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MALARIA PREVENTION

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Hello, I am Dr. Mary Vaeth with the Staff Assistance and Training Team of the Deployment Health Clinical Center. In this presentation, I am going to discuss malaria and malaria prevention. The objectives for this presentation are to:

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- Describe the geographic distribution and risk factors for malaria
- Review the classification and life cycle of the malaria parasite
- Describe personal protective measures for malaria prevention, and
- Discuss malaria chemoprophylaxis

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Malaria is one of the most common parasitic infections in the world and a major international public health problem. Malaria incidence has increased over the last 40 years. The World Health Organization now estimates that about 300 to 500 million individuals are infected annually, 90% of them in sub-Saharan Africa. Malaria infection results in more than 1 million deaths each year, mostly in infants and children. This makes malaria one of the major killers. The malaria problem has worsened in many parts of the world because of development of resistance to control measures in the parasite and the mosquito vector, socioeconomic problems and movement of nonimmune populations into malarious areas. In addition to movements of displaced persons and refugees, tourist and official travel to malarious areas has been increasing. Each year many international travelers fall ill with malaria while visiting countries where the disease is endemic, and well over 10,000 fall ill after returning home. This has resulted in an increase in cases of malaria imported into countries where malaria does not occur naturally. Consequently, healthcare providers should be aware that fever occurring in a traveler up to one year after leaving a malarious area should be investigated urgently. Early diagnosis and appropriate treatment can be life saving.

Malaria strikes during war, during deteriorating social and economic conditions, and after natural disasters, all situations where the military is called to serve. Therefore, implementation of an effective malaria prevention program is critical to maintaining a healthy and effective military force.

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Malaria transmission occurs in large areas of Central and South America, Hispaniola (Haiti and the Dominican Republic) Africa, Asia (including the Indian Subcontinent, Southeast Asia, and the Middle East), Eastern Europe, and the South Pacific.

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It is currently endemic in over 100 countries, threatening the lives of more than 1/3 of the world's population.

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Malaria is both an acute and chronic disease caused by protozoa of the genus *Plasmodium*. The malaria parasite is transmitted by the bite of the female *Anopheles* species mosquito, which bites mainly between dusk and dawn.

Throughout the world, each species of *Anopheles* is peculiar to a localized area. Of the four hundred *Anopheles* species, about sixty are proven carriers of the malaria parasite. Mosquitoes prey on a variety of hosts, including humans, monkeys, lizards and birds. The mosquitoes carry malaria parasites that are specific to each host. Of the 156 named species of Plasmodium parasites that infect various species of vertebrates, only four infect humans:

- *P. falciparum*
- *P. vivax*
- *P. ovale*
- *P. malariae*

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In addition to transmission by mosquitoes, malaria can be transmitted from an infected person to another person through:

- Blood transfusion
- Needle sharing for intravenous drugs
- Organ transplant
- Congenitally from mother to fetus

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The estimated risk for acquiring malaria varies widely from country to country and even between areas in a given country. The risk depends on the intensity of transmission within a given region and the traveler's itinerary, length of time and type of travel. Transmission of malaria is higher in Africa than in other parts of the world. In many endemic countries, except Africa and India, the main urban areas are free of malaria transmission. The risk of infection is highest at the end of the rainy season when mosquitoes are the most plentiful. Malaria is usually restricted to altitudes below 1500 meters because the lower temperatures at higher altitudes decrease the mosquito population and arrest the development in the mosquito gut, but in favorable climatic conditions it can occur at altitudes up to almost 3000 meters.

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Prevention and treatment of falciparum malaria are becoming more difficult because *P.falciparum* is becoming increasingly resistant to various anti-malarial drugs. Resistance of *P. falciparum* to chloroquine has been confirmed in all areas with *P. falciparum* malaria except the Dominican Republic, Haiti, Central America west of the former Panama Canal Zone, Egypt, and some countries in the Middle East.

