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Introduction

A number of different drugs are available to **prevent** malaria. “Chemoprophylaxis” refers to taking a drug as “prophylaxis” to prevent an illness (in this case malaria), as opposed to taking a drug to “treat” an illness.

When used appropriately, chemoprophylaxis is effective in preventing malaria, but does not prevent all cases of malaria. People who do develop malaria while taking preventive medication are much less likely to have severe or fatal malaria. Therefore, measures to prevent mosquito bites must always be used when in a malarial area, even if taking chemoprophylaxis.

Recommendations and selection of a drug should be made on an individual doctor-patient basis. The decision depends not only on the destination (risk of malaria varies with location and season of travel, and malaria in certain regions can be resistant to some medications), the itinerary (risk also depends on type of activities and accommodation), but also on any underlying health conditions (pregnancy, epilepsy, drug-drug interactions, previous adverse effects from chemoprophylaxis etc), age, duration of exposure and personal preference (dosing schedule, cost).

Note that there are differences in drug availability and the duration for which they are licensed for continuous use in different parts of the world. In general, the licensing duration is based on “the cumulative evidence of lack of harm rather than positive evidence of safety”⁷. National and international authorities differ in their advice for chemoprophylaxis, precautions and contraindications (conditions under which drugs should not be used).

Chemoprophylaxis: the benefits and the risks

Malaria is a potentially fatal illness but can usually be prevented. Each year, many international travellers contract the disease whilst abroad. Over 10,000 are estimated to develop illness after return home, yet the true number of cases may be much higher.¹ The majority of cases of malaria diagnosed in the United States (and its territories) in 2015 were acquired in Africa (85%), followed by Asia (9%).² The risk that travellers are infected with malaria appears to increase the longer their stay in a malarious area, as their adherence to preventive measures diminishes.³

Frequent short-stay business travellers to malarial areas may develop malaria more often than tourists.⁴ Although the risk of death is quite low for uncomplicated malaria, once malaria infection becomes severe over a third of patients in high risk groups die.⁵ Non-immune expatriate travellers are considered high risk and “up to 30% of some expatriates develop malaria within two years and many cases can be attributed to poor compliance with prophylaxis”⁷

When chemoprophylaxis is recommended, it must be used in addition to mosquito bite-avoidance measures. Although not 100% effective, appropriate chemoprophylaxis and bite-avoidance can prevent the vast majority of malaria cases. “Effective chemoprophylaxis taken correctly should reduce the risk of malaria by around 90%, especially if combined with sleeping under insecticide-treated nets.”⁶

Chemoprophylaxis may have side effects. Common side effects are usually mild and improve after several doses. Serious adverse events are rare¹. Individual patient review by a doctor allows selection of the medication most appropriate for the itinerary and least likely to cause serious side effects. Severe side effects are reactions that lead to hospitalization or disability. Fortunately however, they are rare; “for mefloquine ranges from 1/607 to 1/20 000 compared with a rate for chloroquine of 1/1181 to 1/13,600”.⁴ If one medication is not well-tolerated, it is possible to change to another medication.

Cost-benefit is not examined in this discussion. Some medications are relatively inexpensive (e.g. doxycycline) whilst others are relatively costly (e.g. Malarone).

Long-term chemoprophylaxis

“Prevention of malaria in long-term travelers is a complex issue and requires expert advice from travel medicine specialists. Recommendations for prevention of malaria in long-term travelers must be individualized.”⁶

“It is important to reassure the traveler that the drugs are safe and effective”³

Chemoprophylaxis for long-term travellers is very important, as the risk of acquiring malaria increases the longer one resides in a malarial area. Public Health England states; “A 3-month visit carries a risk around 6 times greater than a visit of 2 weeks”.⁷

