



衛生防護中心
Centre for Health Protection

Scientific Committee on Vector-borne Diseases

Guidelines on Malaria Chemoprophylaxis for Travellers from Hong Kong

Purpose

This paper details the approaches for clinicians who may need to provide advice or prescriptions against malaria to travellers from Hong Kong.

Approaches to Malaria Prevention for Travellers

2. The majority of infections and deaths due to malaria are preventable. The keys to prevention lie in the following four principles^{1,2}:
 - (a) awareness of the risk of malaria among travellers;
 - (b) preventing mosquito bites;
 - (c) the proper use of chemoprophylaxis and good drug compliance; and
 - (d) a high index of suspicion for breakthrough infection.

Awareness of the Risk of Malaria

3. Malaria is a vector-borne disease transmitted by several species of female Anopheline mosquitoes. It is a disease caused by protozoan parasites belonging to the genus *Plasmodium*, comprising *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium ovale*, and *Plasmodium malariae*.

4. Clinically, malarial infection presents as an acute febrile illness with incubation period ranging from 7 days to up to 1 year or



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even longer. Patients may present with fever, chills, headache, muscular pain and weakness, vomiting, cough, diarrhea, and abdominal pain. Severe malaria is usually caused by *P. falciparum* and may be manifested as renal failure, generalized convulsion, circulatory collapse, and coma. *Falciparum malaria* may be fatal if treatment is delayed beyond 24 hours. *Plasmodium vivax* and *Plasmodium ovale* have dormant liver stages and may cause relapse months or years later. *Plasmodium malariae* has been known to persist in the blood of some persons for several decades.

5. Currently there is no vaccine against malaria. Prevention of exposure to the mosquito vectors in malaria endemic areas is of utmost importance. Individuals need to be reminded to consult medical practitioners when planning visits to places with potential malarial risk and should consider the appropriate use of chemoprophylaxis. They should also be reminded to urgently seek medical advice and provide information on their travel histories if they have a fever during their trip or after returning from endemic areas.

Preventing Mosquito Bites

6. The first line of defence against malaria is to take protective measures to reduce contact with mosquitoes in areas with malaria risks. Measures to prevent mosquito bites include mosquito avoidance, physical barriers, chemical barriers, and the use of insecticides. The best way to prevent mosquito bites is to use all of these measures rather than any single measure.

- (a) Mosquito avoidance refers to measures such as
 - ✧ Living in accommodation areas with mosquito screens;
 - ✧ Staying in mosquito-protected area during dusk to dawn when *Anopheles* mosquitoes are actively biting;
 - ✧ Avoid traveling to malaria endemic areas during the seasons with high transmission.
- (b) Use of physical barriers refers to measures such as
 - ✧ Wearing light-coloured long-sleeved shirts and long pants;
 - ✧ Sleeping under pyrethroid-impregnated mosquito net;
- (c) Chemical barriers:
 - ✧ Synthetic repellents containing DEET (short form for N,N-diethyl-3-methyl-benzamide, also known as N,N-diethyl-m-toluamide) are the most effective agents³ and are recommended for all travellers at risk of exposure unless contraindicated³. DEET is available in a variety of concentrations for use on skin or clothing. DEET at concentration of 30% to 35% provides an approximate protection time of about six hours whilst lower concentration provides a shorter duration of protection⁵. DEET at concentrations above 35% adds very little extra protection but increases the risk of toxicity⁴. Overseas authorities differ in the recommended maximum concentration of DEET, especially for

children and DEET has been reported to be associated with neurotoxicity in children⁴. For instance, Health Canada, recommends concentrations of up to 30% DEET for persons aged 12 or above and concentrations of up to 10% for children under age 12⁵; both Centers for Disease Control and Prevention of US and National Travel Health Network and Centre of UK recommend DEET formulations up to 50% for both adults and children older than 2 months^{7, 14}.

