.2 mg base/kg) given over 1–2 hours, followed by 0.02 mg salt/kg/min (0.0125 mg base/kg/min) continuous infusion for at least 24 hours. An alternative regimen is 24 mg salt/kg (15 mg base/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 9 hours after loading dose.

Baseline Labs/Monitor: It is strongly recommended that consultations with a cardiologist and a physician having experience treating severe malaria be made. Intravenous quinidine can safely be administered by monitoring ECG, blood pressure, and infusion rate. Quinidine blood levels should be kept between 3–7 mg/dl if monitored. Life-threatening arrhythmias are rare with proper doses, but infusion should be stopped temporarily if the ECG 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, quinidine, or mefloquine treatment within the preceding 24 hours.

Contraindications/Precautions: Quinidine is contraindicated in patients who are known to be allergic to it, or who have a history of immune thrombocytopenia or have developed thrombocytopenic purpura during prior therapy with quinidine or quinine. Quinidine is also contraindicated in patients with certain disturbances of cardiac rhythm (these patients would not normally be in a deployable status) and in patients who are known to be adversely affected by an anticholinergic agent. Patients may rarely develop cardiac rhythm disturbances when placed on quinidine, or may develop thrombocytopenia. Cases of renal and/or hepatic toxicity have been reported. Convulsions, syncope, ataxia, and anxiety have been reported.

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

1.8 Quinine (Qualaquin®)

Description: 325 mg capsules.

Product: Quinine, a cinchona alkaloid, was the first successful compound for treatment of malaria. It has been available for three centuries.

Effectiveness: Acts rapidly against asexual stages of all four 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 and Administration:

Prophylaxis: Not indicated.

Treatment: Adult – 650 mg, with doxycycline, tetracycline, or clindamycin, 3 times daily for 7 days.

Baseline Labs/Monitor: None.

Contraindications/Precautions: Quinine is contraindicated in patients with a prolonged QT interval or G6PD deficiency and is not recommended for use with other drugs known to cause QT prolongation.

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

APPENDIX 3: LABORATORY DIAGNOSTIC TECHNIQUES

1.1 Introduction

Several methods are now available for laboratory diagnosis of malarial parasites, but microscopic examination of peripheral blood smears remains the gold standard for laboratory confirmation of malaria. Microscopy requires skill and experience from the lab tech; therefore, in locations where malaria rarely occurs, it may be difficult for the laboratorian to diagnose. In order to simplify malaria diagnosis, in 2007 the FDA approved the use of the first RDT for detection of malaria in the United States. Polymerase chain reaction (PCR) can also be used to detect malaria parasites and is used primarily to confirm the parasite species after diagnosis has been made using an RDT or smear. Serological tests are used to detect past exposure to malarial parasites but do not detect current infections.

The NEPMUs offer training classes on preparation of thick and thin smears and microscopic examination for diagnosis of malaria. The following sections summarize thick and thin blood smear preparation for field reference.

1.1.1 Thick Smears

Red blood cells are hemolyzed in thick smears; leukocytes and any malaria parasites present are the detectable elements. The 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.

1.1.2 Thin Smears

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

1.2 Drawing Blood

Draw blood according to the following guidelines:

- Anytime malaria is suspected
- Repeat if smears are negative until malaria is either ruled in or out
- Maximum frequency: once per hour

1.3 Obtaining Blood

Guidelines for obtaining blood are as follows:

- 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
- Clean end of finger with disinfectant solution.
- Wipe fingertip with sterile material (remove remaining disinfectant that may interfere with diagnostic process).
- Pierce fingertip with sterile lancet.
- 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.

1.4 Slide Preparation (See Figure A3-1)

1.4.1 Thick Smear

- 1) 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.
- 2) Spread drop of blood with corner of another slide to make an area about 1 cm in diameter.
- 3) This is the thick smear. Correct thickness is attained when newsprint is barely legible through the smear.