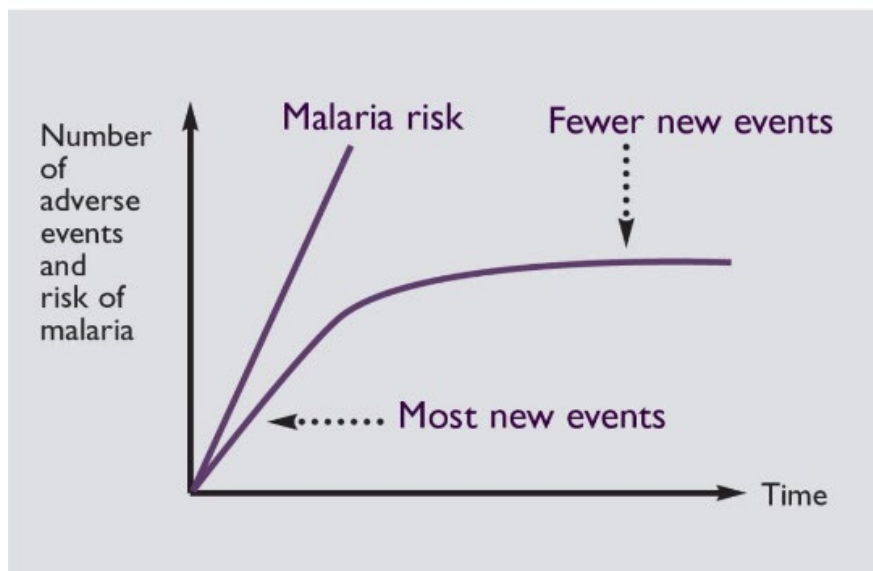
Public Health England provides guidelines for malaria prevention in travellers from the UK.⁷ The World Health Organization provides some information on long-term chemoprophylaxis¹, as does the United States CDC³.

Long-term Malaria Chemoprophylaxis

An overview

Overall, any anti-malarial which is well-tolerated in the short-term is unlikely to cause problems if used longer term. UK guidelines indicate; “there is no evidence of new side effects emerging during long-term use of any currently available prophylactics, though there may be risks associated with long-term use of chloroquine”, and “While the risk of new adverse events falls off over time, the risk of contracting malaria continues to increase roughly linearly as exposure to malaria continues”.⁷

CUMULATIVE RISK OF ADVERSE EVENTS AND OF MALARIA



Cumulative risk of adverse events from taking malaria chemoprophylactic drugs and of contracting malaria over time (Courtesy: Public Health England)

The National Academies of Sciences conducted an Assessment of Long-Term Health Effects of Antimalarial Drugs When Used for Prophylaxis, and published their report in February 2020.¹⁴ They reviewed data on six medications –chloroquine, primaquine, mefloquine, doxycycline, atovaquone/proguanil, and tafenoquine. They found only one “association”, which was for tafenoquine and an eye condition “vortex keratopathy” (a deposit on the eyeball, that rarely caused reduced vision), which resolved within 3 to 12 months, and did not have an ongoing clinical effect. Otherwise “across all drugs and outcome categories considered, the evidence between the drug of interest and persistent or latent adverse events was inadequate or insufficient.” “For three of the drugs—mefloquine, tafenoquine, and atovaquone/proguanil—the committee believes there is a basis for additional research on persistent or latent eye disorders. For doxycycline there is a basis for additional research into persistent gastrointestinal events.” For mefloquine, there is a basis for additional research into persistent or latent neurologic and psychiatric events. For tafenoquine, there is a basis for additional research into persistent or latent psychiatric events.

Chloroquine

Note: chloroquine is rarely prescribed for malaria chemoprophylaxis, as in most areas the parasite is resistant to chloroquine.

Public Health England ⁷	<p><i>Considered safe for long-term use.*</i></p> <p><i>Consider ophthalmic examination for retinopathy 6 to 12 monthly, commencing at 6 years’ cumulative prophylactic usage.</i></p> <p><i>* Considered safe for long-term use but considerable concern regarding level of protective efficacy of the combination of chloroquine plus proguanil in certain geographical areas where the regimen used to be useful</i></p>
World Health Organization ¹	<p><i>The risk of serious side-effects associated with long-term prophylactic use of chloroquine is low, but retinal toxicity is of concern when a cumulative dose of 100g of chloroquine is reached. Anyone who has taken 300mg of chloroquine weekly for more than 5 years and requires further prophylaxis should be screened twice-yearly for early retinal changes. If daily doses of 100mg chloroquine have been taken, screening should start after 3 years.</i></p>
US CDC ⁹	<p><i>CDC has no limits on the use of chloroquine for the prevention of malaria. When chloroquine is used at higher doses for many years, a rare eye condition called retinopathy has occurred. People who take chloroquine for more than five years should get regular eye exams.</i></p>

