



# How to Protect Yourself Against Malaria

2019 Edition

**Canada** 67 Mowat Avenue, Suite 036 Toronto, Ontario M6K 3E3 (416) 652-0137  
**USA** 1623 Military Road, #279 Niagara Falls, New York 14304-1745 (716) 754-4883  
**New Zealand** 206 Papanui Road Christchurch 5

[www.iamat.org](http://www.iamat.org) | [info@iamat.org](mailto:info@iamat.org)



**Fig. 1** Female *Anopheles* mosquito.

Image source: World Health Organization

Malaria parasites are older than humankind. They have accompanied the evolution of primates throughout the geological ages from their earliest ancestors up to the emergence of humans.

## THE ENEMY

Sunset — the hunt for human blood begins. From dusk to dawn the female *Anopheles*, the malaria-carrying mosquito, searches for a host to supply her with blood. Blood is an absolute necessity for her because it provides the protein needed for the development of her eggs which she later deposits in her breeding place.

She has a tiny, elegant body, measuring from 8 mm to 1 cm. She has dark spots on her wings, three pairs of long, slender legs and a prominent tubular proboscis with which she draws blood.

The *Anopheles* enters your room at night. You may recognize her by the way she rests on the wall — she stands on her head with the tail-end of her body tilted upwards, protruding into the air like a rocket on a launching pad. She is unlike the common pests of our temperate climates, the *Culicinae* (*Culex*, *Aedes*, etc.), which assume a position parallel to the surface.

She is your enemy, because only she can harbour the human malaria parasite and carry it from an infected person to a new victim (male mosquitoes do not bite). In fact, in East Africa the same word, *umbu*, means both malaria and mosquito. Around the world, she infects more than 200 million people with malaria and kills an estimated 430,000 people, mostly children.

The unprotected international traveller pays her a heavy toll — she is responsible for infecting thousands with malaria every year. Her bite is the direct cause of death for many who contract the disease in their travels.

The more than 3,500 species of mosquitoes are grouped into the family of *Culicidae*, of which the genera *Aedes*, *Anopheles* and *Culex* are the most widespread. Throughout the world, each species of *Anopheles* is peculiar to a localized

area. Of the 460 *Anopheles* species, approximately 100 can transmit malaria parasites.

Mosquitoes prey on a variety of hosts — humans, monkeys, lizards, birds — carrying different species of malaria parasites which in turn infect only specific hosts. Of the approximately 50 different species of malaria parasites sharing the genetic name *Plasmodium*, only 5 infect humans: *Plasmodium falciparum* (the killer parasite); *Plasmodium vivax*; *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*. The latter, a malaria parasite of Old World monkeys, has been identified to infect humans in Southeast Asia. In the past this parasite has been misdiagnosed as *Plasmodium malariae*.

Malaria parasites are older than humankind. They have accompanied the evolution of primates throughout the geological ages from their earliest ancestors up to the emergence of humans. The parasites, too, underwent adaptive changes and it is believed that the *Plasmodium falciparum*, which causes the fatal form of human malaria, is the latest evolved species of the parasite. The benign *Plasmodium malariae*, the oldest on the scale of evolution, may have been the first to invade humans.

## THE BITE

Now that she has entered your premises, the *Anopheles* waits patiently in a dark corner for the right moment to strike. Attracted by the warmth of your body and the carbon dioxide you exhale, she approaches silently. She does not hum or hover as other mosquitoes do.

In a moment she will land on an exposed part of your body and pull out from her proboscis her armament, consisting of six stylets. First, two needle-pointed stylets will stab your skin, then two

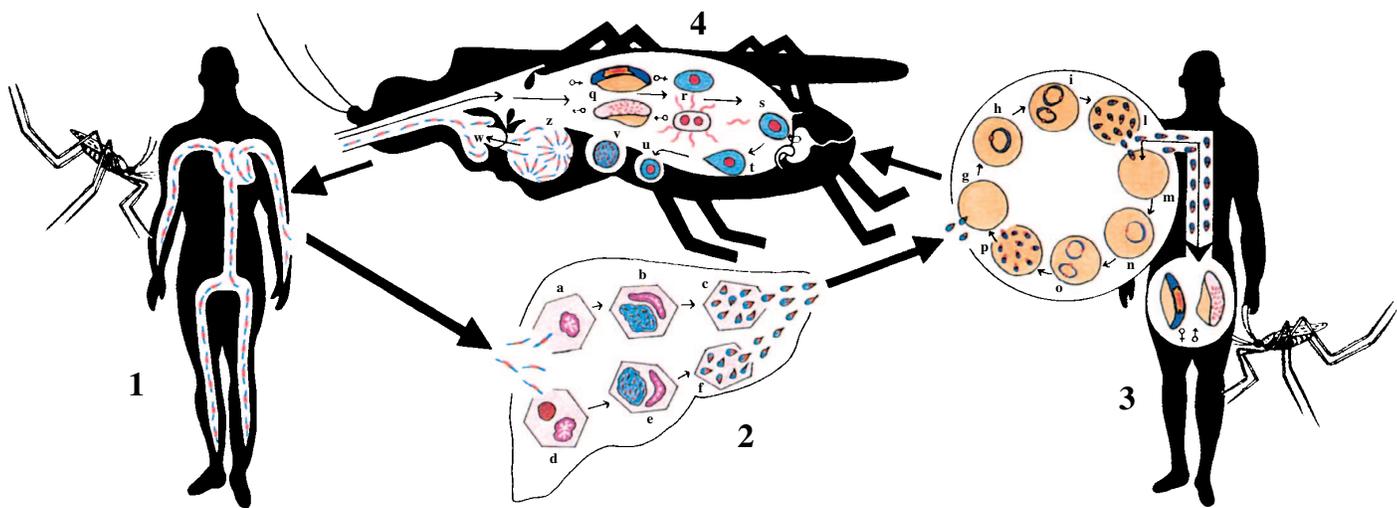


Fig. 2 Life cycle of the malaria parasite.

blades bearing very fine teeth will lacerate the skin like a microscopic saw, searching for a small vein. Soon she pierces the vessel with a flexible tube, the “food canal” through which blood is conveyed into her mouth. During the feeding, she will introduce into the wound her sixth weapon, a hollow stylet containing a duct which is connected to the salivary glands. Through this duct she injects a few drops of her saliva to act as a local anaesthetic so that you do not feel her bite.

Simultaneously with her saliva she will introduce into your bloodstream hundreds of motile *sporozoites* (Gr.: *sporá*=sowing, seed; *zōon*=animal). She acquired these organisms from biting a person infected with malaria. They have been multiplying in her intestine for two weeks.

Soon she will fly away, loaded to twice her unfed weight with blood, to conceal herself in a dark corner of your room. During the forty-eight hours it takes to digest the blood she has taken, her ovaries will completely develop and she will be ready to lay her eggs.

At sundown she will leave your room for her breeding place nearby. She can breed almost anywhere water collects — a footprint, a puddle, a tire track, even a coconut shell or a man-made container. After laying her eggs, her ovarian cycle starts again, and she may return to see you the same night. During her three-month life span she may lay up to three thousand eggs.

This shuttling between blood source and breeding place makes malaria a ‘focus’ disease; that is to say, its area of infective activity is localized and dependent upon the radius of the flight range of the *Anopheles*, usually from a few hundred yards to a mile.

The most dangerous species of *Anopheles* attack humans between dusk and dawn; midnight to 4 am is the peak time. This means you are a prime target when you are most vulnerable — asleep.

### THE THREE LIVES OF THE MALARIA PARASITE

The malaria organism is a *protozoan* (Gr.: *proto*=primitive; *zōon*=animal), that is to say a microscopic, single-celled animal, not to be confused with a bacterium, which belongs to the plant kingdom. The parasite has a complex life cycle, reproducing first in the liver, then in the red blood cells and finally in the mosquito. During these three cycles the parasite transforms itself and emerges each time with new physical and biochemical characteristics.