1.4.2 Thin Smear

- 1) Touch a new drop of blood (smaller than the first) with the edge of a clean slide.
- 2) 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.
- 3) Holding the slide at an angle of 45° , push it forward with a rapid, gentle movement.
- 4) For preparation of separate slides for thick and thin smears, use a second slide in step 2.
- 5) Dry the smears. Air dry, allowing 10 minutes for the thin smear and 30 minutes for the thick smear.
- 6) 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.

1.4.3 Fixing Thin Smears

After drying, only thin smears are fixed. Fixing is done using methanol in one of two ways:

- 1) Dip thin smear into methanol for 5 seconds.
- 2) Dab thin smear with methanol-soaked cotton ball.

Do not fix the thick smear. Even exposure of the thick smear to methanol fumes will prevent 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.

1.5 Staining Slides

Giemsa stain is available in the military supply system, and this staining method is presented below. 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.

1.5.1 Preparation of 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 Schüffner's dots).
- 2) Prepare Giemsa staining solution by mixing the following:
 - 1 part unshaken Giemsa stain concentrate.
 - 9 parts buffered water.

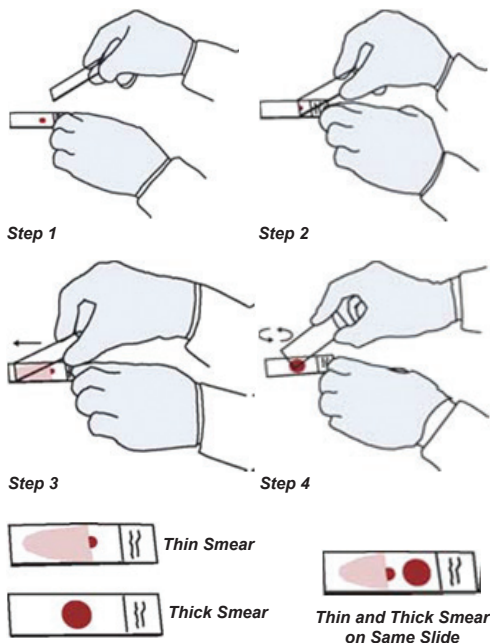
1.5.2 Slide Staining with Prepared Giemsa Solution

- 1) Place slides flat in a staining rack or other suitable surface.
- 2) Cover with 1–2 ml of Giemsa solution. Commercially available Giemsa stain may be used straight as long as it is at the correct PH of 7.2.
- 3) Let stand for 10 minutes.
- 4) Gently rinse by “floating” excess stain off slide with buffered water; be careful not to wash the blood smear away.
- 5) Rinse until no more stain is seen in solution.
- 6) Dry smear-side down, making sure that smear does not touch the slide rack or other surface used for drying.

1.6 Slide Preparation Pointers

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

Figure A3-1. Thick and Thin Blood Smear Preparation



1.7 Microscopic Examination of 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. Parasites are often not readily apparent, and quick visual scans are insufficient for diagnostic purposes. Table A3-1 shows selected microscopic characteristics of human malaria species.

Table A3-1. Selected Microscopic Characteristics

Species	Stages Found in Circulating Blood	Appearance of Red Blood Cells		Appearance of Parasites		
		Size	Stippling	Cytoplasm	Pigment	Number of Merozoites
<i>Plasmodium falciparum</i>	Trophozoites Gametocytes	Normal	Maurer's dots or clefts infrequently seen	Double dots in rings common, rings small and delicate	Black coarse and conspicuous in gametocytes	6-32 Avg=10-24
<i>Plasmodium vivax</i>	All: Schizonts Trophozoites Gametocytes	Enlarged, maximum size may be 1.5-2 times normal	Schüffner's dots may be present	Amoeboid trophs light blue, has irregular "spread out" appearance in troph stage	Golden-brown, inconspicuous	12-24 Avg=16
<i>Plasmodium ovale</i>	All: Schizonts Trophozoites Gametocytes	Enlarged, maximum size may be 1.25-1.5 times normal	Schüffner's dots may be present	Rounded, compact trophs, dark to medium blue, usually dense; chromatin is large	Dark brown, conspicuous	6-14 Avg=8
<i>Plasmodium malariae</i>	All: Schizonts Trophozoites Gametocytes	Normal	Ziemann's dots rarely seen	Rounded, compact trophs, dark blue with dense cytoplasm; band form trophs occasionally seen	Dark brown, coarse, conspicuous	6-12 Avg=8 "Rosette" occasionally seen

