Peace Corps
Technical Guideline 840

PREVENTION OF MALARIA

1. PURPOSE

To provide Peace Corps Medical Officers (PCMOs) with guidance on malaria prevention for Volunteers.

2. BACKGROUND

Malaria is a mosquito-borne parasitic disease endemic to many areas of the world served by Peace Corps Volunteers. It is a serious and sometimes fatal disease. As such, the Office of Medical Services (OMS) employs a comprehensive prevention program to prevent malaria in Volunteers. Medical officers and Volunteers are required to rigorously adhere to the components of the program. Components of the program include:

- *Primary prevention:* the provision of personal protective equipment, i.e., mosquito nets, insect repellent, and insect spray to all Volunteers serving in malaria endemic areas. Screening on windows and doors of Volunteer living areas is strongly encouraged.
- *Secondary prevention:* the provision of malaria chemoprophylaxis, including post-departure prophylaxis and presumptive anti-relapse therapy (PART) when indicated, to all Volunteers serving in malaria endemic areas.
- *Education:* the provision of education to PCMOs and Volunteers on malaria prevention measures, including mosquito avoidance strategies and the proper use of chemoprophylactic medication.
- *Policy:* OMS policy that requires all Volunteers serving in malaria endemic areas to rigorously adhere to malaria prevention measures, i.e., use of personal protective equipment and chemoprophylaxis, throughout their tour of duty.

The OHS Epidemiology and Surveillance Unit coordinates Peace Corps malaria case surveillance.
Specific guidance on the diagnosis and treatment of malaria is addressed in Technical Guideline 845 "Treatment of Malaria."

3. GENERAL CONSIDERATIONS

Malaria is caused by one of five protozoan species of the genus Plasmodium: *P. falciparum, P. vivax, P. ovale, P. malariae, and P. knowlesi*. All are transmitted by the bite of an infected female *Anopheles* mosquito. *P. falciparum* is the most dangerous species among the five. It poses the greatest risk of death to non-immune persons and is the species most likely to develop resistance to antimalarial drugs. *P. vivax* and *P. ovale* have a dormant liver phase

that may persist in the liver for up to four years and cause recurrences after routine chemoprophylaxis is discontinued. PART is used to eradicate these species from the liver and prevent late relapses of malaria. *P. malariae* is the least common species of malaria. It has a dormant blood borne phase that can cause recurrences years after leaving an infected area.

3.1 Geographic Distribution and Resistance Patterns

Malarial transmission occurs in large areas of Central and South America, Hispaniola, Sub-Saharan Africa, the Indian subcontinent, Southeast Asia, the Middle East, and Oceania. **ATTACHMENT A** provides a general illustration of the worldwide distribution of malaria. *P. falciparum* and *P. malariae* are present in most malarial areas. *P. vivax* and *P. ovale* are present in all malarial areas except Haiti and the Dominican Republic.

A detailed list of malaria by country is available at:
http://www.cdc.gov/malaria/travelers/country_table/a.html

Drug resistance — Antimalarial selection should include the considerations of regions with malarial drug resistance.
The resistance of P. falciparum to chloroquine is widespread; regions with chloroquine-resistant and chloroquine-sensitive malaria are summarized below:
Chloroquine-resistant P. falciparum is widespread in endemic areas of Africa, Asia and Oceania.
Chloroquine-sensitive P. falciparum exists in Mexico, the Caribbean, Central America west and north of the Panama Canal, and parts of North Africa, the Middle East, and China.
P. falciparum strains resistant to chloroquine , mefloquine and sulfonamides are rare, but are prevalent in the regions of Thailand bordering Burma (Myanmar) and Cambodia (e.g., eastern provinces of Myanmar and western provinces of Cambodia), and in parts of China, Laos, and Vietnam.
Chloroquine-resistant P. vivax is widespread in Indonesian Papua and Papua New Guinea (See UpToDate for latest information).

3.2 Life Cycle of the Malarial Parasite

The Plasmodium genus of protozoan parasites has a life cycle that is split between a vertebrate host and an insect vector. In general, the host is man and the insect vector is the *Anopheles* mosquito. Asexual development occurs in the human host, and sexual development occurs in the mosquito. The basic life cycle of the parasite is illustrated in **ATTACHMENT B**.

4. PERSONAL PROTECTION MEASURES

The Office of Medical Services requires all Volunteers serving in malaria endemic areas to limit their exposure to infectious mosquitoes and to use personal protection measures to prevent malaria. *Anopheles* mosquitoes bite at night, with peak biting between 10 p.m. and 4 a.m. Medical officers should advise Volunteers to limit their exposure to mosquitoes during these hours.

Use of personal protection measures is an important primary prevention measure. Consistent use of personal protection measures reduces the number of mosquito bites; this can significantly reduce the risk of malaria and can also reduce the risk of other mosquito-borne infections, e.g., dengue. Standard personal protection measures are listed below. Medical officers should insure that Volunteers understand these measures and should encourage their use.

