Practical Guide for the Prescription of Malaria Chemoprophylaxis for the Primary Care Physician

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Malaria is considered an important health threat around the world. Travelers from non-endemic countries are at risk of contracting the parasite that causes malaria. Those traveling on humanitarian missions and military personnel are at the greatest risk. Mosquito avoidance is an important intervention, but chemoprophylaxis is the most effective method for the prevention of this infection. The selection of a specific regimen can be a difficult task. It is a decision that is not based solely on the region in which a given patient is traveling but also on that patient's comorbidities and the potential adverse effects of the medications to be used. This review is intended to be a simple guide for the primary care physician. We discuss the selection of chemoprophylaxis for patients in the general population. We also address the specifics of chemoprophylaxis during pregnancy and breast feeding and in people diagnosed with epilepsy. [*P R Health Sci J 2020;39:300-305*]

Key words: Malaria, Prophylaxis, Prevention, Guide, Chemoprophylaxis

Reported in the mainstream media is the fact that several cases of malaria have been observed in Puerto Rico in the last few years (1). Those infected were Puerto Ricans who had traveled to the Dominican Republic, a malaria-endemic country (2). These infections could have been prevented with proper interventions, such as mosquito avoidance and malaria chemoprophylaxis. There are other groups of individuals who are at risk of infection, including military personnel and those involved in humanitarian relief missions. Other persons at particular risk are those born or raised in endemic regions but who live in non-endemic countries and return to visit friends and relatives. In view of the above, it is essential to discuss how to prevent becoming infected with malaria, including in that discussion an appraisal of the available methods of chemoprophylaxis. The purpose of this review is to provide a simple and practical resource for the adequate selection of malaria chemoprophylaxis, taking into consideration the safety profile of a given medication and the preferences and comorbidities of the travelers.

With a significant global incidence, malaria is a serious disease that can kill the individual who contracts it, despite the level of care that individual receives (3). For this reason, early recognition and optimal prevention are essential. An important historical aspect is that Puerto Rico is a place where malaria was endemic. During the period of 1928 to 1944, the number of people infected with malaria was approximately 11,000 to 45,000, per year, as documented by Palacios (4). However, these infections were controlled after multiple interventions, and only 7 patients with malaria were reported in 1955. Later, in 1962, the World Health Organization (WHO) declared the island of Puerto Rico to be free of malaria, recognizing the island as the first tropical region in the Americas to accomplish this feat (5). Despite this achievement, the presence on the island of the *Anopheles albimanus* mosquito, which acts as a vector of the disease, as well as the increase in global travel, places the island population in a vulnerable position and increases the risk that this disease might be reintroduced.

We aim to provide a simple guide that helps primary care clinicians to select an appropriate chemoprophylaxis regimen. We also discuss the available regimens and limitations based on patient comorbidities and the location of the travel destination. The clinical decisions that such clinicians must make are based on information that is dynamic. Therefore, updated information about the risk of transmission in a particular place and the prevalence of a particular malaria species is of special importance. Available resources for up-to-date information are presented, as well.

Location

The most important factor to consider is the location of a given individual's trip. Knowing this will provide critical information about the risk of infection and the need for a chemoprophylaxis regimen. Resistance to specific drugs also varies by location, another reason that this information is so important.

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Risk of infection

Not all countries represent a risk for travelers. Furthermore, not all regions within a country represent a risk for malaria transmission. An example is the Dominican Republic; Santo Domingo, the capital, is considered to be a low-risk area for transmission. However, given the elevated risk of malaria transmission in Punta Cana, a very popular place for vacationers, the traveler going there should receive chemoprophylaxis (6). The WHO and the Centers for Disease Prevention and Control (CDC) provide reliable information about the risk of transmission by location at https://www.cdc.gov/malaria/travelers/index.html and https://www.who.int/malaria/publications/country-profiles/en/, respectively.

Drug resistance

Chloroquine, a widely utilized drug with a good safety profile and tolerability, has been used for many years for the treatment and prevention of malaria. Unfortunately, most of the species around the world are resistant to this medication. However, this drug can be used for travelers going to the Dominican Republic, Haiti, Mexico, the west side of the Panama Canal, and some countries in Central America where malaria remain sensitive to this medication (7,8). Mefloquine is another antimalarial medication for which resistance has been documented. This medication should not be prescribed for people traveling to certain regions of Thailand, Myanmar, Cambodia, or Burma (9). Table 1 describe the options according to resistance patterns. There are reports of resistance to others antimalarial drugs, but resistance to chloroquine and mefloquine are the most relevant.