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

1.8 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 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 in those same visual fields.
- 3) If after 200 leukocytes have been identified and less than 9 malarial 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 have been counted, record the number of parasites counted per 200 leukocytes.
- 5) Once 500 leukocytes have been identified, record the number of parasites counted.
- 6) Convert the parasite count per leukocytes identified into parasite concentration per ml with one of the following formulas:

$$\frac{\text{Number of parasites}}{\text{Number of leukocytes counted}} \times 8000 = \text{parasites per ml}$$

or

if 200 leukocytes were counted:

$$\text{Number of parasites counted} \times 40 = \text{parasites per ml}$$

or

if 500 leukocytes were counted:

$$\text{Number of parasites counted} \times 16 = \text{parasites per ml}$$

- 7) All parasite species and forms are tabulated together. This includes both sexual (gametocytes) and asexual (trophozoites, merozoites) forms.

1.9 Percent Method (Thin Smear)

This method estimates the percentage of red blood cells infected with malarial 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:

$$\frac{\text{Red Blood Cells Parasitized}}{\text{Total Red Blood Cells Counted}} \times 100 = \text{Percent of Red Blood Cells Parasitized}$$

- 6) If occasional 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.

1.10 Rapid Diagnostic Tests

Rapid diagnostic tests are immunochromatographic tests that detect malaria antigens in blood, and some may be able to differentiate between certain species of malaria. Rapid diagnostic tests typically use test cards or cartridges, and while they do not require a standard cold chain, RDTs do typically require a “cool” chain and proper storage and handling to ensure test accuracy. Storage and handling requirements are specific to the type of RDT used. Performance may be limited in the diagnosis of certain malarial species and at lower levels of parasitemia. Directions for use are specific to the type of kit used and should be followed carefully. The only U.S. FDA-approved RDT available is the BinaxNOW® Malaria test kit.

A positive RDT provides useful information in confirming a diagnosis of malaria. *A negative RDT does NOT rule out malaria.* A negative result could be due to any number of factors, including failure of the test due to equipment/reagent degradation, procedural error, levels of parasitemia below the test’s threshold for detection, or an infecting species not reliably detectable by the test. The RDT should be repeated at intervals if diagnosis confirmation is desired, much in the same way

that microscopic examination of Giemsa-stained blood smears should be repeated until malaria is either ruled in or out.

1.11 Additional Shipping Instructions

In addition to forwarding prepared slides and additional blood to supporting NEPMUs and medical treatment facilities, DoD-GEIS has requested samples in order to conduct additional testing for the purpose of epidemiological analysis. The following is applicable to diagnosis and treatment in the field, and for DoD medical facilities providing post-deployment treatment to American servicemen returning from malaria-endemic areas that consider malaria in their differential diagnoses of fever-producing illnesses. To that end, the following information should be sought and provided with any shipped samples:

- 1) What medications are they taking? If they are taking chloroquine, mefloquine (Lariam), Malarone®, or doxycycline, what was the date of last dose?
- 2) Has a diagnosis of malaria been made? If so, document the basis for the diagnosis (i.e., has the blood slide been read by a competent microscopist to confirm diagnosis? Was a Dip-Stick used in diagnosis?).
- 3) Document the travel (exposure) history (i.e., has the service member been in malaria-endemic areas such as Africa, Iraq, Korea, Asia, or South America during the preceding 12–24 months?).

