衞生防護中心
Centre for Health Protection

Scientific Committee on Vector-borne Diseases

Guidelines on Malaria Chemoprophylaxis for Travellers from Hong Kong

(April 2018)

Purpose

This paper details the guideline recommended by the Scientific Committee on Vector-borne Diseases (SCVBD) under the Centre for Heath Protection of the Department of Health. This serves as a local guideline for reference by clinicians in Hong Kong who provide advice, or prescribe malaria chemoprophylaxis, to travellers from Hong Kong who go to malaria endemic areas.

Background

2. Malaria is a common and serious infection in many tropical and subtropical areas. According to the World Malaria Report 2017 of the World Health Organization (WHO), the incidence rate of malaria was estimated to have decreased by 18% globally, from 76 to 63 cases per 1 000 population at risk, between 2010 and 2016.[1] However, in 2016, there were still an estimated 445 000 deaths from malaria globally, of which 407 000 (approximately 91%) were in the WHO African Region.[1] Prevention of infection is important to reduce mortality and morbidity from malaria.

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Approaches to malaria prevention for travellers

3. The majority of infections and deaths due to malaria are preventable. According to WHO, travellers and their advisers should note the following five principles of malaria prevention (the ABCDE):[1]

(a) Be **A**ware of the risk, the incubation period, the possibility of delayed onset and the main symptoms;
(b) Avoid being **B**itten by mosquitoes, especially between dusk and dawn;
(c) Take antimalarial drugs (**C**hemoprophylaxis) when appropriate, at regular intervals to prevent acute malaria attacks;
(d) Immediately seek **D**iagnosis and treatment if fever develops one week or more after entering an area where there is malaria risk and up to three months (or, rarely, later) after departure from a risk area; and
(e) Avoid outdoor activities in **E**nvironments that are mosquito breeding places, such as swamps or marshy areas, especially in late evening and at night.

Awareness of the risk of malaria

4. Malaria is caused by the protozoan parasite *Plasmodium.* Human malaria is caused by five different species of *Plasmodium: P. falciparum, P. malariae, P. ovale, P. vivax* and *P. knowlesi*.[2] Of these, *P. falciparum* and *P. vivax* are the most prevalent. *P. knowlesi* is a species that normally infects animals but can occasionally infect humans.[2] The malaria parasite is transmitted by female *Anopheles* mosquitoes, which bite mainly between dusk and dawn.

5. Clinically, malaria presents as an acute febrile illness with incubation period ranging from seven days to up to several months or more. Patients may present with fever, chills, headache, muscle pain and weakness, cough, jaundice, anemia, vomiting, diarrhea and abdominal pain.[3] Severe malaria is usually caused by *P. falciparum* and may manifest as generalised convulsion, circulatory collapse, coma and organ failure such as acute renal failure. *Falciparum* malaria may be fatal if treatment is delayed beyond 24 hours after the onset of symptoms.[3] *P. vivax* and *P. ovale* have dormant liver stages and may cause relapse months or years later.[3] *P. malariae* is known to persist in the blood of some infected persons for several decades. Malaria caused by *P. knowlesi* might manifest atypically, and organ failure and sporadic fatal outcomes have been reported.[3]

6. RTS,S/AS01 (RTS,S) is an injectable vaccine that provides partial protection against malaria in young children. The vaccine is being evaluated in sub-Saharan Africa as a complementary malaria control tool that potentially could be added to (but not replace) the core package of WHO-recommended preventive, diagnostic and treatment measures.[4] To prevent 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 use of appropriate chemoprophylaxis. They should also be reminded to urgently seek medical advice and provide information on their travel histories if they have fever during their trip or after returning from endemic areas.[5]

Preventing mosquito bites

7. The first line of defence against malaria is to take protective measures to reduce contact with mosquitoes in areas with malaria risk. Measures to prevent mosquito bites include mosquito avoidance, physical barriers, chemical barriers and the use of insecticides.

(a) Mosquito avoidance refers to measures such as
- Living in accommodation with air-conditioning or mosquito screens;
- Staying in mosquito-protected areas during dusk to dawn when *Anopheles* mosquitoes are actively biting; and
- Avoiding using fragrant cosmetics or skin care products such as perfume, cologne or aftershave as these products may attract mosquitoes.[6]

(b) Use of physical barriers refers to measures such as
- Wearing loose, light-coloured and long-sleeved tops and trousers; and
- Sleeping under an insecticide-impregnated mosquito net.