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In addition, resistance to Fansidar is widespread in the Amazon River Basin area of South America, much of Southeast Asia, other parts of Asia, and, increasingly, in large parts of Africa. Resistance to mefloquine has been confirmed on the borders of Thailand with Myanmar (formerly Burma) and Cambodia, in the western provinces of Cambodia, and in the eastern states of Myanmar (Burma).

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Of the other malaria species, drug resistance has to date been reported for *P. vivax,* mainly from Indonesia and Papua New Guinea. *P. vivax* with declining sensitivity has been reported for Brazil, Colombia, Guatemala, India, Myanmar, the Republic of Korea, and Thailand.

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P. malariae resistant to chloroquine has been reported from Indonesia.

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The malaria parasite is a protozoa, or single-celled animal – not to be confused with a bacterium, which belongs to the plant kingdom. The parasite has a complex life cycle, reproducing in three cycles in the human liver, then the red blood cells and finally in the mosquito. The life cycle involves a mosquito vector and a human host.

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A human infection begins with the bite of an infected female *Anopheles* mosquito. As the mosquito sucks human blood to nourish her eggs, she injects saliva containing malaria parasites into the person's bloodstream. These malaria organisms, called sporozoites, remain in the bloodstream for only a short period of time, usually less than an hour. They disappear from the bloodstream into the cells of the liver, where they begin to reproduce in cycles, a process lasting from six to twelve days, depending on the species.

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This stage corresponds to the incubation period of the disease. Sporozoites of *P. falciparum* and *P. malariae* immediately begin reproducing as soon as they enter the liver and only reproduce for one generation. For persons infected by *P. falciparum* and *P. malariae*, suppressive medication will eliminate the parasites from the red blood cells, and because there are no new parasites released from the liver, the infection will be completely cured.

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However, *P. vivax* and *P. ovale* enter the liver cell as two different forms of sporozoites: one strain immediately begins to reproduce while the other (called hypnozoite from the Greek hypno=sleep and zoon=animal) lies dormant in the liver cell. The hypnozoites enter into reproductive phases at different times, even after months or years, depending on the species, and therefore are responsible for the well-known relapses of *P. vivax* and *P. ovale*. These relapses may persist for months or years despite anti-malarial treatment.

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The increased pressure of the thousands of tiny new parasites called merozoites that have formed by reproduction in the liver cause them to burst from the liver into the bloodstream where they penetrate red blood cells. This may take as little as 8 days or as many as several months. Once inside the red blood cells, the parasites grow and multiply in cycles. When the infected red blood cells burst, the merozoites pour into the bloodstream and invade fresh red blood cells to start new cycles of reproduction. These cycles repeat themselves every two to three days depending on the species.

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The cyclic release into the circulation of so many parasites - estimated at a quarter of a billion – coincides with the characteristic clinical symptoms of malaria: periodic high fever preceded by shivering and followed by profuse sweating.

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Rather than dividing, some merozoites in the red blood cell transform themselves into sexual cells or gametocytes that can only mature outside the human body. During evolution, a relationship developed between the malaria parasite and the *Anopheles* mosquito in which the female mosquito requires blood for the protein she needs to lay her eggs, and the parasite requires a host in which it can reproduce. When the female *Anopheles* mosquito bites an infected person, the gametocytes mature in the intestine of the mosquito and a fertilized egg is produced that gives rise to thousands of new sporozoites. These sporozoites migrate to the mosquito's salivary gland, waiting to be injected into her next victim. This process takes a week or more.

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The four principles of malaria protection are:

Be **A**ware of the risk, the incubation period, and the main symptoms

Avoid **B**eing bitten by mosquitoes, especially between dusk and dawn

Take anti-malarial drugs (**C**hemoprophylaxis) to suppress infection when appropriate

Immediately seek **D**iagnosis and treatment if a fever develops one week or more after entering an area where there is a malaria risk, and up to 1 year after departure

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Because *Anopheles* mosquitoes feed at night, malaria transmission occurs primarily between dusk and dawn. Taking protective measures to reduce contact with mosquitoes, especially during these hours, is key in preventing malaria infection. Preventive measures include: remaining in well-screened areas when possible; wearing clothing that leaves as little exposed skin as possible; using insect repellent containing DEET on exposed skin, and using mosquito nets.