If any of these queries indicate a malaria etiology, it is requested that blood samples (2 EDDTA purple tops or 2 heparinized green top blood specimens [5 ml each]), be shipped on wet ice (not frozen) to the following address:

**DoD GEIS Malaria Drug Resistance Laboratory
Room 2N58
503 Robert Grant Avenue
Silver Spring, MD 20910-7500 USA**

Once received, blood drug levels will be determined and parasite cultures (in the case of *P. falciparum*) established. These will be used to determine drug susceptibility profiles. Molecular analysis of parasites will be conducted to determine malaria species, mixed-species infections, and presence of drug-resistance markers. This information will be added to the Worldwide Antimalarial Drug Resistance Network, which provides timely malaria surveillance information to guide policy planners and decision-makers on the optimal utilization of antimalarial drugs. Results will be reported as soon as possible to submitting stations. **Special attention is needed for suspected prophylaxis failures** (i.e., *P. falciparum* appearing within 7–14 days of last prophylaxis dose). Collection and shipment of those specimens are the same as the above. (Note: If the patient has already undergone therapy, the initial admission CBC tube should be sent with this specimen as well.)

Please notify the following individuals of pending shipments:

LTC Mark Hickman

email: mark.r.hickman@us.army.mil

Ms. Lucia Gerena

mail: lucia.gerena@na.amedd.army.mil

Dr. Thomas Hudson

email: Thomas.hudson@na.amedd.army.mil

LTC Mike O'Neil

email: michael.t.oneil@us.army.mil

DSN: 285-3070/9328/9415

Comm: (301) 319-3070/9328/9415

Senders are encouraged to also send this information to [NMCPHCPTS-ThreatAssessment@med.navy.mil](mailto:NMCPhCPTS-ThreatAssessment@med.navy.mil).

APPENDIX 4: SUPPLIES AND TRAINING AIDS

This section contains an extensive list of useful items available through the federal stock 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 NEPMU and/or Navy Entomology Center of Excellence (NECE) are excellent sources of advice regarding such situations.

Personal Protection Supplies NSN ITEM

- | | |
|-------------------|---|
| 6840-01-345-0237 | Insect repellent, clothing application, Permethrin, IDA Kit, 12 kits per box. |
| 6840-01-493-7334 | Insect Repellent, Personal Application & Camouflage Face Paint (New CFP w/DEET). |
| 6840-01-278-1 336 | Insect repellent, clothing, Permethrin aerosol, 6 ounce can. |
| 6840-01-284-3982 | Insect repellent, personal, 33 percent DEET, 2 ounces. |
| 7210-00-266-9736 | Insect Net Protector, Field Type, MIL -I-10901, 200" X 68", wt 1lb. Used to protect personnel from insects while sleeping. Mildew resistant nylon fabric. |
| 721 0-00-267-5641 | Wood Poles, (for suspending insect Net Protector). |

- 3740-01-516-4415 Bed net, Pop-up, self-supporting low profile bed net (SSLPB). Green Camouflage, treated w/ permethrin repellent.
- 3740-01-518-7310 Bed net, Pop-up, self-supporting low profile bed net (SSLPB). Coyote Brown, treated w/permethrin repellent.
- 3740-01-483-2988 Jacket, Bug-Out outer wear, size Small, P/N 5460A – Navy has item marked for disposal acquisition advice code Y terminal item, but available though all other Services.
- 3740-01-483-3002 Jacket, Bug-Out outer wear, size Med, P/N 5460B.
- 3740-01-483-3004 Jacket, Bug-Out outer wear, size Lrg, P/N 5460C.
- 3740-01-483-3007 Jacket, Bug-Out outer wear, size XLrg, P/N 5460D.
- 3740-01-483-3008 Jacket, Bug-Out outer wear, size XXLrg, P/N 5460E.
- 8415-00-935-3130 Insect Bar, Head Net. Used to protect head and neck from mosquitoes. 30" X 20," wt 1 lb. MIL-I-11489.