#### The Liver: Hiding Place of the Parasite

The malaria organisms (*sporozoites*) injected into the body by the bite of the infected mosquito remain in the bloodstream for only a short period — see the illustration of the Life Cycle of the Malaria Parasite (Fig. 2) — usually less than one hour. They disappear from the circulation and establish themselves in the cells of the liver (2a), where they commence cycles of reproduction, a process lasting from six to twelve days, depending on the species. This stage corresponds to the incubation period of the disease. During this time, each *sporozoite* grows through repeated divisions of the nucleus into one large cell named *schizont* (Gr.: *schizein*=to divide; *ontos*=being), now containing thousands of tiny new parasites (2b).

The increased pressure causes the *schizont* to burst and release these newly formed parasites, called *merozoites* (Gr.: *meros*=part, *zōon*=animal) (2c), which leave the liver and enter the red blood cells where they initiate cycles of reproduction.

On entering the liver, all *sporozoites* of *Plasmodium falciparum*, *Plasmodium malariae*, and *Plasmodium knowlesi* immediately enter into a reproductive phase which exhausts itself after one generation. If you are harbouring an infection

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Like humans, anopheline mosquitoes are concerned with food, shelter and reproduction. Will she feed on humans or on domestic animals? Will she enter human dwellings to bite or will she feed outdoors? Does she prefer to bite soon after dusk, late at night or at dawn?

caused by these parasites, suppressive medication will eliminate the parasites from the red blood cells, and because no new invasions from the liver can occur, you will be completely cured of the infection (**2a, 2b, 2c**).

However, *Plasmodium vivax* and *Plasmodium ovale* enter the liver cell as two different forms of *sporozoites*: one strain immediately enters into a phase of reproduction (**2a, 2b, 2c**); and the other, called *hypnozoite* (Gr.: *hypno*=sleep, *zōon*=animal), lies dormant in the liver cell (**2d red cell**). The *hypnozoites* enter into reproductive phases at different times (**2e, 2f**), even after months or years, depending upon the species, and are therefore responsible for the well-known relapses of *Plasmodium vivax* and *Plasmodium ovale*. These relapses may persist for months or years, even though an antimalarial regimen has been meticulously followed.

### The Red Cell: Life at the Expense of the Red Corpuscle

From the liver, the *merozoites* enter the bloodstream and penetrate the red blood cells (**3g**), where they multiply in cycles. Each *merozoite*, feeding at the expense of the red cell, grows into a ring-shaped parasite called *trophozoite* (Gr.: *trophé*=nourishment; *zōon*=animal) (**3h**). Upon reaching its full size (about .016 mm), each *trophozoite*, through repeated divisions of the nucleus, forms a *schizont*, a cluster containing sixteen to twenty-four new oval-shaped parasites, again called *merozoites* (**3l**). When the infected red blood cells burst, the *merozoites* flood the circulation and invade fresh red blood cells to start new cycles of reproduction (**3m, n, o, p**). These cycles repeat themselves every two to three days depending on the species. The rhythmic release of so many parasites into the circulation — estimated at a quarter of a billion — coincides with the characteristic clinical picture of malaria: periodic high fever, preceded by shivering and followed by profuse sweating.

### The Mosquito: The Sexual Life of the Parasite

Some *merozoites* are distinguished from others in that they grow in the red blood cell without dividing. They transform themselves into sexual cells, the male and female *gametocytes* (Gr.: *gameté*=wife, *gamétes*=husband; *kítos*=cell) which are necessary for the perpetuation of the parasite (**3q**). However, they can mature only outside the human body, and because they cannot leave the bloodstream on their own, they need outside help — the *Anopheles* mosquito. During evolution, an affinity developed between the malaria parasite and the *Anopheles*: the *Anopheles* requires blood for the protein she needs to lay her eggs and the parasite requires a host in which it can reproduce.

When the *Anopheles* bites an infected person, the *merozoites* drawn from the bloodstream are digested in the stomach of the mosquito, while the *gametocytes* (**4q**) develop in the intestine into mature cells called *gametes*, the female ovule and the male spermatozoon (**4r**). The fertilized eggs, *ookinete* (Gr.: *ōon*=egg; *kinesis*=motion) (**4t**), moves to the outside wall of the mosquito gut where, by secreting a cyst wall around itself, it develops into an *oocyst* (**4u, v**), which will give rise to a myriad of new parasites, the *sporozoites*. As soon as these *sporozoites* (**4z**) are released from the *oocyst* they migrate to the salivary glands of the *Anopheles*, waiting to be injected into the next victim. The endless cycle starts all over again.

## HOW TO AVOID ANOPHELES' BITE

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### The World of Anopheles

To visualize the mechanism of malaria transmission in a given area, one must take into consideration the behaviour of the local species of *Anopheles*. Understanding her habits will give you a better chance of protecting yourself against her bite.

Like humans, anopheline mosquitoes are concerned with food, shelter and reproduction. Will she feed on humans or on domestic animals? Will she enter human dwellings to bite or will she feed outdoors? Does she prefer to bite soon after dusk, late at night or at dawn? Will she use houses as a daytime resting place or will she seek shelter in dense vegetation? Will she breed in peridomestic waters such as small ponds, footprints or artificial containers, or far away in large bodies of water? Different preferences characterize each species. Take for instance *Anopheles gambiae*, the mosquito responsible for so many deaths in Africa south of the Sahara. She chooses her breeding place a few yards from your habitation. She may even be travelling with you by car, plane or boat. In fact she once crossed the Atlantic by boat spreading malaria along the northeastern coast of Brazil. On the other hand, the main vector of malaria in the Philippines, the *Anopheles flavirostris*, has different habits. She prefers to breed along the margins of foothill streams and lakes, and her presence is confined to rural areas. That is why, although there is no malaria in large cities like Manila, there is malaria transmission in African cities south of the Sahara.

Two factors influence the reproduction of *Anopheles*: Rainfall and temperature. The rainy season, bringing an increase in the anopheline population, will determine the annual high-risk period of malaria transmission. Lower temperatures will decrease the *Anopheles* populations and more importantly, will arrest

the development of parasites in the mosquito's gut. Since temperature lowers with increased altitude, transmission of the disease is not possible over a certain height above sea level. See IAMAT's *World Malaria Risk Chart* for country details.

### The Super Anopheles

With the knowledge of the habits of the *Anopheles*, humans learned to fight her by poisoning her resting places with DDT. A single indoor spraying, leaving a layer of microscopic crystals, made surfaces lethal to mosquitoes for months. But, although this residual insecticide reversed the odds in the struggle, within a few years the *Anopheles* had developed a resistance to these chemicals. Other pesticides followed, always with the same inglorious result. Today, many species of *Anopheles* have been reported resistant to traditional insecticides. The more recent insecticides, the carbamate compounds, are not suitable because of their high cost and short residual action period. Furthermore, some *Anopheles* are already showing resistance to these new compounds. Because of these 'super *Anopheles*', malaria is making a comeback in areas where infection was reduced or eliminated. This situation puts a renewed emphasis on effective mosquito bite prevention methods and their use.



**Fig. 3** Example of a rectangular mosquito bed net with free-standing aluminum frame.

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## METHODS OF PROTECTION

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When in a malarious area, you need to use multiple methods of protection to prevent mosquito bites and malaria infection. Remember: The *Anopheles* can be difficult to detect and you may never know that you have been bitten until it's too late. For effective protection, use multiple methods to prevent mosquito bites in combination with antimalarial drugs.

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### MOSQUITO BITE PROTECTION: FOUR ESSENTIAL STEPS

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The following precautions require self-discipline and should be taken every day beginning at sunset by anyone visiting malarious areas.