- *Clothing:* Wear light or bright clothing that covers most of the body, e.g., long sleeved shirts, long pants, and socks. Mosquitoes are attracted to dark clothing after dusk. Permethrin-sprayed clothing provides maximum protection.
- *Mosquito Nets:* Sleep under mosquito netting. Netting should have small mesh and should not be damaged. When used properly, nets over cots and beds provide excellent protection against mosquitoes and crawling insects. Nets impregnated with permethrin provide maximum protection. Permethrin-impregnated nets can be procured, at no charge to post, through the Post Logistic Support in Administrative Services (M/AS/PLS). See TG 240, 15.4 "Mosquito Nets."
- *Insect Repellent:* Apply insect repellent. Use preparations that contain 30-35% N, N diethylmethylbenzamide (DEET). . Preparations containing Picaridin 20% have equal efficacy with preparations containing DEET 35%. When applied properly, these preparations are effective for several hours. In addition, Volunteers should: (1) avoid applying repellants with high-concentrations of DEET (>35%) to their skin - high concentration products have rarely been associated with toxic encephalopathy in children; (2) avoid inhaling or ingesting repellents; (3) avoid getting repellents in their eyes, (4) wash repellent-treated skin after coming indoors, and (5) if using both sunscreen and insect repellent, apply sunscreen first, preferably about 20 minutes before the insect repellent. Insect repellents can reduce the effectiveness of sunscreen by about one third. PCVs are encouraged to reapply repellent after bathing or sweating, if they are still at risk
- *Insect Spray:* When needed, use Pyrethroid-containing flying-insect spray in living and sleeping areas during evening and nighttime hours. Sprays should be used for at least a half-hour before retiring. Insect spray may be provided at the discretion of the post. Pyrethroid-containing insect sprays can be procured locally or through PLS. Permethrin may be sprayed on clothing for additional protection against mosquitoes.
- *Screens:* Stay in well-screened areas during mosquito feeding times. In malaria endemic areas, OMS strongly recommends window and door screening of Volunteer living areas.

Local Area Mosquito Control Measures

Mosquitoes breed in stagnant or slow moving water found in places such as water barrels or catchments, discarded tires or pottery, stumps of trees, large leaves, and flower beds. Therefore, PCMOs should instruct Volunteers to cover all household water containers and, when possible, make every effort to eliminate or properly drain standing water within 30 meters of their living areas. This may decrease the number of mosquitoes to which they are exposed. In humid, forested areas, decreasing the mosquito population may not be a practical consideration.

5. CHEMOPROPHYLAXIS

The Office of Medical Services requires PCMOs to provide all Volunteers serving in malaria endemic areas with appropriate chemoprophylaxis during their service and following close of service (COS). This includes the provision of sufficient medication for post-exposure and PART and the provision of chemoprophylaxis during vacation, home leave, medical evacuation, and other departures from country. Volunteers residing in non-malaria endemic areas who travel to malaria endemic areas should also be provided with appropriate chemoprophylaxis.

The Office of Medical Services also requires PCMOs to educate Volunteers about the following: (1) the life cycle of the malaria parasite (see **ATTACHMENT B**); (2) the proper use of chemoprophylactic medication; and (3) the importance of uninterrupted chemoprophylaxis.

Chemoprophylaxis is the use of antimalarial medication to suppress clinically significant disease. Antimalarial medications do not *prevent* infection with the malaria parasite; rather, they *suppress* clinical disease by attacking the parasites at different stages of its life cycle. There are no antimalarials that are 100% effective or without side effects.

Peace Corps primarily uses two types of chemoprophylactics: "suppressive" and PART. Suppressive chemoprophylactics, e.g., chloroquine, doxycycline, mefloquine, and Malarone kill blood (asexual) stages of plasmodia, thereby suppressing clinically significant illness. PART, e.g., primaquine, attacks liver stages of the parasite, thereby preventing disease. PART is directed against the relapsing malarias, *P. vivax* and *P. ovale* (see Section 11 below). Therefore, prophylaxis prior to arriving in country (pre-exposure prophylaxis) or immediately upon arrival in country (loading dose), and prophylaxis following departure from country (PART), is required.

5.1 Choice of Chemoprophylaxis

Optimal malarial prophylaxis takes into consideration the most effective antimalarial agent, side effects and Volunteer adherence.

There is no first-line drug in Peace Corps. All antimalarial drugs are utilized, as appropriate, in suppressing malaria. Drug options include chloroquine, mefloquine, doxycycline and atovaquone-proguanil (Malarone). Medical officers should, therefore,

individualize their choice of chemoprophylactic agent for each Volunteer based on the following considerations:

KEYS TO OPTIMAL MALARIA PROPHYLAXIS

Consider:

- Area-specific OMS recommendations (see Section 5.2 below).
- Drug-resistance profile in country, i.e., the Volunteer's risk of exposure to chloroquine-resistant *P. falciparum* malaria.
- Drug contraindications and precautions.
- Other factors:
  - Tolerance; includes the likelihood of Volunteer adherence to a particular chemoprophylactic regimen (see Sections 5.3 and 8 below).
  - Dosing schedules, i.e., weekly versus daily dosing. Regimens that require daily dosing may increase the opportunity for non-compliance, whether accidental, intentional, or associated with illness.

For additional information on malaria chemoprophylaxis, PCMOs should refer to the most current issues of Health Information for International Travel (Yellow Book) published by the CDC. This book is available on the World Wide Web at www.cdc.gov/travel/reference.htm. Additional references and resources on malaria risk and prophylaxis are included below.