(c) Chemical barriers:
- Insect repellents containing N,N-diethyl-3-methylbenzamide (also known as N,N-diethyl-meta-toluamide [DEET]), IR3535 or Icaridin (also known as Picaridin) are recommended for all travellers at risk of exposure.[2] When using any insect repellent, the label instructions and precautions should be followed.
- DEET-containing insect repellents should not be used in infants under

two months of age.[7] When DEET-containing insect repellents are used in children, a concentration of DEET up to 30% should be used.[7] When DEET-containing insect repellent is used with sunscreen, travellers should apply sunscreen first and then insect repellent.[8] DEET-containing insect repellents should not be applied over cuts, wounds, irritated skin, hands or near the eyes and mouth of young children.[9] After returning indoors, treated skin should be washed with soap and water.[9]

- There are other mosquito repellent products available in the market, but they may not be equally reliable. Products of essential oils included oil of lemon eucalyptus and citronella oil may be considered unsuitable for children under 2-3 years old, whilst citronella oil and soybean oil products may provide protection for a short duration.[10] Methyl nonyl ketone (also known as "wild tomato extract") does not have appreciably long history as a mosquito repellent, and is often absent in peer-reviewed scientific literatures comparing various mosquito repellents.[10]

(d) Pyrethroid insecticides, such as permethrin, are available as sprays or liquid to treat clothes and bednets. There are also commercially available insecticide-impregnated bednets on the market, which offer about 50% protection for travellers visiting high-risk areas.[11] The use of "knockdown" pyrethroid sprays, mosquito coils and electrical devices vaporising pyrethroids are also recommended to kill mosquitoes indoors.[12]

Chemoprophylaxis

8. Recommendations for chemoprophylaxis of malaria should be based on an individual risk assessment which includes factors of the destination (such as endemicity, predominant drug resistant strains of malaria, type of areas being visited, climate and seasonality, altitude), as well as the pattern of activities, duration of stay and characteristics of the individual needing the protection.

Individual risk assessment and counselling

9. 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: 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. According to WHO estimates, an increasing number of countries were moving towards malaria elimination.[13] In 2016, 91 countries and areas had ongoing malaria transmission.[2] Most malaria cases and deaths occurred in sub-Saharan Africa. However, the WHO regions of South-East Asia, Eastern Mediterranean, Western Pacific and the Americas were also at risk.[4]

(b) The predominant drug resistant strains: Malaria endemic areas could be divided into chloroquine-sensitive, chloroquine-resistant and both chloroquine- and mefloquine-resistant areas depending on the predominant drug resistant strains.[5,14,15] *Plasmodium* species in Haiti, the Dominican Republic, Central America north of the Panama Canal, parts of Mexico, parts of South America and parts of Mainland China were, in general, sensitive to chloroquine.[5,15] Malaria resistant to chloroquine occurred in most of sub-Saharan Africa, South America, Oceania and Asia.[5,15] *Plasmodium* species resistant to both chloroquine and mefloquine were found in various countries in Asia, Africa and the Amazon basin. However, it was a significant problem only in the rural, wooded regions where Thailand borders with Myanmar, Cambodia and Laos, as well as in southern Vietnam.[5,14] The latest information of predominant drug resistance strains are available in the most updated Global Malaria Risk Summary at the webpage of SCVBD (https://www.chp.gov.hk/en/static/24009.html).

(c) Urban versus rural areas: Malaria incidence is generally higher in rural than in urban areas, especially in Africa.[12] There is a significant risk of malaria in most urban areas in India.[5] There is no risk of malaria in many tourist destinations in Southeast Asia, the Caribbean and Latin America.[2]

(d) Climate and seasonality: The risk of malaria transmission varies seasonally in many locations, being higher during and at the end of the rainy season due to increased mosquito breeding.[5,12]

(e) Altitude: Transmission decreases at altitudes above 2 000 m (6 500 feet).[5]

(f) Pattern of activities: Travellers who stay outdoors between dusk and dawn are at a higher risk of being bitten by *Anopheles* mosquitoes.[12] Backpackers who tend to have more outdoor activities, night-time travel and unscreened accommodations are also at a higher risk.

(g) Duration of stay: The longer the stay in an endemic area, the higher the risk of contracting malaria.[12]

(h) Characteristics of the individual: Characteristics of the individual, such as age, pregnancy, immune status and chronic illnesses, may modify the risks of severe malaria and affect the choice of antimalarial drug for chemoprophylaxis.[5] If malaria chemoprophylaxis is to be prescribed, the clinician should be aware of all the medications that the traveller is taking and ensure that none of them interacts significantly with the choice of malaria chemoprophylaxis. Clinicians should refer to the package insert of individual drugs and may consider taking reference from online resources, e.g. the MedicinesComplete website (https://www.medicinescomplete.com/mc/bnf/64/PHP-bnf-interactions-list.htm) and the United States Food and Drug Administration website (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm) for information on drug interactions.