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Service members deploying to malarious areas should use the DoD Insect Repellent System that includes:

Wearing permethrin-treated uniforms with trousers bloused and sleeves down

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Using DEET on exposed skin. When using DEET and sunscreen, the sunscreen should be applied first, then wait 30 to 60 minutes before applying the DEET, and finally

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Sleeping under a permethrin-treated bed net

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Chemoprophylaxis is a broad term comprising multiple strategies for the prevention of disease using medications. Primary prophylaxis is the strategy that uses medications prior to, during, and after the exposure period to prevent the initial infection. Terminal prophylaxis is the strategy that

uses medications toward the end of the exposure period (or immediately thereafter) to prevent relapses or delayed-onset of clinical presentations.

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The elaborate life cycle of *Plasmodium* species complicates prophylaxis. Anti-malarial drugs actually act to suppress the clinical symptoms of malaria, not prevent the establishment of malaria infection. If anti-malarial drugs were truly prophylactic, they would prevent malaria infection by killing the parasites the moment they were introduced into the bloodstream by the mosquito bite. There is currently no drug that can absolutely prevent infection by killing sporozoites. Instead, anti-malarial drugs act by eliminating the parasites during their multiplication phase in the red blood cells. This keeps the number of parasites in the blood at a low enough level to prevent symptoms. If taken long enough in adequate doses, these drugs suppressive medications eventually eliminate infections caused by *P. falciparum* and *P. malariae* but will not always prevent a delayed first attack or relapses caused by *P. vivax* and *P. ovale*, which may appear months or years after discontinuing the suppressive drug. This fact explains why malaria "prophylaxis" must continue for a period after departure from the malarious area. In addition, terminal prophylaxis with primaquine is necessary to eliminate the liver stage parasites of *P. vivax* and *P. ovale*.

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The choice of malaria chemoprophylaxis medications is based on:

Type of malaria
Drug resistance in specific locations
Any allergic or other reaction to the anti-malarial drug of choice, or restriction by job (e.g., mefloquine is not authorized for prophylaxis in aviators and divers.)

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Depending on the area visited, the recommended prophylaxis may be:

Chloroquine
Mefloquine (Lariam and generic)
Doxycycline
Atovaquone/proguanil (Malarone)

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Malaria chemoprophylaxis with chloroquine or mefloquine should begin 1 to 2 weeks before travel to malarious areas. Prophylaxis with doxycycline and atovaquone-proguanil can begin 1 to 2 days prior to travel. Beginning the drug before travel allows the antimalarial to be in the blood before exposure to the malaria parasite. Chemoprophylaxis can be started earlier if there are particular concerns about tolerating one of the medications. Starting the medication 3 to 4 weeks in advance allows potential adverse events to occur prior to travel. Should unacceptable side effects develop, there would be time to change the medication prior to departure. Antimalarial drugs are generally well tolerated. However, side effects can occur. Minor side effects usually do not require stopping the drug. When prescribing antimalarial drugs, healthcare providers should find out whether the traveler has ever had an allergic or other reaction to any of the antimalarial drugs of choice and whether medical care will be readily accessible during travel.

Chemoprophylaxis should continue during travel and after leaving the malarious areas. Chloroquine, mefloquine, and doxycycline must be taken for 4 weeks after travel and atovaquone-proguanil must be taken for 7 days after travel. Drugs with longer half-lives, which are those drugs that are taken weekly, provide a wider margin of error if the traveler is late with a dose than drugs with short half-lives that are taken daily. For example, being 1 to 2 days late with

a weekly drug, prophylactic blood levels should remain adequate; however being 1 to 2 days late with a daily drug, protective blood levels are less likely to be maintained.