Book

Centers for Disease Control and Prevention (CDC). Health Information for International Travel 2014. Oxford University Press, New York 10016. Atlanta: Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases, Division of Global Migration and Quarantine; available online at http://wwwnc.cdc.gov/travel/yellowbook/2014/table-of-contents

Internet

CDC malaria map: http://cdc-malaria.ncsa.u/uc.edu
CDC malaria website (includes health information for international travel): http://www.cdc.gov/malaria
CDC travelers' health website: http://wwwnc.cdc.gov/travel
WHO malaria website: http://www.who.int/topics/malaria/en/
Medications sheets published by CDC: http://www.cdcc.gov/malaria/references_resources/fsp.html
CDC stories on people with malaria: http://www.cdc.gov/malaria/stories/index.html
CDC Malaria 101 for the Health Care Provider CME: http://www.cdc.gov/parasites/cme/malaria/index.html

Phone
CDC (800) CDC-INFO
CDC Malaria Hotline (treatment): (770) 488-7788 (M-F 9 a.m.- 5 p.m. EST); (after hours request to speak with the Malaria Branch Clinician).
International Society of Travel Medicine: 1-(770)-736-7060

5.2 Recommended Chemoprophylactic Regimens

The Office of Medical Services bases its recommendations for malaria chemoprophylaxis on the most recent guidance from the CDC. In general, CDC chemoprophylaxis recommendations are based on the overall rate of malaria transmission, i.e., "malaria risk", and the presence of chloroquine-resistant *P. falciparum*, in a given area. Malaria risk estimates, i.e., the estimated risk of a traveler acquiring malaria, are primarily derived from World Health Organization (WHO) surveillance data and can vary markedly from area to area and year to year. The Office of Medical Services does not endorse guidance for malaria prophylaxis that is not consistent with CDC guidelines.

- **Areas with chloroquine-sensitive *P. Falciparum*.**

Chloroquine should be strongly considered for chemoprophylaxis in areas where chloroquine-sensitive P. falciparum exists. Chloroquine is usually well tolerated. Volunteers who experience uncomfortable adverse reactions may tolerate the drug better by taking it with meals. If adverse reactions persist, alternative chemoprophylactic agents should be discussed and initiated.
When possible, chloroquine prophylaxis should begin one to two weeks prior to arrival in country. If this is not possible, Volunteers should start chloroquine prophylaxis just prior to departure or immediately upon their arrival in a malarial area. Chloroquine should be continued once weekly during service and for four weeks following exposure.

Apart from its bitter taste, chloroquine is usually well tolerated. Minor side effects include gastrointestinal disturbances, dizziness, blurred vision, and headache; gastrointestinal problems may be alleviated by taking the drug with food. It has been associated with triggering flares of psoriasis and pruritus, although serious side effects are rare. Pruritus occurs in up to 25 percent of darked skinned individuals of African descent due to concentration of the drug in skin; this is not an allergic reaction. Retinal injury, which can occur when high doses of chloroquine are used to treat rheumatoid arthritis, does not occur with the weekly dosages used for malaria prevention. Chloroquine is safe for use in pregnancy. (See UpToDate for the latest information)

If chloroquine cannot be taken due to co-existing medical conditions or chloroquine intolerance, alternative agents should be used. These include doxycycline, mefloquine, and Malarone.

- **Areas where chloroquine-resistant *P. falciparum* EXISTS.**

There is no first-line drug in Peace Corps. All antimalarial drugs are utilized, as appropriate, in suppressing malaria. Drug options include atovaquone-proguanil

(Malarone), doxycycline and mefloquine. If a particular chemoprophylactic agent cannot be taken due to co-existing medical conditions or drug intolerance, alternative agents should be used.

Atovaquone-proguanil (Malarone) is administered daily beginning one to two days prior to exposure, during exposure, and for one week following exposure. The drug is well tolerated, with excellent profiles of safety and efficacy. Adverse effects may include gastrointestinal upset, insomnia, headache, rash and mouth ulcers. Atovaquone-proguanil is contraindicated in patients with creatinine clearance <30 mL per minute and it is not recommended for use in pregnant women due to insufficient safety data

Doxycycline is administered daily beginning one to two days prior to exposure, daily during exposure, and daily for four weeks following exposure. Noncompliance with this daily regimen is an important reason for doxycycline prophylaxis failure.

Doxycycline is usually well tolerated, but has been associated with gastrointestinal upset; less commonly, ultraviolet photosensitivity, Candida vaginitis, and rare cases of esophageal ulceration may also occur. The drug should be taken with fluids and food; it should not be administered immediately before lying down. Sunscreen should be applied liberally for the duration of prophylaxis. It is advisable to offer women antifungal self treatment for management of Candida vaginitis (eg, fluconazole). Doxycycline is contraindicated in pregnant women and in children <8 years of age.

Mefloquine is administered weekly beginning at least two weeks prior to exposure, during exposure, and for four weeks following exposure. Some individuals experience adverse effects from mefloquine; most are mild, self-limited, and do not require discontinuation of the drug. The most frequent adverse effects are gastrointestinal upset, lightheadedness, headache, difficulty concentrating, mood swings, and strange dreams. About 5 percent of travelers experience disabling neuropsychiatric adverse effects requiring discontinuation of the drug. These include anxiety, depression, nightmares, paranoid ideation, and dizziness. About 1 in 10,000 travelers experience severe neuropsychiatric reactions such as seizures and psychosis. Adverse effects appear to be more common among women and less frequent among children. Most adverse effects requiring mefloquine discontinuation occur within the first three doses.