- ✧ A second line synthetic agent, picaridin can be used if DEET is contraindicated (e.g. persons allergic to DEET). Application of Bayrepel 10-20% (Picaridin/Hepidanin), a piperidine derivative, can be effective for 3 to 10 hours. However, it is not available in Hong Kong and provides a shorter duration of protection. Naturally occurring repellents such as lemon eucalyptus oil (P-menthane-3,8-diol) 10%-30%, soybean oil 2% could also be considered^{3-5,7}. However, they provide a shorter duration of protection and should only be used if DEET is contraindicated.
- (d) Pyrethroid insecticides, such as permethrin, are available as sprays or liquid to treat clothes and bednets. There are also commercially available permethrin-impregnated bednets in the market, which offer about 50% protection for travellers visiting high-risk areas⁶. The use of “knockdown” pyrethroid sprays and mosquito coils is also recommended to kill mosquitoes indoors.

Chemoprophylaxis

7. Recommendations for chemoprophylaxis of malaria should be based on individual risk assessment, geographical distribution and resistance pattern of malaria at the destination, indications and contraindications of various chemoprophylactic agents, and the characteristics of the individual needing the protection.

Individual risk assessment and counseling

8. The purpose of individual assessment is to examine in detail the itineraries of the travellers and provide appropriate advice for prevention of malaria. The assessment should cover the following aspects:

- (a) Endemicity: According to WHO¹⁵, malaria is considered to be eliminated in a country when there are fewer than three ‘epidemiologically linked’ cases of malaria infection per year in the whole country, without an identifiable risk factor other than local mosquito transmission, for three consecutive years. However, there may be grey areas in risk assessment because of the difference in health care systems and the completeness of disease surveillance and delay or under-reporting in each country. In general, malaria transmission occurs

in most of sub-Saharan Africa and New Guinea; in large areas of Southern Asia; in parts of Southeast Asia, Oceania, Haiti, and Central and South America; and in limited areas of Mexico, the Dominican Republic, North Africa and the Middle East³. The travel itinerary should be reviewed in detail and compared with known areas of malaria transmission within a country to determine the likelihood of acquiring malaria.

- (b) The predominant drug resistant strains³: Malaria endemic areas can be broadly divided into chloroquine-sensitive, chloroquine-resistant, and both chloroquine and mefloquine-resistant areas depending on the predominant drug resistant strains. Plasmodium species in Mexico, the Caribbean, Central America (north of the Panama Canal), parts of China, and parts of the Middle East are, in general, still sensitive to chloroquine. Malaria resistant to chloroquine is found in many areas with malaria risk in the world. Plasmodium species resistant to mefloquine are still very rare in Africa and South Asia, uncommon in South America and parts of Southeast Asia excepting the Thailand/Cambodia and Thailand/Myanmar borders where mefloquine resistance is common.
- (c) Urban vs rural areas: Traveling to urban and tourist areas of Southeast Asia, and Central and South America is considered to entail minimal risk, whereas urban travel in other malaria-endemic regions, such as sub-Saharan Africa, the Indian subcontinent, New Guinea (Papua New Guinea and Papua [Irian Jaya]), and parts of Oceania may be associated with significant risk of infection³. There is a higher risk of contracting malaria when traveling to rural areas.
- (d) Climate and seasonality: The risk of malaria transmission varies seasonally in many locations, being highest at the end of the rainy season³.
- (e) Altitude: Transmission decreases at altitudes above 2000 m (6500 feet)³.
- (f) Pattern of activities: Travellers who like to explore between dusk and dawn are at a higher risk of being bitten by *Anopheles* mosquitoes. Backpackers who tend to have more outdoor activities, night-time travel and unscreened accommodations, are also at a higher risk than travellers on business trips³.
- (g) Duration of stay: The risk of malaria is roughly proportional to the duration of stay in an area with malaria risk. A visit of three months carries a risk around six times greater than a visit that lasts a fortnight².
- (h) Characteristics of the individual: Characteristics of the individual, such as age, pregnancy, medication, and chronic illness, may modify the risks

of severe malaria and affect the choice of antimalarial drug for chemoprophylaxis³.

9. Travellers should be counseled on balancing the risks and benefits of various preventive approaches against the risk of infection. While antimalarial medication can markedly decrease the risk of acquiring malaria, none of the agents can guarantee complete protection against malaria. Personal protective measures are an important adjunct to malaria prevention. Moreover, compliance to chemoprophylaxis is as important as choosing the right drug for chemoprophylaxis.