10. Travellers should be counselled on balancing the risks and benefits of various preventive approaches against the risk of infection. While malaria chemoprophylaxis 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

11. Malaria chemoprophylaxis prevents infection by targeting different stages of the *Plasmodium* life cycle. 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 24 to 72 hours to release more

merozoites.[12] Merozoites further infect other erythrocytes and develop into schizonts or gametocytes.[12] 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 strategies:[11,12]

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

12. Depending on the chemoprophylactic agents to be taken, they should be started one day to three weeks before departure and continued till one to four weeks after returning from an area with malaria risk. Taking chemoprophylactic agents before travel allows accumulation of adequate drug levels prior to exposure to malaria parasites. In addition, if prophylaxis is started early, when unacceptable side effects develop, there is time to change the medication before the traveller's departure.[2]

13. All chemoprophylaxis except atovaquone–proguanil should be continued for four weeks after return. Atovaquone–proguanil can be stopped one week after return because it is effective against early liver-stage parasites.[2]

14. The most commonly used drugs for malaria chemoprophylaxis include chloroquine, mefloquine, doxycycline and atovaquone-proguanil. Primaquine can cause fatal haemolysis in patients with G6PD deficiency, and should only be considered as an alternative when the above malaria prophylactic agents are not suitable. The recommendations, usual dosage and potential side effects of these drugs are summarised below and in Annex 1. The availability of these drugs is summarised in Annex 2. The following serves as a general guideline only and clinicians should refer to the package insert of individual drugs for details.

(a) Chloroquine acts against the intra-erythrocytic stages and a weekly adult dose of 300mg is effective to prevent malaria only in the few areas with chloroquine-sensitive malaria.[2,14] It should be taken one to two weeks before departure and continued for four weeks after return.[2,14] It can be used at any age and in pregnant women.[2,5] Side effects include bitter taste,

gastrointestinal disturbance, headache and insomnia, as well as retinal toxic effects when a cumulative dose of 100g is reached.[2] Ophthalmologic examination twice yearly after taking weekly 300mg dose for more than five years is recommended.[5] Chloroquine is contraindicated in travellers with a history of epilepsy and psoriasis.[2] It may prolong the QT interval and should be used with caution in travellers with known cardiac disease, a family history of sudden unexplained death consistent with cardiac arrhythmias or who are already taking medications that can prolong the QT interval.[16] Public Health England recommended using chloroquine with proguanil in areas with little chloroquine resistance.[12] Proguanil acts as a causal and suppressive prophylaxis. There are very few regions in the world where the local *P. falciparum* strains are fully sensitive to proguanil.[12] According to the Public Health Agency of Canada, proguanil should not be used as a single agent.[5] In Hong Kong, chloroquine is used with proguanil infrequently as chemoprophylaxis for travellers visiting areas with little chloroquine resistance.

(b) Mefloquine, taken as an adult dose of 250mg weekly, is an effective prophylaxis.[2] Mefloquine should preferably be started two to three weeks and must be started at least one week before departure.[2] It should be continued for four weeks after return.[2] Side effects include neuropsychiatric, vestibular and gastrointestinal symptoms.[5,12] Common neuropsychiatric symptoms include insomnia and nightmares.[5] Vestibular symptoms include dizziness, tinnitus, balance disorder and vertigo.[12] In a small number of patients, the dizziness, vertigo and loss of balance may continue for months after discontinuing the drug.[12] It is contraindicated in persons with a current or previous history of depression, generalised anxiety disorder, psychosis, schizophrenia, suicide attempt, suicidal thought, self-endangering behaviour or any other psychiatric disorder, epilepsy or convulsions of any origin.[12,17] Mefloquine is not a good option for malaria chemoprophylaxis because of its high rate of side effects. However, it is the chemoprophylaxis of choice in pregnancy.