Contraindications to mefloquine include known hypersensitivity to the drug, a history of seizures or major psychiatric disorder, and a recent history of depression or anxiety. Development of psychiatric symptoms (such as depression, anxiety, restlessness or confusion) while taking mefloquine should be viewed as a possible prelude to other events; in such circumstances it is advisable to stop the drug immediately and switch to a different prophylaxis agent. Mefloquine has also been associated with sinus bradycardia and QT interval prolongation; therefore, it should be used with caution in patients with cardiac conduction disorders.

For pregnant patients who cannot avoid travel to areas with chloroquine-resistant P. falciparum, mefloquine may be safely administered during all trimesters.

- **Areas with localized chloroquine-resistant *P. falciparum***

In some countries, chloroquine-resistant *P. falciparum* may be localized to specific areas of the country. Such areas are shrinking and mainly occur in South America (outside of the Amazon basin) and in Southern Asia (India and Nepal). In these areas, *chloroquine* prophylaxis is reasonable if the incidence of malaria has been closely monitored and where drug resistance has not been observed. Medical officers should consult OMS for guidance on the use of chloroquine in such areas.

5.3 Volunteer Adherence

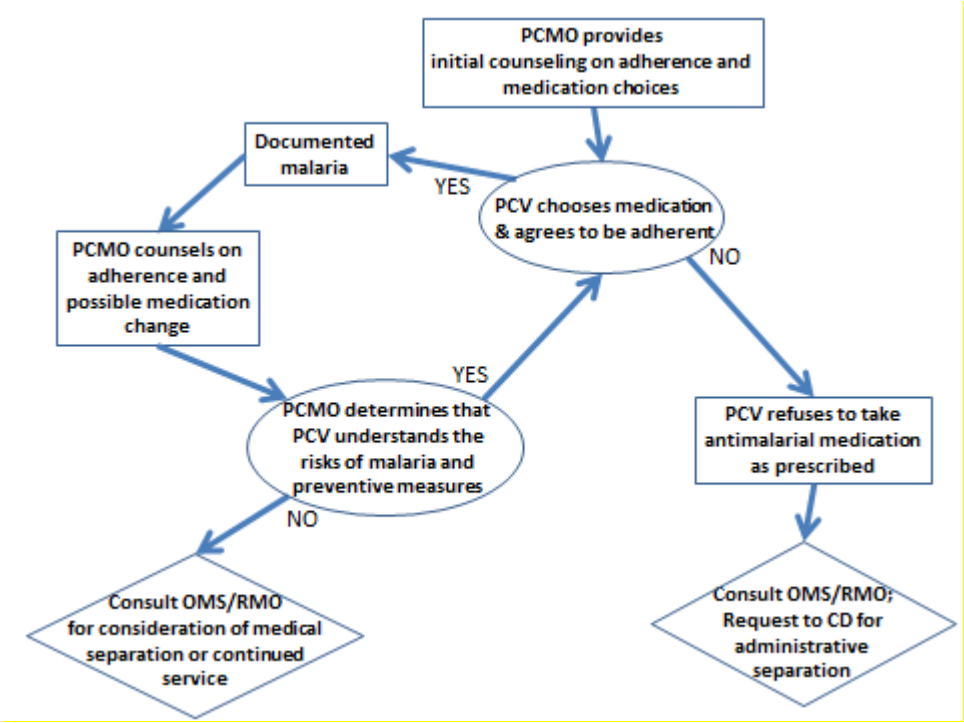
All Volunteers serving in malaria endemic areas are at high risk for infection with the malaria parasite. To suppress clinical infection, OMS requires all Volunteers serving in malaria endemic areas to rigorously adhere to a chemoprophylactic regimen throughout their tour of duty and following COS. This includes the use of chemoprophylaxis during vacation, home leave, medical evacuation, and other departures from country. Volunteer failure to comply with OMS-recommended malaria prevention measures can result in symptomatic malaria infections. These infections cause significant illness, impair Volunteer effectiveness, result in unnecessary financial costs, and, tragically, occasionally result in Volunteer death.

To encourage Volunteer adherence, PCMOs should: (1) educate Volunteers on the importance of primary and secondary malaria prevention strategies; (2) provide Volunteers information on the various chemoprophylactic regimens (see **ATTACHMENT C "Antimalarial Chemoprophylaxis, Advantages and Disadvantages," and ATTACHMENT D** "Antimalarial Medication Information Sheets"); (3) instruct Volunteers to consult the PCMO if adverse reactions to chemoprophylaxis occur; and (4) counsel Volunteers who state they are unwilling or unable to follow OMS-required malaria prevention strategies and, when appropriate, offer alternative prophylactic antimalarial medication (see Section 8 below).

During pre-service training, Trainees will participate in group and individual discussions with a medical officer to decide whether a weekly medication schedule or a daily medication schedule and which agent would be best for the individual Trainee to assure 100% compliance for the entirety of his/her PC service.