#### 1. Wear protective clothing

Beginning at sunset, wear long-sleeved shirts and long pants in light colours such as beige or yellow. Dark clothing attracts mosquitoes, as does the scent of perfume or after-shave lotion.

Spray your clothes with products like REPEL, Sawyer Permethrin Clothing Treatment or Coulston's Duranon Tick Repellent. These repellents have been proven to be very effective at repelling mosquitoes and remain effective

through several washes by binding themselves tightly to fabric. These products are available in many travel health clinics and outdoor equipment stores. (Note: Permethrin solutions and sprays are not sold in Canada.) Follow the manufacturer's instructions.

#### 2. Use mosquito repellent

Apply mosquito repellent – available in sprays, lotions, and towelettes – to all exposed areas of skin, as well as clothes, avoiding the eyes and mouth. Look for repellents containing 20 – 30% DEET or 20% Picaridin. These active ingredients keep mosquitoes away but do not kill them. Since repellent gradually evaporates and some will be lost through perspiration, swimming, and active exercise, re-apply every few hours according to the manufacturer's directions for continuous protection. Caution: Repellent may damage plastic items such as eye-glass frames, watch crystals, and nail polish.

#### 3. Secure dwelling and sleeping area

Ensure that the window and door screens of your room fit tightly and are free of holes. At the same time, check the screens to be sure the mesh is small enough to prohibit the entrance of any mosquitoes.

Use Pyrethrin insecticides (brand name: Raid and others) indoors. Pyrethrin insecticide (active ingredient pyrethrin, extracted from the pyrethrum flower, a member of the chrysanthemum family) kills mosquitoes instantly by acting on the central nervous system. Frequent spraying is necessary since pyrethrin dissipates when exposed to air. Spray your bed net (if not already treated with permethrin) and under the bed, as well as walls, baseboards, corners, furniture, behind picture frames and inside closets in the bedroom, and under the sink in the bathroom. Cover any food and cooking utensils. Do not open windows while spraying, and allow vapour to settle before returning to the room. Products with pyrethrin should be used with caution. Follow the manufacturer's instructions.

#### 4. Use a mosquito bed net

A mosquito bed net is one of the most effective forms of protection against malaria. This is because it prevents mosquito bites while you are asleep at night – the time when the *Anopheles* is most active. In fact, studies have demonstrated that widespread use of bed nets is associated with 17% reduction in child mortality in countries where malaria is endemic.

In malarious areas, unscreened bedrooms require insecticide-treated mosquito bed nets (except in buildings with sealed windows and central air conditioning). If possible, bed nets

► Important...

## About Malaria Infections and Early Diagnosis

**All malaria infections are serious illnesses and must be treated as a medical emergency. Travellers should be aware that infection with *Plasmodium falciparum* malaria is the most dangerous and often fatal form of the disease.**

**The appearance of chloroquine resistant and / or multidrug resistant *P. falciparum* in many malarious areas makes the choice of suppressive drugs problematic as none of the medications currently used are 100% effective. Regardless of which antimalarial medication is being used, it is of utmost importance for travellers and their physicians to consider fever and flu-like symptoms appearing 7 days, weeks or up to several months after leaving a malarious area as a malaria breakthrough. Early diagnosis is essential for successful treatment.**

Reliable information on malarious areas, sound knowledge of your destination's geography, including understanding the feeding and breeding habits of the local *Anopheles* mosquitoes, will help you to take the appropriate protective measures. See IAMAT's *World Malaria Risk Chart* for country details.

should be rectangular in shape. Cone-shaped nets are not ideal because your skin may touch the netting allowing the *Anopheles* to bite through. Ceiling hook bed nets may not be feasible due to the height of the ceiling or problems installing a hook.

Netting should be made of cotton or synthetic thread to allow the movement of air. The net must be white to allow mosquitoes to be seen against the background and should have a wide, tightly woven border to be tucked under the mattress.

A netting of 285 holes per square inch will prevent even the smallest *Anopheles* from penetrating. Not one single tear should be permitted since mosquitoes will spend hours searching for an opening.

**How to use a bed net:** During the day, the bed net should be left hanging in a knot from the frame or the ceiling. Before retiring, lower the net and search carefully for mosquitoes hidden inside. Mend any holes or tears with adhesive tape or thread. From inside, tuck the edge of the bed net under the mattress, making sure there are no openings. If you are camping, check the surrounding area for possible *Anopheles* breeding places.

To provide additional protection, soak your bed net in a permethrin solution like Sawyer Permethrin Soak Treatment Kit. Permethrin can repel and kill mosquitoes upon contact. (Note: Permethrin solutions and sprays are not sold in Canada.)

Bed nets are a highly effective form of protection and should be used in conjunction with other mosquito bite prevention measures and preventive medication. Bed nets also provide protection against other diseases transmitted by mosquitoes, such as filariasis, and prevent other insects, such as ticks, beetles, flies, and spiders, from entering your bed at night.

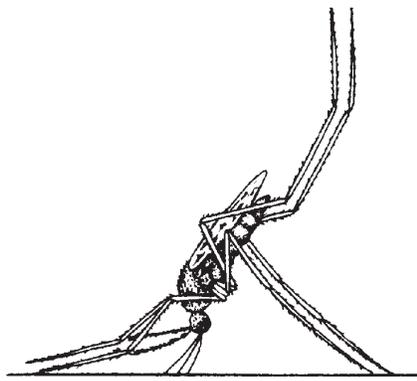
## ANTIMALARIAL DRUGS

There are 2 types of antimalarial drugs used to suppress the clinical symptoms of malaria, but they will not prevent the establishment of a malaria infection. If antimalarial drugs were true prophylactics (Gr.: *prophylasso* = to guard before) they would prevent malaria infection by killing the parasites (*sporozoites*) the moment they are introduced into your bloodstream by the bite of the *Anopheles*.

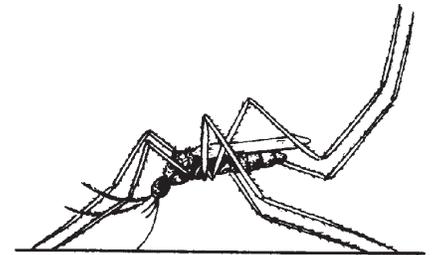
Instead, antimalarial medications act by eliminating the parasites during their multiplication phase in the liver stage (antovaquone-proguanil, tafenoquine, and primaquine) or their replication phase in the red blood cells, red cell cycle (chloroquine, doxycycline, and mefloquine hydrochloride). Suppressive medication will eliminate the parasites caused by *P. falciparum*, *P. malariae*, and *P. knowlesi*, 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.

- It is imperative that you take the medication at regular intervals throughout your stay in a malarious region, and you should continue to do so for 1-4 weeks (depending on the regimen) after leaving the area.
- Taking the full course of suppressants is essential even for a short stay. Remember, one single bite is sufficient to infect you.
- If you are on a weekly regimen, always take your suppressant the same day and if you are on a daily regimen, take it at the same hour every day. Establish this as a habit so you will not forget. Take the suppressant with plenty of water to reduce stomach discomfort which may occur occasionally.

Two factors influence the reproduction of *Anopheles*: Rainfall and temperature. The rainy season, bringing an increase in the anopheline population, determines the annual high-risk period of malaria transmission. Lower temperatures will decrease the *Anopheles* populations and will arrest the development of parasites in the mosquito's gut.



*Anopheles*



*Culex*

**Fig. 4** *Anopheles* and *Culex* mosquitoes.

- Since an adequate concentration of the drug in the blood is reached a few hours after ingestion, you may start the medication on the day of your departure. However, it is advisable to start your regimen one to two weeks before leaving — while still at home you will acquire confidence with the drug and you can seek the advice of your family physician in case of any adverse reaction.
- It would be ideal to take a complete supply of medication with you to avoid any problems getting the antimalarial drugs that were prescribed for you in another country. Be aware of counterfeit malaria medications at your destination. They're packaged very similarly to the real ones and could put your life at risk. Always get your medication from a reputable pharmacist.