(c) Doxycycline 100mg daily can be used in travellers visiting chloroquine-resistant or mefloquine-resistant areas. It should be started one day before departure and continued for four weeks after return.[2,14] As it can be started one day before travel, it is an option for last-minute travellers.[14] Protective efficacy of doxycycline was shown to be

92%-96% for *P. falciparum* and 98% for primary *P. vivax* infection.[18] For trekkers in the countryside, doxycycline has an additional advantage of protection against leptospirosis and rickettsial diseases.[14] Common side effects include gastrointestinal upset, oesophagitis, vaginal candidiasis and photosensitivity.[2,5,12] Irritant effect of doxycycline on the upper gastro-intestinal tract can be minimised by ingesting it with food or a large glass of water on a full stomach and maintaining an erect posture for at least half an hour afterwards.[5,12] Photosensitivity can be prevented by using a highly protective sunscreen and avoiding prolonged direct sunlight.[2] It is contraindicated in pregnant and lactating women and children under eight years of age.[2] For travellers on combined oral contraceptives or progestogen only oral contraceptives, additional precautions are not required when using doxycycline. However, if the traveller develops vomiting or diarrhoea, the usual additional contraceptive precautions should be observed.[12]

(d) 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.[5] However, it is not active against hypnozoites.[12] One tablet daily for prophylaxis is recommended. It should be started one day before departure and continued for seven days after return.[2] As it can be started one day before travel, it is an option for last-minute travellers.[14] Atovaquone-proguanil has a protective efficacy of 96%-100% against chloroquine-resistant *P. falciparum.*[5] It is well-tolerated and is effective in many places including areas where multi-drug resistant malaria prevails.[5] It is effective and with few side-effects, and is safe for short-term travellers.[2] Gastrointestinal upset and headache are common side effects.[12] Atovaquone-proguanil should be taken with food or a milky drink to increase absorption.[2]

(e) Primaquine is used in two major ways to prevent malaria, firstly for prevention of relapse due to *P. vivax* or *P. ovale* infection, and secondly as a primary chemoprophylaxis.[5] Primaquine is the only drug effective against hypnozoites. As such, it can 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.[5,14] The dosage for terminal prophylaxis is recommended to be 30mg daily for 14 days after departure from the areas with malaria risk.[5,14]

When chloroquine, doxycycline or mefloquine is used for primary prophylaxis, primaquine is usually taken during the last two weeks of postexposure prophylaxis.[14] When atovaquone-proguanil is used for prophylaxis, primaquine may be taken during the final seven days of atovaquone-proguanil, and then for an additional seven days.[14] When other malaria prophylactic agents are not suitable, primaquine could be considered as an alternative primary chemoprophylaxis for people without contraindication and who travel to areas with primarily *P. vivax* including Bolivia, Cyprus, Guatemala, Honduras, Mexico, North Korea, Panama and South Korea.[14] When being used as a primary prophylactic agent, primaquine 30mg daily should be started one to two days before travel and continued for one week after returning from the endemic area.[5,14] Primaquine had a protective efficacy of 85%-93% against both *P. falciparum* and *P. vivax* infections.[5] Primaquine can cause fatal haemolysis in people with G6PD deficiency and should never be prescribed as prophylaxis to anyone with G6PD deficiency or unknown G6PD status.[14]

15. In summary, 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.[5] In places where chloroquine-resistant strains are prevalent, mefloquine, doxycycline or atovaquone-proguanil can be used.[12] For travellers who need to visit places where resistance to both chloroquine and mefloquine are present, doxycycline or atovaquone-proguanil should be used. Primaquine may be used as an alternative prophylaxis, provided that the person is G6PD competent, but is generally used as a terminal prophylaxis for travellers visiting places where there is heavy and prolonged exposure to *P. vivax* or *P. ovale*.[14] The choice of malaria chemoprophylaxis based on the predominant drug resistance strains or species travellers would be exposed to is summarised in Annex 3.

Adverse effects of malaria chemoprophylaxis

16. According to WHO, adverse reactions attributed to malaria chemoprophylaxis are common, but most are minor which do not affect the activities of the travellers. Serious adverse events include events constituting an apparent threat to life, requiring or prolonging hospitalisation, or resulting in persistent or significant disability or incapacity are rare and mainly identified in post-marketing

surveillance after a drug has been in use for some time.[2] As chloroquine may cause retinal toxic effects when a cumulative dose of 100g is reached, ophthalmologic examination twice yearly after taking weekly 300mg dose for more than five years is recommended.[2]

Breakthrough infection and standby emergency treatment

17. No chemoprophylaxis gives complete protection. Travellers need to watch out for symptoms and signs of malaria during their stay in the 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.[2] Travellers should seek medical attention if they develop fever after returning from endemic areas.

18. Doctors attending febrile travellers returning from a malaria endemic area should always have a high index of suspicion for malaria irrespective of the history of taking chemoprophylaxis. Early diagnosis and treatment can prevent most of the morbidity and mortality.