Volunteers should not stop any chemoprophylactic regimen without consulting the PCMO. Improper self-discontinuation of prophylaxis places a Volunteer at risk for malaria. Volunteers who are unable to comply with malaria prevention strategies due to willful misconduct or disregard for the Peace Corps Volunteer Health Program should be referred to the Country Director for administrative action (see MS 262 Section 3.2).

The flow chart below is a guideline for dealing with PCVs who contract malaria. Every case must be handled individually and discussions and medical recommendations must be documented appropriately in the medical record. Do not forget to discuss mosquito bite avoidance measures as well as chemoprophylactic use. **For any given PCV, there is no set number of documented cases of malaria that would necessarily lead to an action to separate.**



Mefloquine *Medication Guide*

Medical officers are required to distribute the "Mefloquine Medication Guide" (**ATTACHMENT E**) to all Volunteers taking mefloquine, and to obtain a signed "Mefloquine Medication Guide Acknowledgement" form (**ATTACHMENT F**). The acknowledgement form should be obtained prior to starting the Volunteer on prophylaxis and filed in the Volunteer's health record.

This policy is consistent with the July 2003 FDA-approved patient labeling and legal requirement that a "Mefloquine Medication Guide" is supplied to patients when mefloquine is dispensed. The purpose of the medication guide is to help ensure patients understand the risks of malaria and the rare but potentially serious neuropsychiatric adverse events associated with use of mefloquine. It also provides information on how they can recognize these neuropsychiatric risks and take early action to prevent serious harm.

6. STARTING CHEMOPROPHYLAXIS

In general, the CDC recommends that travelers start chemoprophylaxis one to two weeks prior to arrival in a malarial area. If this is not possible, the CDC advises travelers to start antimalarials just prior to their departure or immediately upon their arrival in a malaria-endemic area. Both strategies, when combined with mosquito avoidance and personal protective measures, i.e., insect repellent, bed nets, and screens, are effective in preventing acute malaria. Therefore, for Peace Corps Trainees, OMS recommends that malaria prophylaxis be started either during staging or immediately upon arrival in country.

Loading Dose
In countries where Volunteers do not receive antimalarial medication prior to departure from the U.S. and the PCMO suspects that Volunteers may be immediately and intensely exposed to malaria upon their arrival in country, they should consult OMS for guidance. In such cases, OMS will consider whether to recommend a loading dose of a chemoprophylactic agent that can rapidly produce protective blood levels. In general, a loading dose is only used for Volunteers taking mefloquine, but this is discouraged by OMS For those PCVs who choose to use mefloquine, it is recommended that the PCV/T be placed on daily doxycycline during the first two weeks of mefloquine treatment. A loading dose is not required for Volunteers taking doxycycline and no data exists to support a loading dose in Volunteers taking chloroquine or Malarone.

7. CHEMOPROPHYLACTIC AGENTS

This following table is a summary of dosing schedules, adverse reactions, and contraindications of common chemoprophylactic agents used by Peace Corps. Additional information is also available in the "Antimalarial Medication Information Sheets" (see **ATTACHMENT D**".

CHEMOPROPHYLACTIC AGENTS

Drug	Tablet size	Dose and Frequency	Discontinuation duration (time after last exposure)	Adverse Reactions	Contraindications
Atovaquone-proguanil (Malarone)	250 mg atovaquone and 100 mg proguanil	One tablet daily	7 days	▪ Adverse reactions include abdominal pain (17%), nausea (12%), vomiting (12%), headache (10%), diarrhea (8%), weakness (8%), loss of appetite (5%), and dizziness. ▪ Mouth ulcers, cough, pruritus, urticaria, blood disorders, and hair loss have also been reported	*Contraindicated* in persons with: ▪ severe renal impairment (creatinine clearance < 30 ml/min). *Should be avoided* in persons who are taking: ▪ tetracyclines. Tetracyclines cause a 40% decrease in atovaquone concentrations. ▪ Metopramide and rifampin. Both drugs reduce the plasma concentration of atovaquone

Chloroquine phosphate (Aralen and generic agents)	500 mg salt (300 mg base)	One tablet weekly	4 weeks	▪ Reports of sleep disturbance and unusual dreams; reactions tend to be no more frequent than for mefloquine users. ▪ May cause depression, blurred vision, nausea, pruritus, headache, or paresthesias. ▪ Reports of rare, severe, adverse reactions including neuropsychiatric, e.g., extra-pyramidal symptoms, neuropathies, agitation, and psychosis (1/13,600 people) ▪ May worsen symptoms of psoriasis. ▪ [Retinopathy in persons with a history of long-term, high dose, chloroquine use, i.e., a total cumulative exposure > 60 gms (approx. 4 years of weekly medication). Routine eye exams q6 months are indicated in these individuals.]	▪ Persons with porphyria. ▪ May interfere with antibody response to human diploid cell rabies intradermal vaccines.
Doxycycline hyclate (Vibramycin, Vibra-Tabs, other brands, and generic agents); doxycycline monohydrate (Monodox, Adoxa, and generic agents)	100 mg	One tablet daily	4 weeks	▪ Minor adverse reactions include photosensitivity, increased incidence of monilial vaginitis, and gastrointestinal disturbance. May cause esophagitis, especially if taken at night.	▪ Pregnancy ▪ Persons allergic to tetracycline or other macrolide antibiotics.
Mefloquine hydrochloride (Lariam and generic agents)	**250 mg salt (228 mg base)**	**One tablet weekly**	**4 weeks**	▪ Minor adverse reactions include GI disturbance and dizziness; reactions tend to be transient and	*Contraindicated* in persons with: ▪ a known hypersensitivity to mefloquine or related compounds, e.g., quinine.