Table 1. Drug used according to resistance pattern

Chloroquine Resistance	atovaquone-proguanil, doxycycline, mefloquine, tafenoquine, or primaquine[δ]
Mefloquine Resistance	atovaquone-proguanil, doxycycline, tafenoquine, or primaquine[δ]

[δ]Can be used for primary prophylaxis only in places with >90% *Plasmodium vivax*.

Distribution of species

There are 5 species of the parasite that cause the malaria infection in humans: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae,* and *Plasmodium knowlesi*. The distributions of these species vary by country, and some locations have more than 1 species circulating, at the same time (10,11). Close attention should be placed on *Plasmodium vivax* and *Plasmodium ovale*. These species are characterized by their ability to cause a relapse or delay the onset of the infection, both of which are made possible by the fact that these species can remain dormant in the liver (hypnozoites). Travelers planning to go to a place (such as Honduras) with a high endemicity of these species should receive primaquine or tafenoquine as primary prophylaxis or at the end of the exposure period, if an alternative regimen was used. This is an important step for the eradication of hypnozoites in the liver (12). In this case, a consultation with an infectious disease specialist or a travel medicine specialist is recommended.

Choosing the right medication

Determining local resistance patterns is the first step prior to the selection of a prophylactic regimen. Healthcare personnel should also be aware of the possible adverse effects of each drug and possible contraindications, according to the patient's comorbidities. The preferences of the traveler should also be taken into consideration, as some might prefer weekly dosing and others, daily.

Chloroquine

Chloroquine is an aminoquinoline that is still considered an effective drug for the prevention of chloroquine-sensitive malaria. This medication has a low cost and has a good safety profile. Its side effects are minimal with short-term use, but this drug should be avoided in patients with psoriasis because exacerbations of the condition have been reported (with the use of the chloroquine) (13). Other side effects are typically associated with higher doses, such as those prescribed for rheumatologic conditions. Some persons may experience gastrointestinal upset, which is alleviated by ingesting the scheduled dose with food. If chloroquine is not available, hydroxychloroquine is a suitable option. The weekly dosing is an attractive characteristic of this regimen. However, it should be taken for 4 weeks after returning from the area of exposure, an aspect that could affect the patient's compliance.

Atovaquone-proguanil

This drug is a combination of a ubiquinone and a biguanidine and has negligible side effects, most of them having to do with gastrointestinal upset (14). It is a good option for short trips and is indicated for use in places where malaria is resistant to chloroquine and mefloquine. Atovaquone-proguanil is taken on a daily basis. This medication is started from 1 to 2 days prior to arriving at the endemic region and continued for 7 days after leaving it; one negative characteristic is the high price of this product compared with the prices of other options. Nevertheless, this medication remains a good alternative, mainly because of its safety profile.

Doxycycline

This well-known antibiotic with a broad spectrum of activity has been used for a while for the treatment of cellulitis, some tick-borne infections, and community-acquired pneumonia, among other illnesses. It is also useful for the prevention and treatment of malaria in areas where the parasite is resistant to chloroquine and mefloquine. This is a low-cost medication, but its potential side effects need to be taken into account. Travelers usually complain of gastrointestinal upset, which can be avoided by ingesting this drug with food. It is unsuitable for pregnant patients and children less than 8 years of age (15–16).

Rash during intense sun exposure is another concern. Another drawback is that it must be taken for a total of 4 weeks after leaving the endemic region. Since doxycycline has activity against the *Leptospira* species, it can be used in the prevention of leptospirosis. People most at risk are emergency personnel responding to water-related disasters, persons involved in water-sport activities in rivers, and those with close contact with some mammals, such as dogs, rodents, and cattle.

Mefloquine

Mefloquine is a highly effective antimalarial medication. Despite reports of resistance in a few specific areas of Southeast Asia, it remains an option for most parts of the world, including those places with chloroquine-resistant malaria. This medication is taken on a weekly basis, which increases the rate of adherence. However, during the last several years, there have been several reports of side effects that cannot be overlooked. In 2013 the Food and Drug Administration (FDA) released a strong communication about neurological and psychiatric side effects, resulting in a black-box warning (17). In summary, mefloquine cannot be prescribed to patients with epilepsy since it has been known to precipitates seizures (18). Mefloquine is also contraindicated in patients with major psychiatric disorders and in those with recent episodes of depression, anxiety, or both. Other side effects include insomnia, depression, anxiety, tinnitus, and vertigo; some of them can persist for months. Mefloquine also has the potential to prolong the QT segment and to cause transient AV nodal block. It should be avoided if the patient is already taking one or more medications that prolong the QT segment. For patients not suffering from one or more of the above-mentioned comorbidities, this medication could be an option, and if it is prescribed, the clinician has the responsibility to discuss the side effects and instruct the patient to report the development of any of them. If a person is to start on mefloquine, it has to be done 2 weeks prior to his or her trip. This period of time will allow time to evaluate the development of the beforementioned effects.