Standby emergency treatment

19. Standby emergency treatment (SBET) refers to antimalarial drugs for self-administration prescribed to travellers staying in remote locations where prompt access to medical care may not be reached within 24 hours.[2,12] Travellers should be advised to take this regimen promptly when they develop symptoms suggesting possible malaria, including fever of 38°C and above, and if professional medical care is not reachable within 24 hours.[11,12] SBET is a first-aid measure for travellers who believe that they may have malaria and is not a replacement for chemoprophylaxis.[2,12]

20. Apart from travellers who are taking effective prophylaxis but who will be in remote areas with difficult access to appropriate medical care, SBET may be recommended for the following travellers: (1) those in some occupational groups who make frequent short stops in countries or areas with malaria risk over a prolonged period of time. Such travellers may choose to reserve chemoprophylaxis for high-risk areas and seasons only; (2) those who will spend one week or more in certain remote rural areas where there is very low risk of infection; and (3) those who are receiving a less than optimal chemoprophylactic regimen due to underlying medical conditions or are receiving other medications with possible drug

interactions.[2,11] The health authority of Switzerland advocates that travellers to low-risk countries should be prescribed SBET rather than chemoprophylaxis.[19]

21. SBET regimens vary according to international and national guidelines. The drug options for SBET are in principle the same as the options for treatment of uncomplicated malaria.[2] The agents used for SBET should be different from the drugs used for chemoprophylaxis, both to minimise drug toxicity and due to concerns over drug resistance and should depend on the type of malaria in the areas to be visited.[2,12] In Hong Kong, atovaquone-proguanil is recommended to be used as SBET for travellers if it has not been prescribed as chemoprophylaxis. The availability of drugs for SBET in Hong Kong is summarised in Annex 2.

22. Travellers provided with SBET should be given clear and precise written instructions on the recognition of symptoms, when and how to take the treatment, possible side-effects and the possibility of inadequate response to treatment.[2] They should be explained that self-treatment is a first-aid measure and that they should still seek medical advice as soon as possible for complete evaluation and to exclude other potentially serious causes of fever.[2]

Malaria protection in special groups

23. Some population subgroups have host factors which warrant special considerations when prescribing chemoprophylaxis for malaria. Examples of such special groups are young children, pregnant women, breastfeeding mothers, immunocompromised people, people with co-morbidities and people returning to endemic areas after staying in non-endemic areas for a long time. The precautions of using malaria chemoprophylaxis in different special groups are summarised in Annex 4.

(a) *Falciparum* malaria in a young child is a medical emergency and may be rapidly fatal.[2] Parents should be advised not to take infants or young children to areas where there is risk of *falciparum* malaria.[2] If this is unavoidable, parents should carefully protect their children against mosquito bites and give them appropriate chemoprophylaxis.[2] Breastfed as well as bottle-fed infants 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 is safe for infants and young children but its use is very limited because of chloroquine

resistance.[2] Mefloquine may be given to infants of more than 5kg body weight. Atovaquone-proguanil is not recommended for prophylaxis in children who weigh less than 11kg according to the package insert, because of the lack of data. Use of atovaquone-proguanil for prophylaxis for infants and children weighing between 5 kg and less than 11 kg constitutes off-label use. Doxycycline is contraindicated in children below eight years of age.[2] Primaquine is contraindicated unless the child has been tested for G6PD deficiency.[14]

(b) Malaria in a pregnant woman increases the risk of maternal death, miscarriage, stillbirth and low birth weight with associated risk of neonatal death.[2] Pregnant women should be advised to avoid travelling to areas where malaria transmission occurs and to adopt effective measures including mosquito bite prevention and chemoprophylaxis when travel is unavoidable as the risk of malaria to both fetus and mother far outweighs any potential teratogenic effect.[2] Chloroquine is safe in pregnancy and may be prescribed in areas with exclusively chloroquine-sensitive *P. vivax* transmission.[2] Mefloquine is the chemoprophylaxis of choice in pregnancy but there are several areas which show mefloquine resistance.[5,14] If a pregnant woman visits a chloroquine- and mefloquine-resistant area, atovaquone-proguanil should be considered as chemoprophylaxis. The safety of atovaquone-proguanil in pregnancy has not been established but limited evidence suggests that it is not a major teratogen.[20] It may be used if there are no other options in situations where it is considered that the risk of contracting malaria outweighs any risk to the fetus from atovaquone-proguanil.[21] Doxycycline and primaquine are contraindicated during pregnancy.[2,5]

(c) The main concern about prescribing malaria chemoprophylaxis for lactating mothers is the potential harmful effects to their babies. Amongst the various drugs, chloroquine and mefloquine are safe to be given to lactating mothers whereas primaquine is contraindicated in lactating mothers unless the infant has also been tested for G6PD deficiency.[2,14] Doxycycline is contraindicated in breastfeeding.[2] Atovaquone–proguanil is not recommended to be given to lactating mothers due to insufficient data, unless the potential benefit to the woman outweighs the potential risk to the infant.[2,5]