				self-limited. ▪ Infrequent reports of chest pain, edema and dyspepsia. ▪ Reports of sleep disturbances and unusual dreams; reactions tend to be no more frequent than for chloroquine users. ▪ May cause psychiatric symptoms ranging from anxiety, paranoia, and depression to hallucinations and psychotic behavior. On occasion, these symptoms have been reported to continue long after mefloquine has been stopped ▪ Reports of rare, severe, adverse reactions, the most common being neuropsychiatric, e.g. tremor, ataxia, mood changes, and panic attacks (1/10,000-13,000 people). ▪ Rare cases of suicidal ideation and suicide, though no relationship to drug administration has been confirmed	▪ active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia or other major psychiatric disorders. ▪ History of convulsions or seizures. *Not recommended* in persons with: ▪ cardiac conduction defects, e.g., A-V block, bundle branch block, or a prolonged QT interval. ▪ atrial or ventricular arrhythmias. ▪ are on beta-blockers for the cardiac conduction defects and arrhythmias listed above. *Use with caution* in persons with: ▪ a previous history of depression.

Mefloquine, Malarone and doxycycline may also be used in chloroquine-sensitive areas as necessary.

7.5 Agents Not Recommended for Chemoprophylaxis

The following chemoprophylactic agents are not listed as malaria prophylactic options by the CDC and are not recommended by OMS.

- *Chloroquine/Proguanil (Paludrine)*

- *Pyrimethamine-sulfadoxine (Fansidar):* Fatal allergic reactions have been reported with prophylactic use of Fansidar (1/11,000-26,000 users) (Mendel, et al., 2000). Life-threatening reactions have not been reported with single doses used for the treatment of malaria.
- *Pyrimethamine (Daraprim)*
- *Pyrimethamine-dapsone (Maloprim)*
- *Amodiaquine*
- *Halofantrine (Halfan)*

8. ASSESSING ANTIMALARIAL TOLERANCE

Preventing acute malaria depends not only upon the effectiveness of specific antimalarial agents, but also upon the Volunteer's compliance with, and tolerance of, a recommended chemoprophylactic regimen.

Medical officers are encouraged to consider antimalarial tolerance when determining optimal chemoprophylactic therapy for Volunteers. Tolerance includes the Volunteer's previous experience with antimalarial medications the likelihood of Volunteer adherence to a particular chemoprophylactic regimen.

When a Volunteer complains of side effects or intolerance which he or she attributes to a particular antimalarial medication, and then requests that the PCMO switch him/her from the recommended chemoprophylactic agent to another agent, the PCMO should do the following:

- If the request for an alternative agent is clinically appropriate, switch regimens.
- If the request for an alternative agent is not climically appropriate, assess the Volunteer's reasons for requesting an alternative agent and consider switching to an alternative agent to improve adherence.
- Consult OMS or the RMO if a Volunteer is unwilling or unable to maintain adherence with their chemoprophylaxis regimen.

8.1 Switching Antimalarials

When switching from one antimalarial to another, care is necessary to avoid a gap in protective blood levels. This is especially important in Trainees as blood levels may be low for several weeks after starting a weekly chemoprophylactic agent. It is also important for Volunteers who have been in a malarial area for many weeks and are likely to already be infected.

- *Daily Dose to a Daily Dose*

When switching from a daily dose of doxycycline or Malarone to a daily dose of doxycycline or Malarone, no overlap is necessary.

- *Daily Dose to a Weekly Dose*

When switching from a daily dose of doxycycline or Malarone to a weekly dose of mefloquine, overlap both regimens for *four* weeks. An alternate, although less preferred, approach may be to provide a three-day loading dose of mefloquine (Not FDA approved: mefloquine 250mg daily for three consecutive days).

- *Weekly Dose to a Daily Dose*

When switching from weekly mefloquine or chloroquine to daily doxycycline or Malarone, no overlap is necessary.

- *Weekly Dose to a Weekly Dose*

It is unusual to switch from weekly chloroquine to weekly mefloquine but in these rare instances, a three-day loading dose of mefloquine should be provided. Medical officers should contact OMS for guidance prior to starting mefloquine therapy in these cases.

9. MISSED DOSES

- *Missed Weekly Dose (Chloroquine or Mefloquine)*

If a dose of a weekly chemoprophylactic agent is missed, the Volunteer should take that missed dose as soon as they remember it, and continue on their regular schedule.

- *Missed Daily Dose (Doxycycline or Malarone)*

If a dose of a daily chemoprophylactic agent is missed, the Volunteer should resume daily dosing immediately. No loading dose is necessary when resuming chemoprophylaxis with these agents. Volunteers should be advised against doubling up on their antimalarial when resuming chemoprophylaxis after missing a dose of their medication.

Volunteers are more likely to forget drugs that are given daily and this may lead to breakthrough cases of malaria. If this occurs, the PCMO should discuss the option of a weekly drug (if clinically appropriate) with the Volunteer..