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Doxycycline

Public Health England ⁷	<i>No evidence of harm in long-term use. Evidence suggests that it may be used safely for periods of at least up to 2 years. Longer term use possible if justified by the risk of exposure to malaria.</i>
World Health Organization ¹	<i>Available data on long-term chemoprophylaxis with doxycycline (i.e. more than 12 months) are limited but reassuring. There are few data on long-term use of doxycycline in women, but use of this drug is associated with an increased frequency of vaginitis due to Candida.</i>
US CDC ^{3,9}	<i>Doxycycline has been well-tolerated for long-term malaria prophylaxis in the military, and CDC has no recommended limits on its duration of use for malaria prophylaxis. CDC has no limits on the use of doxycycline for the prevention of malaria. There is no evidence of harm when the drug has been used for extended periods of time.</i>
Manufacturer information	Available from US National Library of Medicine Website DailyMed (drug listings as submitted to the Food and Drug Administration) https://dailymed.nlm.nih.gov/dailymed/index.cfm e.g. Doryx MPC, Mayne Pharma https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f9277bb8-982d-444d-9325-35d5c53a2d35 [...] indicated for the prophylaxis of malaria due to Plasmodium falciparum in short-term travelers (less than 4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains
Regulatory information	United States Food and Drug Administration: Approved in USA for prophylaxis against malaria due to <i>P. falciparum</i> in short-term travellers (< 4months)
National Academies of Sciences ¹⁴	<i>There is insufficient or inadequate evidence of an association between the use of doxycycline for malaria prophylaxis and persistent or latent gastrointestinal events. Current evidence suggests further study of such an association is warranted</i>

Atovaquone / Proguanil (Malarone® and other brands)

Public Health England ⁷	In the UK, one brand, Maloff Protect, is available in pharmacies without prescription. <i>No evidence of harm in long-term use. Can be used confidently for travel up to 1 year. Longer term use possible if justified by the risk of exposure to malaria.</i>
World Health Organization ¹	<i>Atovaquone–proguanil is registered in European countries with a restriction on duration of use (varying from 5 weeks to 1 year); such restrictions do not apply in the United Kingdom or the United States.</i>
US CDC ⁹	<i>CDC has no limits on the use of atovaquone-proguanil for the prevention of malaria. There is no evidence of harm when the drug has been used for extended periods of time.</i>
National Academies of Sciences ¹⁴	<i>There is insufficient or inadequate evidence of an association between the use of atovaquone/proguanil for malaria prophylaxis and persistent or latent eye disorders. Current evidence suggests further study of such an association is warranted,</i>

Mefloquine

Public Health England ⁷	<i>No evidence of harm in long-term use if tolerated in the short term. Suggest can be used safely for up to 3 years in the absence of side effects. Longer term use possible if justified by the risk of exposure to malaria. The SmPC [manufacturer’s Summary of Product Characteristics] suggests that periodic checks on liver function and eye assessments should be taken if used for a prolonged period. Any person presenting with a visual disorder should be referred to their treating physician as this may require stopping chemoprophylaxis.</i>
World Health Organization ¹	<i>Data indicate no increased risk of serious side-effects with long-term use of mefloquine if the drug is tolerated in the short-term. Pharmacokinetic data indicate that mefloquine does not accumulate during long-term intake.</i>
US CDC ⁹	<i>CDC has no recommended time limits on the duration of use of mefloquine for the prevention of malaria.</i>
US FDA ¹⁰	In 2013, the United States Food and Drug Administration added a “boxed warning” regarding potential neurologic and psychiatric effects. “Neurologic side effects can occur at any time during drug use, and can last for months to years after the drug is stopped or can be permanent.”
National Academies of Sciences ¹⁴	<i>There is insufficient or inadequate evidence of an association between the use of mefloquine for malaria prophylaxis and</i> <ul style="list-style-type: none"> • <i>persistent or latent neurologic events,</i> • <i>persistent or latent psychiatric events, including posttraumatic stress disorder (PTSD) and</i> • <i>persistent or latent eye disorders, including cataract.</i> <i>However further study of such associations is warranted.</i>