Choice of drugs and regimen

10. Malarial chemoprophylaxis prevents established infection by targeting different stages of plasmodium life cycles. When an infected mosquito bites a human malarial sporozoites enter the hepatocytes of the susceptible human host and develop into exo-erythrocytic schizonts. In the intrahepatic cycle, the mature schizonts rupture the infected hepatocytes and release merozoites into the blood stream. The merozoites then invade erythrocytes. Such asexual forms develop into mature schizonts and rupture the erythrocytes within 48 to 72 hours to release more merozoites. Merozoites further infect other erythrocytes and develop into schizonts or gametocytes. An *Anopheles* mosquito that bites a human at this stage will then take up gametocytes and start the sexual cycle. Hypnozoites are the dormant forms of *P. ovale* and *P. vivax* inside the liver and can be activated to cause relapse of disease up to three years later. Malaria chemoprophylaxis refers to the following strategies⁶:

- (a) Causal prophylaxis targeting the intrahepatic stage by killing the parasites before they enter the blood;
- (b) Suppressive prophylaxis suppresses the erythrocytic cycle;
- (c) Terminal prophylaxis targeting the hypnozoites by using medication given at or after the end of the exposure period.

11. Depending on the chemoprophylactic agents to be taken, they should be started 1 day to 3 weeks before departure and be continued till 1 to 4 weeks after returning from an area with malaria risk. Taking chemoprophylactic agents before travel allow accumulation of adequate drug levels prior to exposure to malaria parasites. Also, if prophylaxis is started early enough, when unacceptable side effects develop, there is still time to change the medication before the traveller's departure.

12. Chemoprophylaxis with suppressive drugs must be continued for four weeks after return; whilst chemoprophylaxis with causal drugs such as atovaquone-proguanil should be continued for a week after return².

13. Most commonly used drugs for malarial prophylaxis are: chloroquine, proguanil, mefloquine, doxycycline, and atovaquone-proguanil. The usage and potential side effects of these drugs are summarized below^{1-3,7,14}:

- (a) Chloroquine acts against the intra-erythrocytic stages and a weekly adult dose of 300mg is effective to prevent malaria in areas with chloroquine-sensitive malaria. It should be taken 1-2 weeks before departure and be continued for 4 weeks after return. It can be used at any age and in pregnant women. Side effects include bitter taste, nausea and headache, as well as retinal toxic effects in those taking long-term daily doses of chloroquine (more than 100g total dose). Ophthalmologic examination every 6-12 month after taking weekly 300mg dose for 5 to 6 years is recommended.
- (b) Proguanil 200mg daily may be used in combination with chloroquine 300mg weekly for chloroquine-resistant malaria. This regimen should be taken 1 week before and be continued for 4 weeks after traveling¹⁴. However, this combination is of decreasing efficacy in African countries south of the Sahara, and in Southeast Asia. A common side effect of proguanil is the development of mouth ulcers².
- (c) Mefloquine, taken at an adult dose of 250mg weekly, is an effective prophylaxis. In general, mefloquine should be ideally started 2 to 3 week before travel and must be started at least 1 week before travel^{2,3}. Those travellers who present less than a week before departure can be given mefloquine prophylaxis by a “rapid-loading” protocol viz: 250mg daily for three consecutive days. The drug should be continued for 4 weeks after return. It is generally well tolerated but some may have side effects especially gastrointestinal and neuropsychiatric symptoms. Common neuropsychiatric symptoms include insomnia, nightmares, and mild depression. Rare neuropsychiatric symptoms include feelings of dissociation, panic attacks, severe depression, hallucinations and psychotic episodes. The more serious side effects usually occur within the first three weeks. Mefloquine is widely recommended in North America but less in the UK because of concerns over its side effects^{2,6}.
- (d) Doxycycline 100mg daily can be used in travellers to chloroquine-resistant or mefloquine-resistant areas. It should be started 1-2 days before departure and be continued for 4 weeks after return. Common side effects include nausea, abdominal pain, oesophagitis, vaginal candidiasis and photosensitivity. Irritant effect of doxycycline on the upper gastro-intestinal tract can be minimized by ingesting it with a large glass of water on a full stomach and maintaining an erect posture for half an hour afterwards. Photosensitivity can be prevented by minimizing exposure to the sun and by wearing protective clothing, eye protection, and sunscreens. It is contraindicated in pregnant, and

lactating women, and children under 8 years of age.

