

Guidelines for malaria prevention in travellers from the UK

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Executive summary

These practical guidelines from the UK Health Security Agency (UKHSA) Advisory Committee on Malaria Prevention (ACMP) are updated and reissued annually. They are intended for use by healthcare workers who advise UK-based travellers to malaria-endemic areas but may also be of use to prospective travellers who wish to read about the options themselves.

We recommend health professionals stick to using one resource for country-specific malaria recommendations to optimise consistency of advice. Whilst we recognise that other sources of advice are available, healthcare professionals working in England, Wales or Northern Ireland are advised to use the ACMP guidelines as their preferred source of guidance for malaria prevention.

The ACMP prophylaxis guidelines are intended for UK-based travellers and may not be appropriate for use by those residing in endemic areas.

Malaria prevention advice involves a combination of preventive measures (the ABCD of malaria prevention) including:

- Awareness of risk
- Bite prevention
- Chemoprophylaxis
- Diagnose promptly and treat without delay

Recommendations for antimalarials should be appropriate for the destination and tailored to the individual, taking into account possible risks and benefits to the traveller. As part of an individual stringent risk assessment it is essential that a full clinical history is obtained, detailing current medication, significant health problems and any known drug allergies.

While the focus of these guidelines is on malaria prevention, it should be emphasised that malaria prevention is only one aspect of pre-travel advice. A comprehensive risk assessment-based package of travel health advice should be provided to the traveller. Further resources for health professionals are listed under <u>Information resources</u>.

Main changes in this update of the guidelines

The impact of COVID-19

An epidemiological analysis of global malaria with special reference to the effect of COVID-19 on malaria control in Africa (1) has reached disturbing conclusions. Globally, malaria cases and deaths increased in 2020, with the most serious situation observed in Africa, especially West Africa. Contributory factors include reduced or delayed diagnosis and clinical care, shortage of

medical resources, disruption to control measures, and disruption to the availability of malaria medication.

This resurgence of malaria also has major implications for travellers, given that for malaria imported into the UK in 2021, for which there was a recorded travel history, 94% of patients acquired their malaria in Africa (2).

Clearly, as international travel post COVID-19 recovers further, the need to ensure protection against malaria for all those potentially exposed and maintain awareness of malaria as a posible diagnosis in returned travellers is greater than ever.

ACMP will keep its advice for travellers to individual countries under review as the situation evolves. It may be that due to increased transmission, the risk of malaria acquisition increases for travellers to some areas, with the possibility of re-introduction of malaria to areas recently considered to have interrupted transmission. When this occurs there will be notification on the following page <u>Malaria: news and updates</u> and on <u>NaTHNaC</u>.

Proguanil has been discontinued in the UK

Both Paludrine (proguanil hydrochloride) and Paludrine/Avloclor (proguanil hydrochloride, chloroquine phosphate) Anti-Malarial Travel Pack have been discontinued in the UK. Once current stocks are exhausted, no further supplies will be available. This means that proguanil will no longer be available in the UK and will impact on the malaria recommendations for a small number of countries where the combination of chloroquine and proguanil was recommended for malaria prevention.

Supplies of Avloclor (chloroquine phosphate) and atovaquone plus proguanil combination preparation are not affected.

If chloroquine plus proguanil was recommended previously, an alternative malaria chemoprophylaxis regimen (such as atovaquone plus proguanil combination preparation or doxycycline or mefloquine), may be selected.

These guidelines are available at <u>Malaria: guidance, data and analysis</u>. This page should be checked regularly for subsequent updates and practitioners should ensure that they always use the latest version as recommendations may change.

Authorship

This guidance was written on behalf of the UKHSA ACMP by Professor Peter Chiodini, Dr Dipti Patel, and Professor Larry Goodyer.

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Abbreviations

Abbreviation	Meaning		
AIDS	acquired immune deficiency syndrome		
ACMP	Advisory Committee on Malaria Prevention for UK travellers		
BIA	British Infection Association		
BNF	British National Formulary		
CDC	Centers for Disease Control and Prevention		
DEET	N,N diethyl-m-toluamide (an insect repellent)		
eGFR	estimated glomerular filtration rate		
EDTA	ethylene diamine tetraacetic acid		
FAQ	frequently asked question		
GP	general practitioner		
G6PD	Glucose 6-phosphate dehydrogenase (a metabolic enzyme)		
HIV	human immunodeficiency virus		
HTD	lospital for Tropical Diseases		
INR	nternational normalized ratio		
IPT	ntermittent preventive therapy		
LSHTM	London School of Hygiene and Tropical Medicine		
LSTM	Liverpool School of Tropical Medicine		
NaTHNaC	National Travel Health Network and Centre		
NNRTI	non-nucleoside reverse transcriptase inhibitor		
MHRA	Medicines and Healthcare products Regulatory Agency		
MRL	Malaria Reference Laboratory		
PI	protease inhibitor		
PCR	polymerase chain reaction		
POM	prescription only medicine		
RSTM&H	Royal Society of Tropical Medicine and Hygiene		
SP	sulfadoxine / pyrimethamine		
SPF	sun protection factor		
SmPC	summary of product characteristics or 'data sheet'		
THS	Travel Health Section		
VFR	visiting friends and relatives		
WHO	World Health Organization		

General issues

The ACMP prophylaxis guidelines are intended for UK-based visitors to malaria-endemic areas and may not be appropriate for use by those residing in endemic areas.