(d) Malaria may be rapidly fatal in asplenic patients as malarial parasitaemia in asplenic individuals may rise rapidly to very high levels.[12] Asplenic patients should avoid travel to malaria endemic areas and, if travel is essential, they should prevent infection by rigorous use of anti-mosquito precautions and strict adherence to appropriate chemoprophylaxis.[12] SBET may be considered in addition to prophylactic measures if the visits involve remote regions where access to care is limited.[5] Given the risk of postsplenectomy bacterial sepsis, use of doxycycline as chemoprophylaxis may be preferred over other options due to its antibacterial activity.[5]

(e) There is significant interaction between human immunodeficiency virus (HIV) and *P. falciparum.*[5] HIV infection impairs immune response to malaria and increases both the incidence and severity of malaria, whereas acute malaria stimulates HIV-1 replication, resulting in increased viral loads that may hasten disease progression and increase transmission risk.[5] Therefore, prevention of malaria through avoidance of mosquito bites and the use of chemoprophylaxis is particularly important.[2] Commonly used integrase inhibitors (raltegravir, dolutegravir and elvitegravir) and nucleoside reverse transcriptase inhibitor (emtricitabine, tenofovir disoproxil fumarate and tenofovir alafenamide) combinations (e.g. Descovy-Tivicay and Truvada-Tivicay) have shown no known interaction with malaria chemoprophylaxis, although the cobicistat booster coformulated with elvitegravir (such as Stribild and Genvoya) may theoretically increase mefloquine levels. Similarly, rilpivirine, emtricitabine and the tenofovir alafenamide/ tenofovir disoproxil fumarate combinations have no interaction with malaria chemoprophylaxis.[22] Among the older drugs, efavirenz lowers the serum levels of both atovaquone and proguanil, but there is no evidence for clinical failure of these agents when used concurrently. A number of older, now less commonly used drugs, especially protease inhibitors, have potential interactions with malaria chemoprophylaxis.[23]

(f) Liver or renal dysfunction may result in significant alteration in levels of malaria chemoprophylaxis.[5] Doxycycline may be contraindicated or require dose adjustment in liver dysfunction.[2,5] Atovaquone-proguanil is contraindicated in severe renal insufficiency.[2,5,14] Dosage of chloroquine may need to be adjusted in renal impairment.[5,12]

(g) From time to time, there are people returning to endemic areas to visit friends and relatives (VFRs) after staying in non-endemic areas, e.g. Hong Kong, for a long period of time. They may incorrectly believe they still have some persistent immunity against malaria, which results in insufficient protective measures and lower rates of malaria chemoprophylaxis use.[2] It is therefore particularly important to emphasise both mosquito avoidance and compliance with chemoprophylaxis to this group of travellers.

Chemoprophylaxis in long-term travellers

24. Long-term travellers refers to those who travel through, or visit malaria endemic areas for periods longer than six months.[2,12] Examples of long-term travellers include VFRs, expatriates and backpackers staying in an endemic area. The major concerns about malaria protection strategies in long-term travellers include safety of antimalarial drugs for long-term use, adequate supply of effective malaria chemoprophylaxis, and poor compliance to the malaria chemoprophylaxis.

25. Few studies have been done on chemoprophylaxis use for more than six months.[2] Retinal toxicity due to chloroquine is of concern when a cumulative dose of 100g of chloroquine is reached.[2] Anyone who has taken 300mg of chloroquine weekly for more than five years and requires ongoing prophylaxis should be screened twice yearly for early retinal changes.[2] Atovaquone–proguanil is registered in European countries for chemoprophylatic use with a restriction on duration of use varying from five weeks to one year but this restriction does not apply in the United Kingdom or the United States.[2] In Hong Kong, according to the package insert of atovaquone–proguanil, its safety and effectiveness had been established in studies of up to 12 weeks for residents (semi-immune subjects) of endemic areas, and the average duration of exposure in clinical studies for non-immune subjects was 27 days.[24] Data indicated no increased risk of serious side effects with long-term use of doxycycline and mefloquine.[2]

26. Long-term travellers are more likely to buy their drugs in the countries where they are staying in. As counterfeit drugs are sold in some malaria endemic areas, they have to ensure that the drugs they purchase are safe, real and effective.[2]

27. Data collected from expatriates and deployed military troops suggested poor adherence to recommended malaria chemoprophylaxis. Only 69% of expatriate households in Nigeria appropriately picked up their chemoprophylaxis from the

pharmacy, and among those that did, 58% were nonadherent, resulting in an overall nonadherence rate of 61%.[5] Similarly, of over 1 000 French soldiers assigned to missions in sub-Saharan Africa, only 61% reported taking their chemoprophylaxis.[5] Poor adherence to malaria chemoprophylaxis in long-term travellers increases the risk of contracting malaria.