10. SHORT TERM TRAVEL TO MALARIA ENDEMIC AREAS

Occasionally, Volunteers serving in non-malaria endemic areas will require intermittent malaria prophylaxis for short-term travel. In such cases, OMS recommends that PCMOs follow the guidance outlined in this guideline. Special attention should be paid to Section 5.2 "Recommended Chemophylactic Regimens", Section 5.3 "Volunteer Adherence" noting that PCMOs are required to distribute the "Mefloquine Medication Guide" (**ATTACHMENT E**) to all Volunteers taking mefloquine and to obtain a signed "Mefloquine Medication Guide Acknowledgement" form (**ATTACHMENT F**). Section 11 "Leaving the Malaria Endemic Area" should be reviewed with the Volunteer. Medical officers serving in non-malaria endemic areas should contact OMS if they have questions about malaria prevention.

11. LEAVING THE MALARIA ENDEMIC AREA

11.1 Presumptive Anti-Relapse Therapy (PART)

The Office of Medical Services requires all Volunteers who have been in a malaria endemic area for more than four weeks[1], where *P. ovale* and *P. vivax* exist, to take PART ("terminal prophylaxis"). At present, these areas include all malaria endemic countries except Haiti and the Dominican Republic where these forms of malaria have not been reported.

Primaquine phosphate is the drug of choice for malaria terminal prophylaxis (see Section 11.2 below). Primaquine is effective against the liver stages (hypnozoites) of *P. vivax* and *P. ovale* and decreases the risk of late relapses of malaria. Such relapses typically occur 6-12 months after stopping chemoprophylaxis and can occur as long as four years after prophylaxis is discontinued. Primaquine is the only drug that is effective against the dormant liver stage of the parasite.

Presumptive Ant-relapse Therapy

AREAS WHERE *P.OVALE* AND *P.VIVAX* MALARIA EXIST			
Drug	**Dose**	**Adverse Reactions**	**Contraindications**
Primaquine	▪ *Post Exposure:* 30 mg base (52.6) mg salt) ***once daily*** for 14 days. ▪ Start 2 weeks following final departure from the malaria endemic area if the Volunteer is taking chloroquine, mefloquine, or doxycycline. ▪ Start 1 week following final departure from the malaria endemic area if the Volunteer is taking Malarone.	▪ Minor adverse reactions include headaches, abdominal cramps, nausea, vomiting and pruritus. ▪ Methemoglobinemia is common but rarely necessitates discontinuation of therapy. ▪ Leukopenia and agranulocytosis occur rarely.	▪ May cause severe hemolysis in G6PD-deficient individuals. Before primaquine is used, G6PD deficiency must be excluded by appropriate laboratory testing.

[1] As per CDC: No reasonable data exist to support the use of primaquine in individuals who are exposed to *P. vivax* or *P. ovale* for less than 4 weeks.

11.2 Primaquine Phosphate

- *Post Exposure Dose:* Primaquine phosphate 30 mg base (52.6 mg salt) once daily for 14 days. Primaquine should be started 2 weeks following final departure from the malaria endemic area if the Volunteer is taking chloroquine, mefloquine, or doxycycline; and 1 week following final departure if the Volunteer is taking Malarone. Primaquine should be given concurrently with all antimalarials except Malarone.
    - The enzyme G6PD is required for Primaquine metabolism. Because G6PD deficiency is associated with severe hemolysis, all Volunteers must be tested for G6PD deficiency prior to being given primaquine. *Medical Officers must clearly document G6PD test results in the Volunteer health record and should not issue primaquine to Volunteers with any degree of G6PD deficiency (see Section 12 below).*
- *Regular Malaria Prophylaxis:* Volunteers should continue to take their regular malaria prophylaxis regimen (with the exception of Malarone) for four weeks after leaving a malarial area. Volunteers taking Malarone should continue for one week after leaving a malarial area.
- *Adverse Reactions:* Minor side effects include headaches, abdominal cramps, nausea, vomiting and pruritus. Methemoglobinemia is also common, but rarely necessitates interruption of therapy. Leukopenia and agranulocytosis occur rarely.
- *Contraindications:* Primaquine can cause hemolysis in persons with G6PD deficiency. Hemolysis may be mild or severe. Medical Officers should not give Volunteers with an "abnormal" or "low" G6PD test result primaquine (see section 11 below).
- *Pregnancy:* Primaquine is contraindicated during pregnancy. Pregnant Volunteers departing malaria endemic areas should be issued a PC-127C "Authorization for Payment of Medical/Dental Services" for an OB/GYN prenatal consultation, to include recommendations regarding terminal malaria prophylaxis (see TG 170 "Pregnancy").

11.3 Close of Service Procedures in Malaria Endemic Areas

Medical Officers must provide all Volunteers leaving malaria endemic areas with the following:

- See also "Malaria Prophylaxis" in TG 330 under Section 4.4 "Physical Exam".
- Malaria prophylaxis according to the guidance outlined above. This should include: (1) post-exposure prophylaxis as outlined above and in TG 330 Attachment G, and (2) an additional 30 day supply of a malaria prophylaxis medication, e.g., mefloquine, doxycycline, or Malarone, *if the Volunteer will be traveling in a malaria endemic area prior to returning to the U.S* If the Volunteer will be traveling for more than 30 days, provide them with the website (http://www.istm.org/AF_CstmClinicDirectory.asp)where they can find a travel clinic in the country they will be visiting to obtain prophylaxis.