500 mg (300 mg base). START 1 WEEK BEFORE ENTERING MALARIOUS AREA, CONTINUE WEEKLY DURING YOUR STAY AND CONTINUE FOR 4 WEEKS AFTER LEAVING. TAKE IT AFTER A MEAL TO AVOID STOMACH UPSETS.

**b. Alternative:**

**Hydrochloroquine sulfate (brand name: Plaquenil, Axemal and others; generics available)**  
TAKE IN WEEKLY DOSES OF 400 mg (310 mg base). START 1 WEEK BEFORE ENTERING MALARIOUS AREA, CONTINUE WEEKLY DURING YOUR STAY AND CONTINUE FOR 4 WEEKS AFTER LEAVING.

**c. Other options are atovaquone-proguanil, doxycycline, mefloquine hydrochloride, or tafenoquine (see #2 for details).**

**d. Travellers on short-term trips to areas with mainly *P. vivax* malaria can take primaquine phosphate (brand name: Primaquine, Malarid):**  
TAKE 1 TABLET of 52.6 mg (30 mg base) DAILY. START 1-2 DAYS BEFORE ENTERING MALARIOUS AREA, CONTINUE DAILY DURING YOUR STAY AND CONTINUE FOR 7 DAYS AFTER LEAVING.  
**Note:** Screening for G6PD levels must be done prior to taking this drug.

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## CHEMOPROPHYLAXIS GUIDELINES

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In offering guidance on the choice of antimalarial drugs, the main concern is to provide protection against *Plasmodium falciparum*, the most dangerous form of the illness. The dosages below are for adults. For children see 'Pediatric Malaria Chemoprophylaxis Dosages' on page 12. Contraindications, precautions, and side effects for the following medications are listed on page 10.

- 1. Travellers to areas with *P. falciparum* malaria sensitive to chloroquine should take the following regimen:**
  - a. Chloroquine phosphate or sulfate (brand names: Aralen, Resochin and others; generics available)**  
TAKE IN WEEKLY DOSES OF

*The recommendations for malaria prophylaxis outlined here are intended as guidelines only and may differ according to where you live, your health status, age, destination, trip itinerary, type of travel, and length of stay. Seek further advice from your physician or travel health clinic for the malaria prophylactic regimen most appropriate to your needs.*

**2. Travellers to areas with chloroquine resistant and / or multidrug resistant *P. falciparum* malaria should take ONE of the following regimens:**

**a. Atovaquone-Proguanil (brand names: Malarone, Malanil and others; generics available)**

TAKE 1 TABLET DAILY (ATOVAQUONE 250 mg + PROGUANIL 100 mg). START 1-2 DAYS BEFORE ENTERING THE MALARIOUS AREA, CONTINUE DAILY DURING YOUR STAY AND CONTINUE FOR 7 DAYS AFTER LEAVING.

**b. Doxycycline (brand name: Vibramycin and others; generics available)**

TAKE 1 TABLET OF DOXYCYCLINE (100 mg) DAILY. START 1 DAY BEFORE ENTERING MALARIOUS AREA, CONTINUE DAILY DURING YOUR STAY AND CONTINUE FOR 4 WEEKS AFTER LEAVING.

**c. Mefloquine hydrochloride (brand names: Lariam, Mephaquin, Mefliam and others; generics available)**

TAKE 1 TABLET OF 250 mg (228 mg base) ONCE A WEEK. START 1-2 WEEKS BEFORE ENTERING THE MALARIOUS AREA, CONTINUE WEEKLY DURING YOUR STAY AND CONTINUE FOR 4 WEEKS AFTER LEAVING.

**d. As an alternative to the above regimens, travellers on short trips can take Tafenoquine (brand name: Arakoda):**

TAKE 1 TABLET OF 200 mg. START TAKING DAILY FOR 3 DAYS BEFORE ENTERING MALARIOUS AREA AND CONTINUE WEEKLY DURING YOUR STAY. AFTER LEAVING THE RISK AREA, TAKE ONE TABLET 1 WEEK AFTER THE LAST DOSE.

**Note:** Tafenoquine is only available in the USA and Australia. Screening for G6PD levels must be done prior to taking this drug.

**e. Antimalarial regimen for travellers who cannot follow one of the above regimens:**

Take chloroquine or hydrochloroquine (see #1 above). Note that these drugs are much less effective in this country than atovaquone-proguanil, doxycycline or mefloquine hydrochloride. Seek immediate medical attention if you have flu-like symptoms — fever, headache, nausea, general malaise — appearing about 7 days or later after entering the malarious area.

**Note:** It is imperative to use a mosquito bed net to avoid the bite of the nocturnal Anopheles mosquito. Use repellents and insecticides as described in 'Four Steps to Mosquito Protection' on page 4.

**3. Travellers going to mefloquine hydrochloride and multidrug resistant *P. falciparum* malaria areas should take an atovaquone-proguanil or doxycycline regimen as described above. Persons who cannot follow one of these regimens or contemplate a long term visit to these areas should seek advice for a possible alternative drug regimen from a travel medicine specialist. Contact IAMAT for referrals.**

Treatment of a breakthrough with multidrug resistant malaria should be given under medical supervision and may include a variety of drugs in different combinations. Fast medical attention is imperative for successful treatment.

The following areas report *P. falciparum* malaria resistance to chloroquine, mefloquine hydrochloride and sulfadoxine-pyrimethamine:

**Cambodia:** The provinces of Siem Reap, Preah Vihear, Oddar Meanchey, Banteay Meanchey, Battambang, Pailin, Pursat, Kampat, and Koh Kong. The southern and western provinces also report resistance to artesunate, lumefantrine and piperazine. Chloroquine resistance to *P. vivax* malaria has also been reported in this country.

**China:** Rural areas in Yunnan province and the southeastern tip of Tibet.

**Laos:** The northwestern provinces of Bokeo and Louang Namtha bordering Myanmar|Burma and China; and the southern provinces of Salavan and Champasak bordering Thailand.

Take a complete supply of medication on your trip to avoid any problems getting the antimalarial drugs that were prescribed for you. Be aware of counterfeit malaria medications at your destination. They're packaged very similarly to the real ones and could put your life at risk. Always get your medication from a reputable pharmacist.

## ADULT MALARIA CHEMOPROPHYLAXIS DOSAGES

For recommended antimalarial drugs at your destination, consult IAMAT's *World Malaria Risk Chart* for country details.

Antimalarial Drug <sup>1</sup>	Brand Name	Tablet base + salt content	Number of tablets	Timing of dosage in a malarious area <sup>2</sup>	Indications for Use
<b>Atovaquone-Proguanil</b>	Malarone and others; generics	250 mg Atovaquone + 100 mg Proguanil	1	Start: 1-2 days before During: Daily After: 7 days after leaving	All malarious areas. Breastfeeding mothers. Children > 5 kg / 11 lb.
<b>Chloroquine phosphate or sulfate</b> <i>Dosages may differ slightly among manufacturers</i>	Aralen and others; generics	300 mg (500 mg salt)	1	Start: 7 days before During: Once a week After: 4 weeks after leaving	For chloroquine-sensitive areas. Pregnancy (all trimesters). Breastfeeding mothers.
		Alternative dose: 150 mg (250 mg salt)	2		
<b>Hydroxychloroquine sulfate</b> <i>Dosages may differ slightly among manufacturers</i>	Plaquenil and others; generics	310 mg (400 mg salt)	1	Same as above.	Same as above.
<b>Doxycycline</b>	Vibramycin and others; generics	100 mg	1	Start: 1-2 days before During: Daily After: 4 weeks after leaving	All malarious areas.
<b>Mefloquine hydrochloride</b>	Lariam and others; generics	228 mg (250 mg salt)	1	Start: 1-2 weeks before During: Once a week After: 4 weeks after leaving	All malarious areas. Pregnancy (all trimesters considered safe). Breastfeeding mothers.
<b>Tafenoquine</b> <i>Only available in the USA and Australia.</i>	Arakoda	200 mg	1	Start: 3 days before During: Once a week After: Once 7 days after leaving	Persons 18 years of age and over. All travellers, including mothers and their breastfeeding babies must be screened for G6PD levels before taking this drug.
<b>Primaquine phosphate</b>	N/A	30 mg (52.6 mg salt)	1	Start: 1-2 days before During: Daily After: 7 days after leaving	For areas with primarily <i>P. vivax</i> malaria. All travellers, including mothers and their breastfeeding babies must be screened for G6PD levels before taking this drug.