- (e) Atovaquone-proguanil (or malarone) is a fixed combination of two drugs (Atovaquone 250mg and proguanil 100mg per tablet) with synergistic actions and can be used as a causal and suppressive prophylactic agent. It is not however active against hypnozoites. One tablet daily for prophylaxis is recommended. It should be started 1-2 days before departure and be continued for 7 days after return. It is well-tolerated and is effective in many places including areas where multi-drug resistant malaria prevails. It is effective and with few side-effects, and is safe for short term travellers but the safety profile has not yet been established for use longer than 9 months. Abdominal pain, nausea, vomiting and headache are common side effects.

14. Chemoprophylactic regimen can be broadly divided into three groups in accordance with the prevalent drug-resistance plasmodium species. Chloroquine is the first line agent when a person plans to visit malaria endemic areas where the *Plasmodium* species are sensitive to chloroquine. In places where chloroquine-resistant strains are prevalent, mefloquine, doxycycline, or atovaquone-proguanil can be used. Chloroquine combined with proguanil is sometimes recommended in areas where chloroquine-resistant strains are emerging but this combination is of decreasing efficacy. For travellers who need to visit places where resistance to both chloroquine and mefloquine are present, doxycycline or atovaquone-proguanil should be used.

15. Primaquine is the only drug effective against hypnozoites. It is the drug used for treating *P. vivax* and *P. ovale* aiming at the prevention of relapse by killing their hypnozoites. It can also be used as a terminal prophylaxis to prevent relapse of *P. vivax* or *P. ovale* and is only indicated for persons who have had prolonged and extensive exposure to *P. vivax* or *P. ovale*, e.g. long-term travellers. Strains of *P. vivax* with reduced sensitivity to primaquine are reported from widely divergent areas, including many parts of Indonesia, Papua New Guinea, Somalia, and India. In view of the reduced sensitivity of *P. vivax* and *P. ovale*, the dosage for terminal prophylaxis is recommended to be 30 mg daily for 14 days after departure from the areas with malaria risk^{3,6}. When other malaria prophylactic agents are not suitable, primaquine could be considered as an alternative for person without contraindication. When using as a primary prophylactic agent, primaquine 30mg daily is effective against all forms of malaria^{3,6}. Primaquine can cause fatal haemolysis in G6PD deficiencies and should never be prescribed as prophylaxis to anyone with G6PD deficiencies. For this reason the G6PD status should always be determined before prescribing Primaquine.

Monitoring and follow up

16. It is important to observe contraindications to the use of specific

antimalarials, and especially not to give mefloquine to people with a history of epilepsy or psychiatric illness, including depression. Chloroquine is relatively contraindicated in people who have had fits or who have psoriasis. Doxycycline is being used more often for those unable to take these drugs intending to travel to high-risk areas, but it does carry a risk of photosensitization². The risk of drug adverse events accumulates swiftly at the start of dosing, then occurs less frequently. Adverse reactions to antimalarials tend to occur most often after the first dose for rapidly excreted drugs and after one of the first few doses for drugs that are excreted more slowly².

Breakthrough infection and Stand-by self treatment

17. No chemoprophylaxis gives complete protection. Travellers need to watch out for symptoms and signs of malaria during their stay in malaria endemic areas and for months or even years after they return to non-endemic areas. Travellers to areas with malaria risk should ensure they have access to medical care within 24 hours. Travellers should seek medical attention if they develop fever after returning from these regions.

18. Doctors attending febrile travellers returning from areas with malaria risk should always have a high index of suspicion for malaria irrespective of the history of taking chemoprophylaxis. Early diagnosis and treatment prevents most of the morbidity and mortality.