- Medications for one course of interim self-treatment of malaria for use should the Volunteer develop symptoms of acute malaria (see TG 845.5.1 "Interim Self-Treatment Regimens" for medications and dosing schedules).
- PART according to the guidance outlined in Section 11.1 "Presumptive Anti-Relapse Therapy" above.
- Handout titled "Instructions for Volunteers: COS Guidelines for Preventing Malaria" (see TG 330**, ATTACHMENT G**), to include:
  - Education and instruction on p*ost-departure* malaria prophylaxis.
  - Education and instruction on PART.
  - Instructions to report their Peace Corps service and exposure to malaria to their HOR physician. *P. vivax* and *P. ovale* may relapse despite compliance with primaquine PART.

12. G6PD TESTING

The Office of Medical Services requires that all Volunteers be tested for G6PD deficiency prior to the administration of primaquine. Glucose-6-Phosphate Dehydrogenase (G6PD) is an enzyme in red blood cells that is involved with glucose metabolism. Persons with G6PD deficiency are at risk for hemolytic anemia when taking primaquine. Hemolysis may be severe in some people.

All Trainees going to malaria endemic areas of Africa are tested for G6PD deficiency prior to Peace corps service. If a Trainee's G6PD status is unknown, and the Trainee is serving in a malaria endemic area, testing should be done in country if a reliable laboratory exists in country. Preferably, the test should be done during pre-service training (PST) so that if a Trainee terminates service early, his/her G6PD status will be known prior to departure.

If a reliable laboratory is not available in country, PCMOs should provide Volunteers with a PC-127C "Authorization of Payment of Medical/Dental Services" for G6PD deficiency testing in the U.S. This may be done during service or at COS.

Medical officers may use Quest Diagnostics for G6PD level determination *if* post can *reliably* ship blood to the U.S. in less than 48 hours. Blood should be sent anticoagulated in a lavender-top tube. Samples received more than 48 hours after collection may be falsely reported as having low G6PD activity due to sample deterioration (see TG 360 "Use of U.S. Laboratories").

Volunteers who have not been tested for G6PD deficiency prior to COS should not be issued primaquine. These Volunteers should be issued a 127C authorization for, "primary care consultation for G6PD testing and terminal malaria prophylaxis as indicated."

In addition, Volunteers: (1) whose test results have not been received, (2) whose test results are not clearly documented in the health record, or (3) whose test results report any degree of G6PD deficiency should not be issued primaquine. Medical officers may contact OMS for assistance obtaining results.

G6PD Test Results

Test results must be obtained and clearly documented on the cover of the Volunteer health record prior to the administration of primaquine. The laboratory report should be filed in the health record under "In-Service Diagnostics".

- *Normal:* "Normal" or "G6PD present" test results done in country or at a U.S. lab are acceptable. When indicated, these Volunteers may be given primaquine.
- *Abnormal:* Medical officers should issue the Volunteer a 127C authorization for "primary care consultation for evaluation of G6PD deficiency and terminal malaria prophylaxis as indicated." A copy of the lab report should be attached to the 127C.

  PCMOs should instruct Volunteers with abnormal results to remain on their malaria prophylaxis until their G6PD status is confirmed. Medical officers should not give primaquine to a Volunteer with an abnormal or abnormally low G6PD result.
- *No result available at COS:* Volunteers who have not been tested for G6PD deficiency prior to COS should not be given primaquine.

13. CHEMOPROPHYLAXIS IN PREGNANCY

In addition to the following guidance, PCMOs should refer to the current edition of Health Information for International Travel published by the CDC for additional information on antimalarial recommendations in pregnant women, nursing mothers, and children.

- **Pregnant Volunteers:** Severe cases of malaria can occur during pregnancy. Pregnancy alters the immune system and malaria may adversely affect the outcome of pregnancy. Therefore, all pregnant Volunteers are required to take malaria chemoprophylaxis. The CDC recommended drugs of choice in pregnancy are:
  - Chloroquine-sensitive areas: Chloroquine 300 mg (500 mg base) *weekly*.
  - Chloroquine-resistant areas: Mefloquine 250 mg *weekly* if the potential benefit justifies the potential risk to the fetus.
  - Doxycycline and primaquine are contraindicated during pregnancy.
  - Malarone is not currently recommended by the CDC for use in pregnancy. Medical officers should consult OMS in situations where a pregnant Volunteer is unable to take mefloquine.
- Pregnant Volunteers located in areas with chloroquine-resistant malaria should be placed on mefloquine and evacuated or separated from the malarial area within one week of pregnancy diagnosis (see TG 170.4.1 "Pregnancy in Areas with Chloroquine-resistant Malaria). Weekly mefloquine should be continued for 4 weeks after leaving the endemic area.

14. STORAGE OF ANTIMALARIAL DRUGS

An overdose of antimalarial drugs can be fatal, especially in children. Medical officers should dispense antimalarial drugs in childproof containers. Medical officers should also instruct Volunteers to *always* store medication in childproof containers and out of the reach of children.

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