Primaquine

Primaquine is a potent agent that is reserved for travelers to countries with a high prevalence (>90%) of *Plasmodium vivax*. Its side effects are minimal, but patients with a glucose-6-phosphate dehydrogenase (G6PD) deficiency can develop severe hemolytic anemia while using this drug. The presence of G6PD deficiency in a group of people in Puerto Rico has been documented (19). A significant rate (12.2%) has been reported within a single population group (African American males) within the United States Army (20). Testing for G6PD activity should precede any prescription of primaquine. If the activity of G6PD is within a specific range, this antimalarial drug can be safely used (21). Primaquine is also indicated for the prevention of relapse in individuals exposed to *Plasmodium vivax* and *Plasmodium ovale*. This concept is also known as presumptive anti-relapse therapy (PART).

Tafenoquine

Tafenoquine is an antimalarial drug that was approved in 2018 by the FDA for the prevention of *Plasmodium vivax* and for use in presumptive anti-relapse therapy. The safety profile of this medication and that of primaquine are similar. Prior to their being prescribed tafenoquine, patients must be evaluated for G6PD deficiency; this drug should be avoided in patients with a history of psychosis. Its weekly administration schedule makes this agent a convenient option compared to primaquine.

A summary of the regimens, dosages, and side effects of all the above drugs is displayed in Table 2.

Some travelers go to places where medical supplies are limited and where the selling of counterfeit medications ("fake drugs") is a common practice. These travelers should have enough of the drug they have been prescribed for the whole trip. In addition, clinicians should prescribe a course of treatment for malaria in the event of chemoprophylaxis failure.

Special populations

Patients with epilepsy

There is limited evidence about the safety profile of malaria chemoprophylaxis in patients diagnosed with epilepsy. However, some of the anti-malarial drugs are known to be precipitants of seizures. The most notable is mefloquine, which is contraindicated in this group of patients. Chloroquine and hydroxychloroquine have also been associated with seizure exacerbations (22). Doxycycline and atovaquone-proguanil are suitable options (23). However, drug interactions limit the use of doxycycline in patients who are on carbamazepine, phenytoin, or phenobarbital, because all these drugs decrease the concentration of doxycycline (24).

Pregnant women

During pregnancy, traveling to malarious areas should be avoided. Malaria can be detrimental to the mother and the fetus (25). Chemoprophylaxis regimens are also limited in this group of patients. Those who cannot avoid or postpone a trip to malarious areas should receive chloroquine or mefloquine (26–27). Primaquine and tafenoquine should be avoided in this population because of the inability to test the fetus for G6PD deficiency.

Breast feeding mothers

Prior studies have shown that the detected amounts of mefloquine and hydroxychloroquine in the breast milk of a lactating mother undergoing this kind of antimalarial prophylaxis are low enough to be safe for both the mother and her child. If primaquine or tafenoquine are needed, then the mother and the child should first be tested for a G6PD deficiency. It should be noted, however, that what is protective for the mother is inconsequential for the child. The breast milk of a lactating mother undergoing this kind of chemoprophylaxis will neither harm nor help that mother's child. Doxycycline and atovaquone-proguanil should be avoided.

Table 2. Drugs and dosage according to CDC recommendations

Drug	Adult dose	Child dose	Notes
Chloroquine	500 mg (300 mg base), weekly Initiate: 1 – 2 weeks before travel Until: 4 weeks after leaving endemic area	8.3 mg/kg salt (up to 500 mg), weekly	Avoid: Patients with epilepsy or psoriasis • Only in chloroquine-sensitive places • Can be used by pregnant women
Atovaquone-proguanil	250/100 mg, daily Initiate: 1 – 2 days before travel Until: 7 days after leaving endemic area	Pediatric tablet (62.5/25 mg) 5 – 8 kg: ½ tablet 8 – 10 kg: ¾ tablet 10 – 20 kg: 1 tablet 20 – 30 kg: 2 tablets 30 – 40 kg: 3 tablets >40 kg: adult dose	Avoid: Pregnant women • Can be used by patients with epilepsy • Should be ingested with food
Doxycycline	100 mg, daily Initiate: 1 – 2 days before travel Until: 4 weeks after leaving endemic area	For children >8 years of age 2.2 mg/kg up to 100 mg	Avoid: Pregnant women and children less than 8 years of age • Safe in epileptics, except for those taking carbamazepine, phenytoin, or phenobarbital
Mefloquine	250 mg, weekly Initiate: 2 – 4 weeks before travel Until: 4 weeks after leaving endemic area	<9 kg: 4.6 mg/kg base (5 mg/kg salt) >9 – 19 kg: ¼ tablet > 19 – 30 kg: ½ tablet > 30 – 45 kg: ¾ tablet > 45 kg: 1 tablet	Avoid: In the presence of epilepsy, major psychiatric disease, or heart conduction disease; avoid, as well, concurrent use with other drugs that prolong the QT interval • Can be used in pregnancy • Avoid in Southeast Asia due resistance
Primaquine	30 mg, daily Initiate: 2 days before travel Until: 14 days after leaving endemic area PART: 30 mg, daily, for 14 days after leaving endemic area§	0.5 mg/kg, daily; up to 30 mg/day	*Mandatory test for G6PD deficiency. Avoid: Pregnant women and those who are breastfeeding (if child's G6PD status is unknown) • For prevention of *P. vivax* and *P. ovale* • For prevention of relapse
Tafenoquine	Initiate: 200 mg, daily, x 3, dose prior to travel During exposure: 200 mg, weekly After leaving endemic area: 200 mg x one week PART: 300 mg, once, during the last dose of chemoprophylaxis§	Not recommended in persons younger than 16 years of age	*Mandatory test for G6PD deficiency. Avoid: Pregnant women and women who are breastfeeding (if child's G6PD status is unknown). • For prevention of *P. falciparum, P. vivax*, and *P. ovale* • For prevention of relapse