Long-term Malaria Chemoprophylaxis

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Primaquine

NOTE – Primaquine must not be used in people who have a deficiency of an enzyme called Glucose-6-phosphate dehydrogenase (G6PD), as it can cause severe haemolytic anaemia in this group. This is a common inherited genetic condition. Before commencing Primaquine, people **must** have a blood test to ensure they have adequate levels of G6PD.

Public Health England	<i>Not licensed in the United Kingdom</i>
US CDC ⁹	<i>CDC has no time limits on the use of primaquine for the prevention of malaria. There is no evidence of harm when the drug has been used for extended periods of time.</i>

Tafenoquine

NOTE – Tafenoquine must not be used in people who have a deficiency of an enzyme called Glucose-6-phosphate dehydrogenase (G6PD), as it can cause severe haemolytic anaemia in this group. This is a common inherited genetic condition. Before commencing Tafenoquine, people **must** have a blood test to ensure they have adequate levels of G6PD.

Australia ¹⁵	<i>Tafenoquine should not be taken for longer than six months.</i>
United States ^{14, 16}	<i>Because tafenoquine is a newly approved drug, published data containing information on adverse effects are limited compared with what is available for drugs that have been in use longer. [...] can be administered for up to 6 months of continuous dosing.</i>
National Academies of Sciences ¹⁴	<i>There is insufficient or inadequate evidence of an association between the use of tafenoquine for malaria prophylaxis and persistent or latent psychiatric events, however further study of such an association is warranted. There is sufficient evidence of an association between the use of tafenoquine for malaria prophylaxis and vortex keratopathy, but with unclear clinical significance. There is insufficient or inadequate evidence of an association between the use of tafenoquine for malaria prophylaxis and other persistent or latent eye disorders. Current evidence suggests further study of such an association is warranted but with unclear clinical significance.</i>

Frequently Asked Questions

Q. I have been advised by my local doctor that there has not been sufficient research into the longer term use of these drugs and should not take them regularly.

A: More studies are called for. However, when anti-malarial drugs are taken and there are no problems in the short-term, there is little evidence of harm with longer term use. The risk of malaria may outweigh the risk of possible adverse effects from these drugs. Please see the tables above for more information.

Q. I have been told I will develop liver disorders with prolonged use of anti-malaria drugs.

A: Some anti-malaria drugs can have a side-effect of liver problems. However if they occur, they are almost always completely reversed after the medication has been discontinued. These adverse effects are also rare and usually occur within the first few weeks to months of taking the medicine.

Q. I have been told that using anti-malaria can affect your mental / psychological state and cause issues such as disorientation, depression or anxiety or hallucinations.

A: Some anti-malarial drugs (mefloquine in particular) can have this uncommon side effect. These side effects are usually mild or sometimes moderate but very rarely severe enough to require hospitalisation. Different people may be more susceptible (such as women, and those who have had previous mental health problems). Your doctor will prescribe a medication suitable for you, to minimize the risk of adverse effects. If such effects occur, they usually occur soon after the drug is started. That is why, if starting a drug for the first time, it is recommended to start some anti-malarial drugs 4 to 6 weeks prior to travel – it allows for the drug to be changed should side-effects occur.

Q. I have been told that I should not be taking anti-malaria drugs for more than 6 months.

A: The longer you spend in a malarious area, the higher the risk that you will contract malaria. Generally medication should be taken for the duration of your stay, even if it is longer than 6 months. Regulatory bodies in the UK have recently lengthened the recommended duration of use for some of these drugs as concerns over possible adverse effects from long term use have reduced.