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Now, I will briefly review the following antimalarial medications:

- Chloroquine
- Mefloquine
- Doxycycline
- Atovaquone-proguanil (Malarone)
- Primaquine

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For travel to areas where chloroquine-resistant *P. falciparum* has NOT been reported, once-a-week use of chloroquine alone should be recommended for primary prophylaxis. The adult dose is one 500mg tablet per week, which provides 300 mg of base. It should be started 1 to 2 weeks before entering the malarious area and continued until 4 weeks after leaving the malarious area. Chloroquine can be used in travelers of any age as well as in women who are pregnant or breast-feeding. Insufficient amounts are excreted in breast milk to protect infants who are breastfeeding however, so they must take the drug directly. Chloroquine must be kept out of the reach of children because an overdose can be fatal. Chloroquine is generally well tolerated with few side effects. Side effects that can occur include; gastrointestinal disturbance, headache, dizziness, blurred vision, insomnia, and pruritus, but generally these effects do not require that the drug be discontinued. Chloroquine and related compounds have been reported to exacerbate psoriasis. For those who may get mild gastrointestinal upset, chloroquine can be taken with meals. As an alternative, the related compound hydroxychloroquine sulfate (Plaquenil) may be better tolerated. For those unable to take chloroquine or hydroxychloroquine, alternative medications are doxycycline, atovaquone/proguanil or mefloquine.

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For individuals traveling to a chloroquine-resistant area, the choice is primarily between mefloquine, doxycycline, and the newer drug Atovaquone-Proguanil, or Malarone.

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I'll begin by discussing mefloquine. The adult dose of mefloquine is one 250mg tablet weekly. It should be started 1 to 2 weeks before travel and continued once a week, on the same day of the week during travel and for 4 weeks after leaving the malarious area. Mefloquine is safe for use in the second and third trimesters and inadvertent use in the first trimester has resulted in no statistically significant difference in spontaneous abortions or malformations. Breastfeeding women can also take mefloquine, but again the baby must take his or her own separate dose.

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Malaria prophylaxis with mefloquine has been well tolerated by most persons. The use of mefloquine, however, is contraindicated in patients with know hypersensitivity to mefloquine or related compounds, for example quinine and quinidine. Mefloquine should also not be prescribed for prophylaxis in patients with active depression or recent history of depression; generalized anxiety disorder, psychosis or schizophrenia or other major psychiatric disorders; or with a history of seizure disorder or epilepsy.

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Clinicians must also be aware of the following cautionary warnings regarding the use of mefloquine. When used for prophylaxis mefloquine may cause psychiatric symptoms at a rate of

one per 2,000-13,000 persons. These symptoms include anxiety, paranoia, depression, hallucinations and psychotic behavior. Rarely these symptoms have been reported to continue after mefloquine has been stopped. Rare cases of suicidal ideation and suicide have been reported although no relationship to drug administration has been confirmed. Patients should be advised that if they experience psychiatric symptoms such as excessive acute anxiety, depression, restlessness or confusion, these may be considered prodromal to a more serious event related to mefloquine. In these cases, the drug must be discontinued and an alternative medication should be substituted.

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The Food and Drug Administration has developed a Medication Guide to provide consumers with information about the risks and benefits of mefloquine and as of July 2003 healthcare providers prescribing mefloquine are required by law to provide the patient with a copy of the Medication Guide.

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Now I'll discuss doxycycline. Doxycycline is recommended for individuals going to chloroquine resistant areas who cannot take mefloquine, either because of contraindications or because they are traveling to an area with mefloquine resistance. The dose is one 100 mg capsule per day, starting one to two days before entry into the malarious area and continuing for four weeks after departure. The fact that doxycycline is a daily drug may lower compliance, as may some of its possible side effects, including GI upset and photosensitivity, for which sunscreen is recommended. Doxycycline must be taken with sufficient fluid to ensure that the capsule is washed into the stomach to avoid esophageal ulceration, which occurs, but rarely. It can be taken with food to reduce the GI side effects. Women who take doxycycline may be at risk for vaginal yeast infection and may want to carry a course of treatment with them when they travel. Doxycycline's effectiveness is equivalent to that of mefloquine and chloroquine (in chloroquine-sensitive areas), that is, greater than 90% and often approaching 100%. Doxycycline should not be taken by children age 8 or younger or by pregnant or lactating women because of staining of teeth in the child or fetus.