Antimalarial Drugs

- 6505-01-491-9430 Atovaquone 250mg – Proguanil 100 mg tablets, 100's
- 6505-00-117-6147 Tetracycline hydrochloride 250 mg capsules, 100s,

6505-00-117-6450	Chloroquine phosphate 500 mg tablets, 500's
6505-01-348-2465	Primaquine phosphate 26.3 mg tablets, 100's
6505-00-957-9532	Quinine sulfate 325 mg capsules, 100's
6505-01-095-4175	Doxycycline hyclate 100 mg tablets, 50's
6505-00-864-6298	Quinidine gluconate injection 80mg, 10 ml vials
6505-01-315-1275	Mefloquine hydrochloride 250 mg tablets, 25's
6505-01-573-6500	Artemether 20 mg – Lumefantrine 120 mg (Coartem®) tablets, 24's

APPENDIX 5: GLOSSARY

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. Chemoprophylaxis is 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.”

Directly Observed Therapy (DOT) – most effective method of ensuring drug compliance, where drug administration is observed by an appointed authority.

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).

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 mosquito’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.

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

Hepatocytes – liver cells.

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.

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.

Lemon-Eucalyptus Oil – an insect repellent registered by the EPA that contains oil from the leaves of eucalyptus trees. Products contain a range of 30 to 40 percent of the active ingredient.

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.

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.

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.”

Presumptive Anti-Release Therapy (PART) – treatment of the dormant liver stage of patients infected with *P. vivax* or *P. ovale*.

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.

Picaridin – an insect repellent registered by the EPA. This is a colorless, nearly odorless liquid active ingredient that is used as an insect repellent against biting flies, mosquitoes, chiggers, and ticks. Products contain a range of 5 to 20 percent of the active ingredient.

Presumptive Treatment – administration of antimalarial drugs in suspected cases before results of laboratory tests are available to confirm diagnosis. See “PART.”

Prophylaxis – see “chemoprophylaxis.”

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

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

Rapid Diagnostic Test – immunochromatographic tests that detect malaria antigens in blood and some may be able to differentiate between certain species of malaria.

Recrudescence – reappearance of *P. falciparum* due to insufficient treatment or drug resistant parasites.

Relapse – a repeated attack weeks, months, or sometimes years after initial *P. vivax* or *P. ovale* infection. Due to re-infection of red blood cells from malaria parasites (hypnozoites) that persisted in liver cells (hepatocytes).

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.

Severe Malaria – complicated malaria.

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

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.”

Terminal Prophylaxis – chemoprophylaxis given to individual at the time that they leave areas that are endemic for *P. vivax* and *P. ovale*. Terminal prophylaxis is necessary in order to destroy the stages of these species that may be dormant in the liver. Terminal prophylaxis now is referred to as Presumptive Anti-Relapse Therapy (PART).

Trophozoite – early developmental stage of blood schizont.

ACRONYMS

ABU	Airman Battle Uniform
AFRICOM	United States African Command
ARDS	Acute Respiratory Distress Syndrome
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
DNBI	Diseases and Non-Battle Injuries
DoD	Department of Defense
DOT	Directly Observed Therapy
DRSi	Disease Reporting System Internet
EHRA	Environmental Health Risk Assessment
FDA	U.S. Food and Drug Administration
FDPMU	Forward Deployable Preventive Medicine Unit
G6PD	Glucose-6-Phosphate Dehydrogenase
GI	Gastrointestinal
IDA	Individual Dynamic Absorption
IDRA	Infectious Disease Risk Assessment
LFTs	Liver Function Tests
MEDIC	Medical Environmental Disease Intelligence and Countermeasures
MER	Medical Event Report
MEU	Marine Expeditionary Unit
MTF	Medical Treatment Facility
NCMI	National Center for Medical Intelligence
NCOs	Non-Commissioned Officers
NECE	Navy Entomology Center of Excellence
NEPMU	Navy Environmental and Preventive Medicine Unit
NMCI	Navy/Marine Corps Intranet
NMCPHC	Navy and Marine Corps Public Health Center
NWU	Navy Working Uniform
PART	Presumptive Anti-Release Therapy
PCR	Polymerase Chain Reaction
PCWP	Pulmonary Capillary Wedge Pressure
PMD	Methyl Ester Menthane Diol
PMO	Preventive Medicine Officer