<sup>1</sup> All antimalarial drugs have precautions and contraindications. See 'Description of Antimalarial Drugs: Contraindications, Precautions, and Side Effects' on this page. Talk to your healthcare provider to choose the best regimen for you.

<sup>2</sup> Depending on the regimen, take your antimalarial daily at the same time every day or weekly during the same day of the week. This will help you remember to take the medication.

**Myanmar|Burma:** The states of Bago, Kayah, Kachin, Kayin, Shan and Tanintharyi (eastern half of the country including the areas bordering China, Laos and Thailand). Resistance to artemisinin is reported from southeastern parts of the country. Chloroquine resistance to *P. vivax* malaria has also been reported in this country.

**Suriname:** This country reports *P. falciparum* resistance to chloroquine, mefloquine hydrochloride, sulfadoxine-pyrimethamine and some decline in quinine sensitivity.

**Thailand:** The western border areas with Myanmar|Burma: forested hilly areas of Chang Rai, Chang Mai, Mae Hong Son, Tak, Kanchanaburi, Ratchaburi and Petchaburi provinces (these areas also report *P. falciparum* resistance to quinine and artemisinin); the eastern border areas with Cambodia: forested hilly areas of Ubon Ratchathani, Si Sa Ket, Surin, Buriram, Sa Kaeo, Chantaburi, and Trat provinces.

**Vietnam:** The provinces of Dak Lak, Dak Nong, Gia Lai, Khan Hoa, Kon Tum, Lam Dong, Ninh Thuan, Song Be and Tay Ninh.

### DESCRIPTION OF ANTIMALARIAL DRUGS: CONTRAINDICATIONS, PRECAUTIONS, AND SIDE EFFECTS

#### 1. Atovaquone-Proguanil

This antimalarial is effective for the prevention of chloroquine-resistant and multidrug-resistant *P. falciparum* malaria. CAUTION: May cause mild side effects when used for prophylaxis such as stomach upsets, vomiting, headaches, nausea. Take with food or milk.

#### CONTRAINDICATIONS:

Persons suffering from renal (kidney) disorders or with known allergies to atovaquone or proguanil should not use this drug. The safety of this drug

in pregnancy, nursing mothers and children weighing less than 5kg / 11 lb has not been established. Atovaquone-proguanil is available by prescription for prophylaxis and treatment.

## 2. Chloroquine

This antimalarial drug is commonly used around the world for the suppression of *P. falciparum* malaria in areas where the parasites are still sensitive to it. In case of infection, chloroquine will completely cure malaria caused by sensitive strains of *P. falciparum*. For chloroquine-sensitive malarious areas see IAMAT's *World Malaria Risk Chart*.

Chloroquine is also the drug of choice for the suppression of malaria caused by *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Travellers should be aware that chloroquine will not always prevent delayed first attacks or relapses of malaria months to years after departure from malarious areas even when the chloroquine regimen has been followed meticulously. Depending on the strain (subspecies) of the parasite, these delayed attacks develop in 30-70% of people.

**INCONVENIENCES:** The bitter taste makes the drug unpalatable. Minor stomach upsets, itching skin, nausea and diarrhea may occur; it may also cause blurred vision and a transitory headache. Hydroxychloroquine is an alternative drug that may be better tolerated than chloroquine.

**CAUTION:** Since chloroquine is deposited in high concentration in the liver and white blood cells, it should be used with caution if you have a liver condition, alcoholism or a blood disorder. Patients on phenylbutazone should discontinue this drug while taking chloroquine since it may enhance the chances of dermatitis. It may also aggravate the condition of persons suffering from porphyria and psoriasis.

**CONTRAINDICATIONS:** Due to the adverse effect of chloroquine on the optic nerve, persons with diseases of the retina and optic nerve (e.g. diabetic retinopathy, optic neuritis) should not use this drug. Persons contemplating a prolonged course with chloroquine should have an eye

examination at least once a year to detect any changes in the retina. Travellers with a history of epilepsy should not take chloroquine.

## 3. Doxycycline

This drug belongs to the tetracycline group of antibiotics and is effective in preventing malaria in multidrug resistant areas. It is also used in combination with quinine for the treatment of severe and multidrug resistant malaria.

**CAUTION:** Doxycycline may cause photosensitive skin reactions. Avoid exposure to direct sunlight and use sunscreen with high protection against UVA (long range ultraviolet radiation) to minimize risk of photosensitive reaction. It may also cause vaginal yeast infections in women, and produce antibiotic-resistant pathogenic bacteria. Antibiotic-associated colitis, a severe form of diarrhea, can also follow with prolonged use of this drug.

**CONTRAINDICATIONS:** Doxycycline should not be used by persons with known photosensitive skin reactions. It is contraindicated for pregnant and breastfeeding women, and children younger than 8 years of age. Tetracyclines permanently stain the teeth of unborn babies, infants and children up to eight years of age.

## 4. Mefloquine hydrochloride

This antimalarial is very effective for the prevention of chloroquine-resistant and multidrug-resistant *P. falciparum* malaria. However, it may not always prevent a delayed first attack or relapses caused by *P. vivax*.

**CAUTION:** Side effects include nausea and headache, including neurological side effects such as dizziness, ringing of the ears, and loss of balance. Psychiatric side effects include anxiety, depression, mistrustfulness, and hallucinations. Neurological side effects can occur any time during use and can last for long periods of time or become permanent even after the drug is stopped. Seek medical advice if any neurological or psychiatric side effects occur.

**CONTRAINDICATIONS:** Persons with a history of depression, anxiety, psychosis, schizophrenia or other psychiatric disorders, as well as cardiac abnormalities,

In offering guidance on the choice of antimalarial drugs, the main concern is to provide protection against *Plasmodium falciparum*, the most dangerous form of the illness.

liver diseases, or epilepsy should not use this drug. Mefloquine hydrochloride may interact with agents such as beta blockers, digoxin, calcium channel blockers, and metoclopramide. If mefloquine hydrochloride is taken for long term prophylaxis periodic liver function tests and ophthalmic examinations should be performed.

#### 5. Tafenoquine

This drug is used for prophylaxis for persons typically on short-term travel. It is also used for the treatment of *P. vivax* and *P. ovale* parasites in the liver stage to prevent future malaria attacks.

**Note:** Tafenoquine is only available in the USA and Australia.

**CAUTION:** Tafenoquine may cause nausea, dizziness, abdominal pain, vomiting, diarrhea, and back pain.

**CONTRAINDICATIONS:** This drug is contraindicated for persons with glucose-6-phosphate dehydrogenase deficiency (G6PD). All travellers must be tested for G6PD levels before this drug is prescribed or administered. It is contraindicated during pregnancy. Breastfeeding children must be tested for G6PD deficiency before the mother can take the medication. This drug is also contraindicated for persons under 18 years of age and those with a history of psychiatric disorder or ongoing psychotic symptoms.

#### 6. Primaquine

This drug is used for prophylaxis for persons on short term travel to areas with mostly *P. vivax* malaria or as an alternative drug regimen for travellers who cannot take other antimalarial drugs. It is also used for treatment to eradicate *P. vivax* and *P. ovale* parasites in the liver stage to prevent future malaria attacks.