28. Guidelines for preventing malaria in long-term travellers should be similar to standard recommendations for short-term travellers. In addition, pre-travel advice regarding malaria precautions should also include a description of malaria symptoms and emphasis on the need for early diagnosis and treatment, a discussion of the need to develop a plan for accessing competent medical care in the event of illness, detailed advice regarding personal protective measures, the use of SBET if applicable and the possibility of counterfeit malaria drugs procured locally.[5]

Conclusion

29. Malaria prevention in travellers to malaria endemic areas should comprise awareness of the risk of malaria, preventing mosquito bites, use of chemoprophylaxis and prompt diagnosis and treatment. Special considerations are warranted in people with special host factors and long-term travellers.

Centre for Health Protection
Department of Health
April 2018

Acknowledgement

This document has been developed by the Working Group on Malaria Prophylaxis (WGMP), chaired by Prof John SIMON and with the following Members: Dr Albert KW AU, Dr Jacky MC CHAN, Dr Raymond LM HO, Dr Thomas ST LAI, Dr David C LUNG, Dr TL QUE and Dr Owen TY TSANG. The Centre for Health Protection would like to thank the Members of SCVBD and WGMP for their valuable inputs.

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Annex 1 Recommendations, dosage regime, precautions, side effects and main contraindications of drugs used for malaria chemoprophylaxis

Drug	**Areas of usage**	**Dosage regime**	**Duration of prophylaxis**	**Use in special groups**			**Side effects**	**Remarks**
				Pregnancy	**Breastfeeding**	**Children**		
Chloroquine	Chloroquine-sensitive areas (Annex 3)	300mg weekly	Start 1 -2 weeks before departure and continue for 4 weeks after return	Safe	Safe	Safe	Bitter taste, gastrointestinal disturbance, headache, insomnia and retinal toxic effects*	**Main contraindication(s):** History of epilepsy and psoriasis
Mefloquine	Avoid in mefloquine-resistant areas (Annex 3)	250mg weekly	Start 2 to 3 weeks before departure (must start at least 1 week before) and continue for 4 weeks after return	Safe	Safe	May be given to infants of more than 5kg body weight	Neuropsychiatric symptoms (e.g. insomnia and nightmares), vestibular symptoms (e.g. dizziness, tinnitus, balance disorder and vertigo) and gastrointestinal symptoms	**Main contraindication(s):** Current or previous history of depression, generalised anxiety disorder, psychosis, schizophrenia, suicide attempt, suicidal thought, self-endangering behaviour or any other psychiatric disorder, epilepsy or convulsions of any origin **Advantage(s):** Chemoprophylaxis of choice in pregnancy

* Chloroquine has retinal toxic effects when a cumulative dose of 100g is reached. Ophthalmologic examination twice yearly after taking weekly 300mg dose for more than five years is recommended.

Annex 1 Recommendations, dosage regime, precautions, side effects and main contraindications of drugs used for malaria chemoprophylaxis (continued)

Drug	**Areas of usage**	**Dosage regime**	**Duration of prophylaxis**	**Use in special groups**			**Side effects**	**Remarks**
				Pregnancy	**Breastfeeding**	**Children**		
Doxycycline	Areas with both chloroquine and mefloquine-resistant (Annex 3)	100mg daily	Start 1 day before departure and continue for 4 weeks after return	Contraindicated	Contraindicated	Contraindicated under 8 years of age	Gastrointestinal upset, oesophagitis, vaginal candidiasis and photosensitivity	**Main contraindication(s):** Liver dysfunction **Advantage(s):** Protection against leptospirosis and rickettsial diseases
Atovaquone-proguanil (or Malarone)	Areas with both chloroquine and mefloquine-resistant (Annex 3)	Atovaquone 250mg and proguanil 100mg per tablet (1 tablet daily)	Start 1 day before departure and continue for 7 days after return	Its safety in pregnancy has not been established but limited evidence suggests that it is not a major teratogen	Not recommended due to insufficient data	Not recommended for prophylaxis in children who weigh less than 11kg because of the lack of data*	Gastrointestinal upset and headache	**Main contraindication(s):** Severe renal insufficiency **Advantage(s):** Good for last-minute travellers

* Use of atovaquone-proguanil for prophylaxis for infants and children weighing between 5 kg and less than 11 kg constitutes off-label use.