PMTs.	Preventive Medicine Technicians
RDT	Rapid Diagnostic Test
VECTRAPS	Vector Risk Assessment Profiles
WHO.....	World Health Organization

INDEX

acute renal insufficiency	38
acute tubular necrosis	36
anemia.....	5, 35, 36, 37, 39, 48, 50, 52, 53
arrhythmias.....	78, 79
artemisinin	51, 70
atovaquone.....	23, 24, 25, 49, 51, 69, 71, 77, 95
aviators	22
bed nets.....	17, 20, 21
blackwater fever	38
blood schizontocides	23, 69, 70
blood smears	40, 42, 44, 58, 81, 91
breeding sites	11, 27, 29
cerebral malaria.....	35, 36
chemoprophylaxis.....	iii, 3, 13, 21, 22, 23, 24, 39, 53, 55, 56, 57, 58, 60, 62, 63, 72, 94, 97, 99, 100
chloroquine.....	24, 25, 48, 49, 50, 53, 69, 71, 72, 73, 75, 76, 78, 91, 96
chloroquine-resistant <i>P. falciparum</i>	49, 78
cinchonism.....	79, 80, 97
citronella	15
coma.....	32, 35, 48, 52
compliance	3, 15, 62, 74, 97
convulsions.....	32, 48, 52, 79
cough.....	33, 34, 37
countermeasures.....	1, 3, 13, 14, 25, 55, 56, 57, 58, 67, 101
cyanosis.....	34
DEET	15, 16, 17, 20, 61, 94
dehydration.....	38
Directly Observed Therapy.....	23, 97, 101
DNBI.....	55, 57, 58, 101
dormant	4, 5, 6, 7, 22, 30, 44, 47, 50, 69, 72, 76, 99, 100
DOT	23, 24, 56, 97, 101
doxycycline	24, 25, 49, 51, 53, 73, 74, 76, 80, 91, 96
drug resistance	1, 10, 21, 24, 48, 49, 97
eosinophilia.....	38
erythrocytes	7, 82, 97, 98

erythrocytic	5, 7, 8, 10, 23, 73, 97
exoerythrocytic	6, 7, 10, 23, 69, 97, 99
exposure	14, 22, 23, 27, 28, 30, 32, 45, 46, 53, 74, 81, 84, 91, 97
falciparum malaria	4, 8, 24, 34, 36, 43, 44, 45, 49, 51, 71, 73, 74, 78
G6PD	2, 22, 36, 50, 52, 53, 54, 60, 73, 77, 80, 101
gametocytes	73, 87, 89, 97
gastrointestinal	33, 74, 79, 101
Giemsa	84, 85, 91
glucose	2, 22, 32, 35, 38, 44, 50, 52, 53, 77, 101
hematocrit	36, 38
hemodynamics	37
hemoglobin	36, 38, 48, 52
hemoglobinuria	32, 36, 38, 48, 52
hemolysis	36, 37, 38, 73, 81, 82, 84, 98
hyperparasitemia	32, 40, 52
hypersensitivity	79
hyperthermic	34
hypnozoites	7, 22, 44, 47, 50, 69, 72, 76, 98, 99, 100
hypnozoitocidal drugs	69
hypoglycemia	32, 35, 38, 39, 52, 80
hypotension	34, 36, 48, 52, 79
insecticide	17
kidneys	43
knobs	43
laboratory personnel	58, 59
larval	59
leukopenia	37, 39
life cycle	1, 2, 5, 9, 69, 97, 98
lysis	33
macrogametocytes	8, 97
Malarone®	23, 25, 71, 91
medical intelligence	2, 12, 14, 56, 57, 64, 67
mefloquine	22, 24, 25, 49, 51, 53, 69, 74, 75, 76, 79, 91, 96
merozoites	6, 7, 8, 10, 23, 87, 89, 98, 100
microgametocytes	8, 97
microvascular	35, 40, 43