**CAUTION:** Primaquine may cause nausea and abdominal pain. Take tablets with food.

**CONTRAINDICATIONS:** This drug is contraindicated for persons with glucose-6-phosphate dehydrogenase deficiency (G6PD). All travellers must be tested for G6PD levels before this drug is prescribed or administered. It is also contraindicated during pregnancy. Breastfeeding children must be tested for

G6PD deficiency before the mother can take the medication.

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## DRUGS USED FOR MALARIA TREATMENT

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The following are some of the drugs used for the treatment of malaria.

#### Artemether-lumefantrine (brand name: Coartem)

This drug is used for the treatment of severe malaria. It is a compound drug derived from the Chinese medicinal plant Qinghao (*Artemisia annua*) also known as sweet wormwood and is an Artemisinin Combination Therapy (ACT).

**Do not use as malaria prophylaxis.**

#### Atovaquone-Proguanil (brand name: Malarone; generics available)

This drug is used for treatment of uncomplicated malaria, but should not be used as treatment if taken for prophylaxis.

#### Tafenoquine (brand name: Krintafel, Kozenis) and Primaquine phosphate (brand name: Primaquine, Malarid)

These drugs are used for the eradication of liver stage malaria parasites of *P. vivax* and *P. ovale* to prevent future malaria attacks.

Tafenoquine and primaquine can also be used as prophylaxis for persons on short term travel. They are contraindicated for persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency. They are also contraindicated during pregnancy. Patients (including breastfeeding children) must be tested for G6PD before these drugs can be prescribed or administered. Tafenoquine is also contraindicated for treatment (prevention of relapse) for persons under 16 years of age and should be used with caution for persons with a history of psychiatric disorder or ongoing psychotic symptoms.

**Note:** Tafenoquine is only available in the USA and Australia.

#### Quinine and Quinidine

Quinine sulfate (brand name: Qualaquin and others), Quinine dihydrochloride (brand name: Quininject and others) and Quinidine gluconate (brand name: Quinaglute and others) are drugs derived from the cinchona bark and used in combination with other antimalarial drugs for the treatment of severe multidrug resistant *P. falciparum* malaria when Artemisinin Combination Therapies (ACTs) are not available. They must be administered under close medical supervision due to potential side effects. **Do not use for malaria prophylaxis.**

You will undoubtedly encounter fellow travellers who are on a different malaria suppressive regimen. It is highly recommended that you continue with the medication prescribed for you by your doctor or travel health specialist and never switch to any medication offered as a “better choice” by other travellers.

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## MALARIA DRUGS AVAILABLE ABROAD

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Travellers to malarious areas will encounter fellow travellers who are on a different malaria suppressive regimen. It is highly recommended that you continue with the medication prescribed for you by your doctor or travel health specialist and never switch to any medication offered as a “better choice” by other travellers.

The following is a short discussion of some medications used abroad.

### Artemisinin Combination Therapies (ACT)

Artemisinin (Qinghaosu) and its derivatives Artemether, Artesunate, Dihydroartemisinin are isolates of the Chinese medicinal plant Qinghao (*Artemisia annua*) also known as sweet wormwood. These drugs are used in combination with other antimalarial drugs for the treatment of severe malaria. **Do not use for malaria prophylaxis.**

- **Artemether-lumefantrine**  
(brand names: Coartem, Riamet)
- **Artesunate + Amodiaquine**  
(brand name: Coarsucam)
- **Artesunate + Mefloquine hydrochloride**  
(brand name: Mefliam Plus and others)
- **Artesunate + Sulfadoxine-pyrimethamine** (brand names: Artescope, Supysunate and others)
- **Dihydroartemisinin + Piperaquine**  
(brand name: Artequick)

### Amodiaquine Dihydrochloride (brand names: Camoquin, Flavoaquine, others; generics)

Belonging to the same chemical family as chloroquine (4-aminoquinoline), this drug offers similar protection to chloroquine, but experience has shown that it causes serious side effects such as hepatitis and agranulocytosis. Amodiaquine is used in combination with artesunate as an Artemisinin Combination Therapy (ACT) for the treatment of severe malaria.

**Do not use for malaria prophylaxis.**

### Chloroquine-Proguanil (brand name: Savarine)

This combination drug eliminates the difficulty of taking chloroquine on a weekly basis and proguanil on a daily basis. However, its usefulness is compromised by the high resistance of *P. falciparum* malaria to both chloroquine and proguanil.

### Dapsone-Pyrimethamine (brand name: Maloprim)

This alternative to sulfadoxine-pyrimethamine (Fansidar) **should not be used for malaria prophylaxis.**

### Halofantrine (brand name: Halfan)

Halofantrine is used for the treatment of chloroquine-resistant and sulfadoxine-pyrimethamine resistant *P. falciparum* malaria mostly in Africa. **Not recommended for prophylaxis or treatment** since this drug causes severe adverse effects (including death) in persons with or without pre-existing cardiac conditions.

### Proguanil (brand name: Paludrine)

Although proguanil hydrochloride is the oldest and safest of malaria suppressants, *P. falciparum* parasites have become so highly resistant to it that its usefulness is seriously compromised in all malarious areas. Studies have shown that using proguanil is less effective against *P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi* malaria than chloroquine. **Proguanil should not be used on its own as a malaria suppressant.**

### Sulfadoxine-pyrimethamine (brand name: Fansidar)

There is widespread resistance of *P. falciparum* malaria parasites against this drug. **It should not be used for prophylaxis** as potential serious side effects may develop after multiple doses. Sulfadoxine-pyrimethamine is used in combination with artesunate as an Artemisinin Combination Therapy (ACT) for treatment of severe malaria.

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## EMERGENCY SELF TREATMENT (EST)

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Travellers should take an Emergency Self Treatment regimen if: Fever, chills, and flu-like symptoms occur in a remote area where qualified medical attention cannot be reached within 24 hours; using a prophylactic regimen that is not optimal due to resistance; or antimalarial prophylactics cannot be taken for medical reasons.

Discuss Emergency Self Treatment options with your physician before your trip and ensure that you get specific written instructions, including indications, dosages, and information on side effects. After taking Emergency Self Treatment, seek medical care for evaluation as soon as possible.

Atovaquone-proguanil (Malarone) or artemether-lumefantrine (Coartem) are the drugs of choice for EST for both adults and children, however, they both have contraindications. Also note that the Emergency Self Treatment cannot be the same as your prophylactic regimen. See table

If you have fever and flu-like symptoms appearing 7 days, weeks or up to several months after your trip, don't forget to tell your doctor that you were in a malarious area. Early diagnosis is essential for successful treatment.

## PEDIATRIC MALARIA CHEMOPROPHYLAXIS DOSAGES

For recommended antimalarial drugs at your destination, consult IAMAT's *World Malaria Risk Chart* for country details.