Annex 1 Recommendations, dosage regime, precautions, side effects and main contraindications of drugs used for malaria chemoprophylaxis (continued)

Drug	**Areas of usage**	**Dosage regime**	**Duration of prophylaxis**	**Use in special groups**			**Side effects**	**Remarks**
				Pregnancy	**Breastfeeding**	**Children**		
Primaquine	Areas with primarily *P. vivax*	30mg daily for both primary and terminal prophylaxis	Start 1 to 2 days before departure and continue 1 week after returning from a malaria endemic area as primary prophylaxis; for 14 days after departure as terminal prophylaxis	Contraindicated	Contraindicated unless the infant has been tested for G6PD deficiency	Contraindicated unless the child has been tested for G6PD deficiency	Nausea and abdominal pain	**Main contraindication(s)** G6PD deficiency **Advantage(s):** Can be used as a terminal prophylaxis, good for last-minute travellers

Annex 2 Availability of drugs for malaria chemoprophylaxis and SBET in Hong Kong

Generic name of drug	**Whether it is registered in Hong Kong as of February 2018**	**Preparation(s) available in Hong Kong**	**Availability in Hospital Authority Drug Formulary as of February 2018**	**Availability in Travel Health Centres of the Department of Health as of February 2018[NB1]**
Chloroquine[NB2]	Yes	200mg tablet	No	Yes
Mefloquine	Yes	250mg tablet	No	Yes
Doxycycline	Yes	50mg tablet	Yes	No[NB3]
		50mg capsule		No
		100mg tablet		Yes
		100mg capsule		Yes
Atovaquone-proguanil	Yes	Malarone tablet	Yes	Yes
		Malarone paediatric tablet		No[NB4]
Primaquine	No	-	No	No
Artemether-lumefantrine	No	-	No	No
Dihydroartemisinin-piperaquine	No	-	No	No

NB1 For latest drug availability, enquiries should be made with the Travel Health Centres.

NB2 Chloroquine can be used with proguanil. Proguanil is not registered in Hong Kong and is rarely used as a single agent.

NB3 If 50mg doxycycline is needed, 100mg tablets can be split into halves.

NB4 For children, adult tablets can be split according to body weight.

Annex 3 Choice of malaria chemoprophylaxis based on the predominant drug resistance strains or species travellers would be exposed to

Strains/ species travellers would be exposed to	**Examples of countries and areas**	**Drug(s) of choice**
Chloroquine-sensitive	Haiti, the Dominican Republic, Central America north of the Panama Canal, parts of Mexico, parts of South America and parts of Mainland China	Chloroquine
Chloroquine-resistant	Most of sub-Saharan Africa, South America, Oceania and Asia	Mefloquine, doxycycline or atovaquone-proguanil
Both chloroquine and mefloquine-resistant	Various countries in Asia, Africa and the Amazon basin^	Doxycycline or atovaquone-proguanil
Primarily *P. vivax*	Bolivia, Cyprus, Guatemala, Honduras, Mexico, North Korea, Panama and South Korea	Primaquine

^It was a significant problem only in the rural, wooded regions where Thailand borders with Myanmar, Cambodia and Laos, as well as in southern Vietnam.

Annex 4 Precautions of malaria chemoprophylaxis in different special groups

Special groups	**Chloroquine**	**Mefloquine**	**Doxycycline**	**Atovaquone-proguanil**	**Primaquine**
Children	Safe	May be given to infants of more than 5kg body weight	Contraindicated under 8 years of age	Not recommended for prophylaxis in children who weigh less than 11kg*	Contraindicated unless the child has been tested for G6PD deficiency
Pregnant women	Safe	Safe	Contraindicated	Its safety in pregnancy has not been established but limited evidence suggests that it is not a major teratogen	Contraindicated
Lactating mothers	Safe	Safe	Contraindicated	Not recommended due to insufficient data	Contraindicated unless the infant has been tested for G6PD deficiency
HIV-positive patients (on commonly used integrase inhibitors and nucleoside reverse transcriptase inhibitor combinations)	Safe	Safe	Safe	Safe	Safe
Patients with co-morbidities	Dosage may need to be adjusted in renal impairment	Caution for use in liver impairment	May be contraindicated or require dose adjustment in liver dysfunction	Contraindicated in severe renal insufficiency	In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range

* Use of atovaquone-proguanil for prophylaxis for infants and children weighing between 5 kg and less than 11 kg constitutes off-label use.