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Atovaquone/proguanil is a fairly new malaria medicine, which is a fixed combination of 250mg atovaquone and 100mg proguanil. The dose is one tablet daily, beginning one to two days before entry into the malarious area and continuing until only 7 days after exiting. Though compliance with the daily dose may not be complete, compliance compared to doxycycline may be better because of the shorter post-exposure regimen. Unlike proguanil, absorption of atovaquone from the GI tract is poor, but increases with a fatty meal, so the drug should be taken with food or a milky drink. The most common adverse effects that have been reported are abdominal pain, nausea, vomiting, and headache. It should not be used in children less than 11 kilograms, pregnant women, women breast-feeding infants weighing less than 11 kilograms, or patients with severe renal impairment.

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Malaria infection in pregnant women can be more severe than in nonpregnant women. Malaria can increase the risk for adverse pregnancy outcomes, including prematurity, abortion, and stillbirth. For these reasons and because no chemoprophylactic regimen is completely effective, women who are pregnant or likely to become pregnant should be advised to avoid travel to areas with malaria transmission if possible.

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None of the drugs discussed so far can eradicate the liver stage of *P. vivax* or *P. ovale*, that can cause relapses for as long as 4 years or more after routine chemoprophylaxis is discontinued. Terminal prophylaxis with primaquine decreases the risk of relapses by acting against the liver stage. It is administered as a 14 day course typically taken during the last 2 weeks of the 4 week post-exposure course of chemoprophylaxis. When atovaquone/proguanil is used for primary prophylaxis, primaquine may be taken either during the final 7 days of atovaquone/proguanil and then for an additional 7 days, or for 14 days after the other medication has been completed. The Centers for Disease Control and Prevention have recently increased the recommended dose of primaquine for terminal prophylaxis from 15 mg to 30 mg for adults.

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Primaquine can be taken with food to lessen possible GI distress. Most persons can tolerate the standard regimen of primaquine, the exception being persons who are G6PD deficient. Primaquine can cause hemolysis in G6PD deficient individuals so testing may be advisable before prescribing the drug. G6PD is an inherited sex-linked trait with full expression in males that occurs most frequently in persons of African, Mediterranean, and Asian ancestry. In the Mediterranean and Canton variants, hemolysis is more severe and can continue even after discontinuation of the drug in contrast to the other variants in which hemolysis is usually self-limited.

Because most malarious areas of the world (except Haiti and the Dominican Republic) have at least one species of relapsing malaria, individuals who travel to these areas have some risk for acquiring either *P. vivax* or *P. ovale*, although the actual individual risk is difficult to define. Terminal prophylaxis is generally indicated only for persons who have had prolonged exposure in malaria-endemic areas.

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Persons who have been in a malaria risk are not allowed to donate blood for a period of time after returning from the malarious area in order to ensure that donated blood is not contaminated with malaria parasites. The Standards for Blood Bank and Transfusion Services requirements are as follows:

Persons who are residents of nonmalarious countries are not allowed to donate blood for 1 year after returning from a malarious area

Persons who are residents of malarious countries are not allowed to donate blood for 3 years after leaving a malarious area

Persons who have had malaria are not allowed to donate blood for 3 years after completion of treatment for malaria

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Sources of information on the geographic risk of malaria and guidelines for malaria prophylaxis include:

Centers for Disease Control and Prevention

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World Health Organization
Navy Environmental Health Center

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US Army Center for Health Promotion and Preventive Medicine
Armed Forces Medical Intelligence Center

Website addresses for these organizations are listed on the accompanying slide.

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Information on malaria can also be obtained from the Deployment Health Clinical Center's website: PDHealth.mil.

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