Antimalarial Drug <sup>1</sup>	Brand Name	Tablet base + salt content	Weight	Number of tablets <sup>2</sup>	Frequency
<b>Atovaquone-Proguanil</b>	Malarone Pediatric	62.5 mg Atovaquone + 25 mg Proguanil	< 5kg / 11lb	Contraindicated	Start: 1-2 days before During: Daily After: 1 week after leaving
			5-8 kg / 11-18 lb	1/2	
			> 8-10 kg / 18-24 lb	3/4	
			> 11-20 kg / 24-44 lb	1	
			> 20-30 kg / 44-66 lb	2	
			> 30-40 kg / 66-88 lb	3	
			> 40 kg / 88 lb	1 adult tablet	
<b>Chloroquine phosphate or sulfate</b> <i>Dosages may differ slightly among manufacturers</i>	Aralen and others; generics	5 mg / kg (8.3 mg / kg salt)	Measure dose according to body weight	Calculated up to a maximum of 300 mg base / week	Start: 1 week before During: Once a week After: 4 weeks after leaving
<b>Hydroxychloroquine sulfate</b> <i>Dosages may differ slightly among manufacturers</i>	Plaquenil and others; generics	5 mg / kg (6.5 mg / kg salt)	Measure dose according to body weight	Calculated up to a maximum of 310 mg base / week	Start: 1 week before During: Once a week After: 4 weeks after leaving
<b>Chloroquine sulfate syrup<sup>3</sup></b>	Nivaquine Syrup	1 tsp. = 5 ml (25 mg) of chloroquine base	<i>Corresponds approximately to:</i>	1/2 tsp.	Start: 1 week before During: Once a week After: 4 weeks after leaving
			5-9 kg / 11 lb = 2.5 mL	1 tsp.	
			10-19 kg / 24-43 lb = 5 mL	2 tsp.	
			20-29 kg / 44-65 lb = 10 mL	3 tsp.	
			30-39 kg / 66-87 lb = 15 mL	4 tsp.	
			40-49 kg / 88-109 lb = 20 mL	5 tsp.	
<b>Doxycycline</b> <i>Dosages may differ slightly among manufacturers</i>	Vibramycin and others; generics	2.2 mg / kg	< 8 years	Contraindicated	Start: 1-2 days before During: Once a week After: 4 weeks after leaving
			≥ 8 years	Measure dose according to body weight	
<b>Mefloquine hydrochloride</b>	Lariam and others; generics	4.6 mg (5 mg salt)	≤ 9 kg / 20 lb	Calculated according to 4.6 mg base / kg / week	Start: 1-2 weeks During: Once a week After: 4 weeks after leaving
			> 9-19 kg / 20-42 lb	1/4	
			> 19-30 kg / 42-66 lb	1/2	
			> 30-45 kg / 66-99 lb	3/4	
			> 45 kg / 99 lb	1	
<b>Primaquine phosphate<sup>4</sup></b>	N/A	0.5 mg (0.8 mg salt)	Measure dose according to body weight	Calculated up to a maximum of 30 mg base / day	Start: 1-2 days During: Daily After: 1 week after leaving

<sup>1</sup> All antimalarial drugs have precautions and contraindications. See 'Description of Antimalarial Drugs: Contraindications, Precautions, and Side Effects' on page 8. Talk to your healthcare provider to choose the best regimen for your child.

<sup>2</sup> Your pharmacist will be able to crush tablets and prepare pediatric dosages in gelatin capsules if needed.

<sup>3</sup> Nivaquine Syrup is not available in the United States or Canada, but can be purchased in Europe and malarious areas.

<sup>4</sup> Children must be screened for G6PD levels before using this drug.

‘Emergency Self Treatment – Adult and Pediatric Dosages’ on page 14.

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### ANTIMALARIAL REGIMENS FOR CHILDREN

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Parents should keep malaria medications out of reach of children since misuse can result in death. Breastfed infants are not protected by their mother’s prophylactic regimen, but must be given their own dosages according to their weight. Children should always sleep under a bed net. Anti-mosquito repellents are safe but should be applied sparingly to the exposed parts of the body, avoiding the hands and face entirely.

School age children are very vulnerable to malaria. Children on holidays to visit parents working in the tropics should be watched to ensure that they continue taking the suppressive regimen after their return to school. Their guardians must be warned that fever and flu-like symptoms appearing 7 days, weeks or up to several months after their return may signify a malaria breakthrough and early diagnosis is imperative for successful treatment. See table, ‘Pediatric Malaria Chemoprophylaxis Dosages’ on page 12.

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### ANTIMALARIAL REGIMENS DURING PREGNANCY

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Since all drugs taken by a pregnant woman reach her unborn child, it is never advisable to take any medications if not absolutely necessary. However, if travel to a malarious region cannot be avoided, the risk of miscarriage or premature delivery as a result of contracting malaria far outweighs the risk of possible side effects from antimalarial drugs. Chloroquine is safe during pregnancy in doses used for malaria prophylaxis. Mefloquine hydrochloride can be used during the second and third trimesters, but studies suggest that it is also safe during the first trimester. Atovaquone-proguanil, doxycycline, tafenoquine, and primaquine are contraindicated during pregnancy.

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### WHEN YOU RETURN...

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Back home, you may experience flu-like symptoms such as a general malaise, headache, and some fever. These can be signs of a malaria infection. Symptoms may appear 7 days, weeks, or up to several months after your trip. Contact your doctor and tell them where you have been – even if the fever develops months after you have returned. These signs could be a first attack of

*P. falciparum*, *P. malariae*, *P. knowlesi*, or a relapse of *P. vivax* or *P. ovale* malaria. For this reason, people who recently travelled to or lived in a malarious area cannot donate blood for 1 to 3 years, depending on the length of their stay.

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### THE SEARCH FOR THE KILLER

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#### 1880 – Constantine, Algeria: The end of a superstition

Thousands of years of superstition attributing malaria (L.: *mala aria* = bad air) to some kind of airborne poison is overthrown by French army surgeon, Charles Louis Alphonse Laveran. He identified the malaria parasite for the first time while microscopically examining the fresh blood of a patient infected with *P. falciparum* malaria. But it would take six years for the medical profession to recognize the importance of Laveran’s discovery, as it was widely believed that malaria was caused by bacteria instead of parasites.

#### 1886 – Pavia, Italy

Camillo Golgi definitively identified two human malaria parasites: *Plasmodium vivax* and *Plasmodium malariae*. He described the asexual multiplication of the parasite in the red corpuscle of the blood and demonstrated its relationship to the periodic appearance of the fever characteristic of malaria.

#### 1889 – Rome, Italy

Three years later, Ettore Marchiafava differentiated a third species of human malaria parasites, *Plasmodium falciparum*, named for the crescent shape of the sexual form of the parasite (L.: *falx* = sickle; *parere* = to bring forth). However, the mechanism of transmission of the disease was still a mystery.

#### 1894 – London:

##### Patrick Manson, The grey eminence behind malaria research

Patrick Manson, an eminent Scottish physician, had discovered that mosquitoes could suck up the microscopic threadlike worms from the blood of patients infected with a disease called filariasis. He believed that mosquitoes might also draw out the malaria parasites from human blood, and that transmission would occur by ingestion of water contaminated by infected mosquitoes.

#### 1898 – Calcutta:

##### Ronald Ross, “It is the bite”

Manson, realizing he could never experiment enough in England to prove his theory, convinced Ronald Ross, a British army surgeon who visited



**Fig. 5** Patrick Manson, Scottish physician who demonstrated how mosquitoes play a role in the spread of parasites.

Image source: London School of Hygiene & Tropical Medicine (painting by H.H. Salomon)