Q. How long can I take anti-malaria drugs without any other health issues?

A: In general, when an anti-malarial drug has been taken and there are no problems in the short-term, there is little evidence of harm with longer term use.

Q. I have heard that pregnant women should not be taking anti-malaria drugs?

A: Yes some anti-malarial medication must not be taken by pregnant women. However if a pregnant woman must travel to a malarial area, a safe drug can be selected.

Q. If I take the drug for a long time, will I become immune to malaria?

A: No. Partial immunity can only be gained if you were born and raised as a child in a malaria area. Immunity fades over 6 to 12 months once you leave that area for a non-malaria area.

Q. Can I change drugs once I started on one type?

A: Yes, and this should be discussed with your travel health doctor to determine how best to do this.

Q. I have been offered an assignment to a country where malaria is a problem, how should I prepare myself and my family to protect them against malaria?

A: Ensure you have read the International SOS Country Guide articles on “Malaria” and preventive measures (“Using Insect Repellents”, “Preventing Mosquito, Tick and Other Insect Bites”).¹¹ You should always take steps to prevent being bitten by mosquitoes. See a travel health specialist at least 6 weeks prior to departure. In addition to bite prevention, an anti-malarial preventive medication and / or a “emergency standby treatment” kit may be recommended. Remember the ABCDE of malaria prevention. A for Awareness of risk and symptoms of malaria, B for Bite prevention, C for Chemoprophylaxis, D for prompt Diagnosis and treatment, and E for Emergency Standby Treatment kit and how to access medical assistance in an emergency.

Q. Which malaria drugs provide the best protection against malaria?

A: It depends on the location to which you are travelling. Some areas have malaria resistant to certain medications. You need to discuss this with your travel health doctor.

Q. Where can I go to receive expert information on the possible side effects of long-term use of anti-malaria drugs?

A: Please read this leaflet and visit your own travel health doctor or the International SOS clinic.

Q. Should I be having regular medical checks if I am using anti-malaria drugs?

A: If you are taking anti-malaria drugs other than chloroquine or mefloquine you do not need regular medical checks. You only need a medical check if you think you may be developing an adverse effect from the drug.

For **mefloquine**, the manufacturer suggests periodic checks on liver function and eye assessments if used for a “prolonged” period. Any visual disorder should be reviewed by a doctor and you may need to stop chemoprophylaxis.

For chloroquine, twice-yearly eye checks should be started after 3 to 5 years of use, depending on the dosage taken. *If daily doses of 100mg chloroquine have been taken, eye checks should start at 3 years, if weekly doses 300mg of chloroquine have been taken, eye checks should start at 5 years. (Note: chloroquine is rarely prescribed for malaria chemoprophylaxis, as in most areas the parasite is resistant to chloroquine).*

Q. What is the medical definition of “long-term”; is this months, 1 year 3 years or 10 years?

Generally this means months. The exact definition depends on who is using the term. Many authorities use the term to mean more than 6 months.

Q. For areas that only have LOW risk of malaria, should I still take malaria chemoprophylaxis if I am there for a long period of time?

In areas of LOW malaria risk, some authorities, especially in Europe do not recommend using chemoprophylaxis.^{12,13} In addition to mosquito bite prevention, they recommend carrying **malaria Standby Emergency Treatment (SBET) medication to be started if symptoms develop**. For instance this would apply to parts of Central America, and parts of Asia where the risk of malaria is considered LOW. See the International SOS location guide for your destination for more detail

For higher risk areas, malaria chemoprophylaxis is always recommended. Ask International SOS for more information on malaria standby emergency treatment kits.

Q. The location I am in only has a high risk of malaria just after the rainy season. Do I need to take chemoprophylaxis year-round?

For locations that have a seasonal risk of malaria, you can, under the supervision of your doctor, use preventive chemoprophylaxis during the high risk period, and stop in the low risk period. However, you need to continue to prevent mosquito bites all year. You should always be aware of malaria symptoms and ensure prompt diagnosis and treatment even in the low risk period. Your doctor may also recommend you always have SBET available,

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