Stand-by emergency treatment

19. Stand-by emergency treatment refers to a complete course of effective antimalarial treatment regimen prescribed to travellers to malaria endemic areas who may have difficulties accessing medical services within 24 hours. Travellers should be advised to take this regimen promptly when the clinical picture is compatible with malaria (i.e., fever, chills, flu-like symptoms) and if professional medical care is not reachable within 24 hours.

20. There are occasions when stand-by emergency treatment may be recommended for some travellers: (1) those who elect not to take prophylaxis; (2) those who will be traveling to areas with low levels of malaria transmission; (3) those who are receiving a less than optimal antimalarial drug regimen due to underlying medical conditions or are receiving other medications with possible drug interactions; and (4) travellers who are taking effective prophylaxis but who will be in remote areas with difficult access to appropriate medical care⁶.

21. Stand-by emergency treatment regimens vary according to national and international guidelines. According to WHO, the drugs used for stand-by emergency treatment should always be different from the drugs used for prophylaxis, and should be one to which no resistance has been reported in

the countries visited. The drugs of choice for SBET are in principle the same as those for treatment of uncomplicated malaria¹.

22. Travellers should be educated about the fact that stand-by emergency treatment is only a temporary measure, and prompt medical attention should be sought immediately. They should also be reminded that stand-by emergency treatment should not replace effective chemoprophylaxis and mosquito preventive measures.

Malaria Protection in Special Groups

23. Special considerations should be noted in the following groups: young children; pregnant woman; breastfeeding mothers; the immunocompromised; long term travellers/expatriates; people returning to endemic area after staying in malaria free areas for long time; and frequent travellers like businessmen and air crew;

- (a) Falciparum malaria in a young child is a medical emergency and may be rapidly fatal. Parents should be advised not to take babies or young children to endemic areas. If this is unavoidable, parents should carefully protect the children against mosquito bites and give them appropriate chemoprophylaxis. Babies, including those who are breastfed, should be given chemoprophylaxis since they are not protected by the mother's prophylaxis. Dosage schedules for children should be based on body weight. Chloroquine and proguanil are safe for babies and young children but only suitable for areas with low levels of chloroquine resistance. Mefloquine may be given to infants of more than 5 kg body weight. Atovaquone-proguanil is not recommended for prophylaxis in children who weigh less than 11 kg, because of the lack of data. Doxycycline is contraindicated in children below 8 years of age¹.
- (b) Malaria in a pregnant woman increases the risk of maternal death, miscarriage, stillbirth and low birth weight with associated risk of neonatal death. Pregnant women should be advised to avoid traveling to areas where malaria transmission occurs and to adopt effective measures when travel is unavoidable. Chloroquine and proguanil can be safely prescribed throughout the pregnancy. In areas with high chloroquine resistance, mefloquine prophylaxis may be given during the second and third trimester, but there is limited information on its safety during the first trimester. Doxycycline is contraindicated during pregnancy. Atovaquone-proguanil has not been sufficiently investigated to be prescribed for chemoprophylaxis in pregnancy¹.
- (c) The main concern about prescribing malaria prophylaxis for lactating mothers is the potential harmful effects to their babies. It is noted that

the quantity of antimalarial medication transferred in breast milk is small and insufficient to provide adequate protection against malaria. Amongst the various drugs, the very small amount of chloroquine, mefloquine, and proguanil secreted in the breast milk of lactating women is unlikely to be harmful whereas primaquine is contraindicated in lactating mothers if the infant is G6PD deficient. Doxycycline is contraindicated in breastfeeding. Atovaquone-proguanil should not be given to lactating mothers as the efficacy in infants weighing less than 11 kg (25 lbs) has yet to be established unless the potential benefit to the woman outweighs the potential risk to the infant (such as for a lactating woman with multidrug-resistant falciparum malaria and cannot tolerate other treatment options)³.