mosquito control	28, 55
nasogastric	70
netting.....	15, 19, 20, 26, 27, 61
neurologic.....	36
ookinetes	8
orthostatic hypotension.....	34
oxidant.....	36
parasitemia.....	31, 38, 41, 42, 45, 48, 80, 88, 90, 99, 100
parasites.....	1, 7, 8, 22, 23, 36, 43, 44, 45, 47, 52, 53, 61, 62, 72, 76, 81, 82, 85, 86, 87, 88, 89, 90, 92, 97, 98, 99, 100
Permethrin.....	17, 26, 94
personal protective measures	2, 3, 4, 14, 15, 20, 21, 26, 55, 56, 57, 58, 59, 61, 66
<i>P. falciparum</i>	iii, 4, 5, 6, 7, 8, 10, 11, 12, 21, 24, 31, 33, 34, 35, 36, 38, 40, 42, 43, 44, 45, 46, 48, 49, 50, 51, 70, 72, 73, 75, 78, 80, 92, 97, 100
<i>P. knowlesi</i>	5, 10, 24, 46, 47
plasmodium	2, 5, 6, 13, 22, 36, 40, 42, 43, 44, 45, 46, 47, 69, 80, 87
<i>P. malariae</i>	5, 6, 7, 8, 10, 21, 24, 33, 36, 45, 46, 47, 51, 72
<i>P. ovale</i>	3, 5, 6, 7, 8, 10, 21, 22, 24, 25, 30, 33, 36, 44, 45, 47, 50, 51, 53, 69, 72, 76, 98, 99, 100
Primaquine	25, 50, 69, 72, 76, 96, 98
Proguanil	69, 71, 95
protective clothing.....	15, 18, 19
proteinuria.....	38
prothrombin time.....	38
psychiatric.....	75
<i>P. vivax</i>	iii, 3, 5, 6, 7, 8, 10, 11, 12, 21, 22, 24, 25, 30, 31, 33, 36, 44, 45, 47, 49, 50, 51, 53, 69, 72, 73, 75, 76, 98, 99, 100
QT.....	70, 78, 79, 80
quinidine	51, 69, 75, 78, 79, 96, 97
quinine.....	49, 50, 69, 75, 78, 79, 80, 96, 97
radical cure.....	72, 97
recrudescence.....	45, 100
relapses.....	10, 25, 44, 45
repellents.....	15, 16, 17
reticulocytes.....	10, 36, 45

reticulocytosis	39
schizogony	6, 7, 8, 98, 100
seizures	34, 35, 52, 75, 76
side effects	61, 69, 73, 74, 76, 77, 79, 80, 97
spleen	34, 35, 44, 99
splenomegaly	5
sporogony	9, 11
sporozoites	6, 7, 9, 98, 100
surveillance	3, 29, 56, 57, 58, 76, 92
systolic	52
tachycardia	34
terminal primaquine prophylaxis	2, 3
tetracycline	49, 51, 74, 80, 95
thick smears	81, 82, 88
thin smears	40, 81, 82, 83, 84, 88
thrombocytopenia	37, 39, 79
tissue schizontocides	69
transfusion	5, 62
transmission	1, 5, 10, 11, 24, 27, 32
trophozoites	7, 87, 89
uniform	17, 18, 19, 20, 26, 101
unit protective measures	25
urinalysis	38
urticaria	79, 80
VDRL	39
vectors	1, 14, 29, 66
vector surveillance	56, 58