## EMERGENCY SELF TREATMENT – ADULT AND PEDIATRIC DOSAGES

Antimalarial Drug <sup>1</sup>	Brand Name	Adults	Children	
<b>Atovaquone-Proguanil</b> <i>Do not use if you're taking this drug for prophylaxis, are pregnant or breastfeeding children &lt; 5 kg   11 lb. Discuss alternatives with your healthcare provider.</i>	Malarone and others; generics	<b>Dose: 250 mg atovaquone + 100 mg proguanil</b> Take 4 tablets (as a single dose) once a day for 3 consecutive days, for a total of 12 tablets. Seek medical care as soon as possible.	<b>Dose: 62.5 mg atovaquone + 25 mg proguanil</b> Take indicated dose once a day for 3 consecutive days. Seek medical care as soon as possible.	
			< 5kg / 11lb	Contraindicated
			5-8 kg / 11-18 lb	2 pediatric tablets
			> 8-10 kg / 18-24 lb	3 pediatric tablets
			> 11-20 kg / 24-44 lb	1 adult tablet
			> 20-30 kg / 44-66 lb	2 adult tablets
			> 30-40 kg / 66-88 lb	3 adult tablets
> 40 kg / 88 lb	4 adult tablets			
<b>Artemether-Lumefantrine</b> <i>Do not use if you have taken mefloquine hydrochloride for prophylaxis, are pregnant or breastfeeding children &lt; 5 kg   11 lb. Discuss alternatives with your healthcare provider.</i>	Coartem, Riamet	<b>Dose: 20 mg artemether + 120 mg lumefantrine</b> The number of tablets to take is based on your weight. For adults > 35 kg / 77 lb take 4 tablets per dose twice a day for 3 consecutive days, for a total of 24 tablets. On day 1, take the 2 <sup>nd</sup> dose 8 hours after the 1 <sup>st</sup> dose. On days 2 and 3, take your dose twice a day.	<b>Dose: 20 mg artemether + 120 mg lumefantrine</b> Take indicated dose twice a day for 3 consecutive days. On day 1, take the 2 <sup>nd</sup> dose 8 hours after the 1 <sup>st</sup> dose. On days 2 and 3, take your dose twice a day.	
			< 5kg / 11lb	Contraindicated
			5-15 kg / 11-33 lb	1 tablet
			15-25 kg / 33-55 lb	2 tablets
			25-35 kg / 55-77 lb	3 tablets
			> 35 kg / > 77 lb	4 tablets

<sup>1</sup> All antimalarial drugs have precautions and contraindications. See 'Description of Antimalarial Drugs: Contraindications, Precautions, and Side Effects' on page 8. Talk to your healthcare provider to choose the best regimen for you or your child.

him in 1894, to carry on this research. Together they planned a series of experiments which Ross carried out upon his return to India. Ross began by raising *Culex* and *Aedes* larvae, and let the adult mosquitoes feed on patients with malaria. Then he let these mosquitoes bite volunteers, but with no result — since he wasn't an entomologist he wasn't aware that he was using the wrong species of mosquito. After several unsuccessful experiments, in April 1897, while working in Ootacamund (Ooty) near Madras, he saw for the first time the dapple-winged *Anopheles*, and started to experiment with this species. On August 20, 1897, looking through his microscope at the gut of mosquitoes which had fed on a patient with malaria, he saw for the first time the human malaria parasite growing in the gut of *Anopheles*.

Unwillingly he had to interrupt his investigations, and when he moved to his new post in Calcutta he started working with the avian malaria parasites, which are transmitted by a *Culex* species. He proved that the spindle-shaped malaria organisms (*sporozoites*), freed by the rupturing of the fertilized eggs, migrate from the gut of the mosquito to its salivary glands, to be injected into the victim when the insect bites. As such, Ross is credited with the discovery that malaria is transmitted by the mosquito's bite.

### 1898 – Baltimore

Later in the same year William George McCallum, a Canadian pathologist also working with birds, was able to interpret and describe the fertilization process of the parasite taking place in the gut of the mosquito.

### 1886-1899 – Rome: The magnificent four

Simultaneously, a group of Italians were working to solve the puzzle of the transmission of malaria in humans. From 1886 to 1896, Giuseppe Bastianelli, Amico Bignami, Angelo Celli and Giovanni Battista Grassi had been actively investigating the life cycle of the human malaria parasites and making accurate descriptions of the lesions produced by the parasites in the different organs of the body. A breakthrough came with the observations by Grassi, a physician with a keen interest in zoology, particularly mosquitoes. He noticed that when malaria was present there was always a large population of *Anopheles*, while in areas of large *Culex* populations there was no malaria.

From the Campagna Romana near Rome he collected *Anopheles* mosquitoes which his colleague Bignami allowed to feed on a volunteer patient from the Santo Spirito Hospital, a few steps away from St. Peter's Basilica. On November 1, 1898, the patient, Abele Sola, developed the classic symptoms of *P. falciparum* malaria. Together with Bastianelli and Celli, they were able to reproduce malaria infections

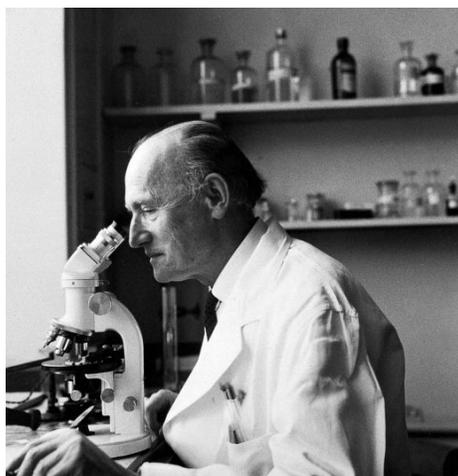
in other volunteers and prove that only the *Anopheles* mosquito, and no other species, transmits malaria in humans.

#### **1936 – Rome: Giulio Raffaele discovers the liver cycle**

It was soon discovered that a link was missing in the knowledge of the life cycle of the malaria parasite. Still unexplained was the time elapsed between the introduction of the parasites through the bite of the mosquito and the appearance of the symptoms of malaria. Giulio Raffaele discovered while working with birds that malaria parasites entering the host first undergo a cycle of transformation within the blood-forming cells of the liver.

#### **1948 – London: The final touch**

Now the road was open for British researchers Colonel H.E. Shortt and Percy Cyril Claude Garnham to demonstrate the liver cycle of the malaria parasite in humans. Following a period of extensive trials on monkeys, in 1948 a human volunteer — a Mr. Howard — was bitten during three days by nearly eight hundred *Anopheles* infected with *Plasmodium falciparum*. On the fifth day, a surgeon removed a small piece of tissue from his liver which, examined under the microscope, demonstrated the growth of the parasites in the liver cells. The last mystery of the life cycle of the malaria parasite was finally unraveled.



**Fig. 6** Percy Cyril Claude Garnham, who demonstrated the liver cycle of malaria parasites in humans.

Image source: Wellcome Collection

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## **THE RACE AGAINST DRUG RESISTANCE AND HOPE FOR A VACCINE**

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In the late 1950s there were reports of *P. falciparum* resistance to chloroquine, the first line drug used to prevent malaria. During the

1960s and 1970s, research focused on finding new antimalarial drugs partly spurred by US soldiers getting ill and dying from malaria in the Vietnam War. Much of the antimalarial drug research at that time was done by scientists at the Walter Reed Army Institute of Research. While mefloquine hydrochloride and the tetracycline group of antibiotics were discovered to be effective antimalarials, they were not available to travellers.

The 1980s saw the introduction of effective antimalarial drugs in the marketplace such as sulfadoxine-pyrimethamine (Fansidar) and halofantrine (Halfan). These drugs however, have serious side effects and are no longer recommended. The antimalarial medications recommended for use today are relatively new. In the US, mefloquine hydrochloride was licensed in 1989, doxycycline was approved as an antimalarial in 1994, and atovaquone-proguanil in 2000. Also during this time, *P. knowlesi* was positively identified as the 5th malaria parasite responsible for infecting humans in Southeast Asia, being previously mistaken for *P. malariae* and *P. falciparum*.

Currently, there are several intensive efforts to develop a vaccine against malaria. RTS,S / AS01 or Mosquirix is the first vaccine almost ready to be marketed – it is undergoing pilot testing now. Clinical trials have shown that it provides partial protection against *P. falciparum*, the fatal form of malaria. Another vaccine, PfSPZ, has been shown to provide up to 100% protection against *P. falciparum* in laboratory testing. It is now moving to clinical trial testing to assess its effectiveness in the field. It is these types of initiatives that are key to successfully prevent, control, and eventually eradicate malaria. 

Sources: CATMAT, CDC, DTG, WHO, 2018 World Malaria Report, Malaria Atlas Project, *Hunter's Tropical Medicine and Emerging Infectious Diseases, 9th ed.*, *Tropical Infectious Diseases, 3rd ed.*, Prof. DDr. Martin Haditsch.

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