- (d) Malaria may be rapidly fatal in asplenic patients. The spleen facilitates phagocytosis and promotes removal of parasitized red blood cells and asplenia has been shown to exacerbate malaria disease in animal models. Hence, maximal preventive measures should be recommended for travellers with functional or anatomical asplenia. Stand-by self-treatment may be considered in addition to prophylactic measures if the visits are to remote regions where access to care is limited³.
- (e) In vitro and human data indicate that malaria infection stimulates HIV-1 replication, resulting in increased viral loads that persist for weeks after the infection and worsens the clinical progression of HIV disease. Those infected with HIV have an increased risk of Plasmodium parasitemia and clinical malaria infection. Infection risk and parasite density increase as the immune status deteriorates. There have been only a few studies on the interactions between malaria and HIV drug. Before further research can shed light on the proper use of both antimalarial and anti HIV drugs, those infected with HIV should be reminded of the importance of personal protection against mosquitoes and of chemoprophylaxis³.
- (f) Pilots have high psychomotor requirements and the possibility of antimalarial drugs adversely affecting psychomotor skills is of concern⁸. Mefloquine is therefore generally an unacceptable prophylaxis for pilots. On the other hand, atovaquone-proguanil and primaquine have been shown to result in no differences in psychomotor testing and questionnaires when compared to those taking placebos in a Canadian placebo-controlled double-blinded crossover design study⁹.
- (g) From time to time, there are people returning to endemic area after staying in non-endemic area, like Hong Kong, for long period of time. They may believe they still have some persistent immunity against malaria, but in fact they will have lost their immunity. It is therefore particularly important to emphasize both mosquito avoidance and

compliance with chemoprophylaxis to this group of travellers².

Chemoprophylaxis in Long-term Travellers

24. The term “Long-term travellers” refers to those who travel through, or visit malaria-endemic areas for periods longer than six months¹⁰. Examples of long-term travellers include individuals visiting friends or relatives, expatriates and backpackers staying in malaria endemic area.

25. The major concerns about malaria protection strategies in long-term travellers are (a) safety of antimalarial drugs for long-term use; (b) adequate supply of effective antimalarial drugs; and (c) poor compliance to the antimalarial drugs.

26. There is insufficient data supporting the upper limit on the duration of safe use of antimalarial drugs for prophylaxis. Currently, there are licensed limits to the duration of prophylaxis in UK and the United States. The Health Protection Agency Advisory Committee on Malaria Prevention for UK travellers (ACMP) has also examined the available evidence and made recommendations¹¹. In general, there is no upper limit for long term use of chloroquine and proguanil. There is an upper limit of up to 6 months for Atovaquone-proguanil, up to 2 years for doxycycline and up to 3 years for Mefloquine¹¹. Amongst the agents which can be used in long-term travellers (chloroquine, proguanil, atovaquone-proguanil, doxycycline and mefloquine), the track record of efficacy and weekly dosing of mefloquine makes it the drug of choice in this group of travellers.

27. Long-term travellers are more likely to buy their drugs in the countries where they are staying in. They have to ensure that the drugs they purchased are safe, real and effective. Counterfeit drugs are available in many Southeast Asian countries.

28. Poor compliance to chemoprophylaxis is known to be associated with an increased risk of malaria especially among long-term travellers^{12,13}. Possible reasons for unsatisfactory compliance may include their fear of long-term side effects from drugs, experiencing an adverse reaction to the drugs, receiving conflicting advice on drug regimen from different clinicians, being disturbed by a complicated or daily regimen, and a reduced confidence in the chemoprophylaxis should they contract malaria despite chemoprophylaxis. A proper risk assessment, good communications with the travellers, and giving clear and simple instructions will help to improve compliance.

29. A recent review¹¹ proposed alternative approaches to malaria prevention in long-term travellers, for instance, seasonal prophylaxis for knowledgeable and responsible travellers visiting countries with a clear season of malarial transmission. The disadvantage is that a good understanding of

local malaria epidemiology is necessary. While the use of stand-by self treatment alone is generally not recommended for long-term travelers to any malarious areas, it may be an option for use in combination with other alternative strategies given all factors including malaria risk, individual characteristics and access to medical care have been thoroughly assessed.

30. There are various approaches to be taken for malaria prevention for long-term travellers. The importance of drug compliance and seeking medical attention promptly whenever malaria symptoms arise are fundamental.

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