§If primaquine or tafenoquine were used for chemoprophylaxis, PART is not needed.

Patients on minocycline for the treatment of acne

Minocycline is a tetracycline and an analog of doxycycline. It has been theorized that this medication might be protective against malaria. However, at this time, there is no evidence proving this assertion to be true. Those patients who are receiving this treatment can be switched to doxycycline while traveling and then switched back to minocycline, 4 weeks after their return.

Resources

Before prescribing a prophylaxis regimen, the provider must review any updated information about resistance patterns and the distribution of the species of malaria parasites. The most accessible are the abovementioned websites of the CDC and the WHO. Every 2 years the CDC publishes an updated guidebook named *CDC Health Information for International Travel* (also known as "The Yellow Book"), which serves as a good resource for both travelers and healthcare professionals. This is a useful guide that covers the topic of malaria and other issues of importance for travelers, such as yellow fever and traveler's diarrhea. Another source is the website of the International Society of Travel Medicine (https://www.istm.org/), which features an online directory of travel medicine clinics around the globe. This information is also provided by the American Society of Tropical Medicine and Hygiene on their website (https://www.astmh.org/).

Other interventions

The traveler should be educated about the appropriate use of repellents and bed nets. It is important to instruct the traveler about the behavior of the mosquito, which has a preference for dusk and dawn, the periods in which the risk of transmission is greatest. Repellents recommended by the CDC are diethyltoluamide (>20%), lemon–eucalyptus oil, picardin (also known as icaridin or KBR 3023), para-menthane-3,8-diol, 2-undecanone (also known as methyl nonyl ketone), and ethyl butylacetylaminopropionate (trade name IR3535) (28). Healthcare personnel need to remember to instruct traveling patients to frequently reapply repellent and to apply it after having put on sun-block, if both are being used at the same time. Sleeping with bed nets and in rooms with screened windows should be encouraged.

Summary

Chemoprophylaxis is an important part of the prevention of malaria infection and its transmission and should be integrated into mosquito-bite-avoidance strategies, such as the application of repellent and the use of bed nets. The selection of the right drug for a given patient is not based solely on patterns of resistance but also on that patient's comorbidities and preferences. Preventing the re-introduction of malaria to places where it has been eradicated (e.g., Puerto Rico) is the responsibility of the healthcare community operating where the disease is no longer endemic, and primary care providers have a vital role. This review aims to be a simple and practical guide for the primary care physician in the selection of a proper regimen. However, no one should hesitate to refer a patient with multiple comorbidities and who will be undertaking or has undertaken prolonged travel to malarious areas to a specialist in infectious diseases or travel medicine.

Resumen

La infección de la malaria continúa siendo una amenaza a la salud a nivel global. Los viajeros de países no-endémicos están a riesgo de contraer el parasito causante de la malaria. Aquellas personas viajando en misiones de ayuda humanitaria y los militares están a mayor riesgo. Evitar la picadura del mosquito es una intervención importante, sin embargo, la quimioprofilaxis continúa siendo el método más efectivo para evitar esta infección. Seleccionar un régimen específico puedo ser una tarea complicada. Esta decisión no solo toma en cuenta el lugar del viaje sino también las comorbilidades del paciente y los posibles efectos adversos de los medicamentos. Este artículo pretende ser una guía simple para el médico primario. Discutimos en el mismo la selección de quimioprofilaxis contra la malaria en la población general. También abordamos las peculiaridades de la quimioprofilaxis en el embarazo, en mujeres lactantes y en personas diagnosticadas con epilepsia.

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