We recommend health professionals stick to using one resource for country specific malaria recommendations to optimise consistency of advice. Whilst we recognise that other sources of advice are available, healthcare professionals working in England, Wales or Northern Ireland are advised to use the ACMP guidelines as their preferred source of guidance for malaria prevention. They are also available on the NaTHNaC website. Separate guidance is available in Scotland for health professionals, produced by the Scottish Malaria Advisory Group – see the NHS Travax website.

Whilst these guidelines deal with malaria, malaria prevention is only one aspect of pre-travel advice. An overall risk assessment-based package of travel health advice should be provided to the traveller. Guidance on general travel risk assessment can be obtained from NaTHNaC, and from TRAVAX for those working in Scotland (see <u>Information resources</u>).

For doctors and nurses providing travel services in England who are regulated by the Care Quality Commission (CQC), the CQC website states that GP practices that provide travel health services can also offer advice, including preventing malaria.

In these guidelines, which have been specifically developed for travellers from the UK, there are a small number of instances where the advice given differs from that in guidelines from other countries or the World Health Organization (WHO). This is because travellers from the UK do not usually visit all possible localities of malaria-endemic countries and may not visit the same localities as travellers from other countries. Many travellers from the UK who enter malaria-endemic countries are visiting friends and relatives in localities from which people tend to migrate to the UK. They do not therefore suffer the same patterns of malaria exposure as permanent residents or tourists or those visiting for other reasons.

How to give the advice

Emphasise to the traveller the ABCD of malaria prevention:

- Awareness of risk
- Bite prevention
- Chemoprophylaxis
- Diagnose promptly and treat without delay

Emphasise that while no regimen is 100% effective, the combination of preventive measures advised will give significant protection against the potentially severe consequences of malaria acquisition.

Make use of visual aids, especially malaria distribution maps, and show examples of the preventive measures advised, such as aids to bite prevention.

Based on individual risk assessment, discuss the choices of chemoprophylaxis regimens and their individual advantages and disadvantages, including cost.

Provide the traveller with written information on malaria and its prevention. UKHSA has information leaflets on mosquito bite avoidance and travelling abroad to visit friends and relatives in English, Arabic, Bengali, French, Gujarati, Hausa, Igbo, Punjabi, Spanish, Swahili, Yoruba, Urdu, Xhosa, and in BSL, large print, braille, and Easy Read (see Information resources).

These may be downloaded, photocopied and distributed free of charge. English versions are also available to order.

Medical history of the traveller

As part of an individual stringent risk assessment it is essential that a full clinical history is obtained, detailing current medication including those drugs prescribed by hospitals which may not appear on GPs' drug lists for repeat prescriptions, significant health problems and any known drug allergies.

Safe and effective malaria prevention requires a sound knowledge of the medical history of the traveller. When their patients seek pre-travel advice in primary care, this information will be available from their own practice records but in the case of specialist travel clinics, malaria prevention advice may be sought at the first attendance. The General Medical Council (3) states:

"If you are not the patient's general practitioner and you accept a patient for treatment without a referral from the patient's practitioner, then you must: (a) explain to the patient the importance and benefits of keeping their general practitioner informed and (b) inform the patient's general practitioner unless the patient objects."

ACMP suggests that in all scenarios where advice is given, a written record of the malaria prevention measures advised is given to the traveller so that they may pass it on to their GP. A template for risk assessment and summary of advice given is provided at Appendix 2, which can be used for gathering the information required for risk assessment when advising on malaria prevention. It may be adapted for the particular circumstances of individual clinics.

Awareness of risk

Malaria facts

Malaria is a serious febrile illness due to infection of red blood cells with a parasite called Plasmodium. It is transmitted by mosquitoes.

Five species of *Plasmodium* (*P*) regularly infect humans (see Table 1 below).

Mixed infections with more than one species of malaria parasite are not commonly reported (2 in the UK in 2021).

In recent years, the incidence of *P. vivax* in UK travellers has dropped, but in regions where it is a problem, the risk of acquiring vivax malaria is year round (4).

Table 1. Plasmodium species that infect humans

Species	Comment	Number of cases reported in the UK in 2021 out of 1,012 ¹
Plasmodium falciparum	The most dangerous, responsible for the vast majority of malaria deaths worldwide	868 (85.8%)
Plasmodium vivax	A relapsing malaria. See Life cycle section, below	50 (4.9%)
Plasmodium ovale	A relapsing malaria. See Life cycle section, below	66 (6.5%)
Plasmodium malariae	May present with late recrudescence after many years	26 (2.6%)
Plasmodium knowlesi	Very rarely imported at present, but capable of producing severe illness	0 (0.0%)

Life cycle

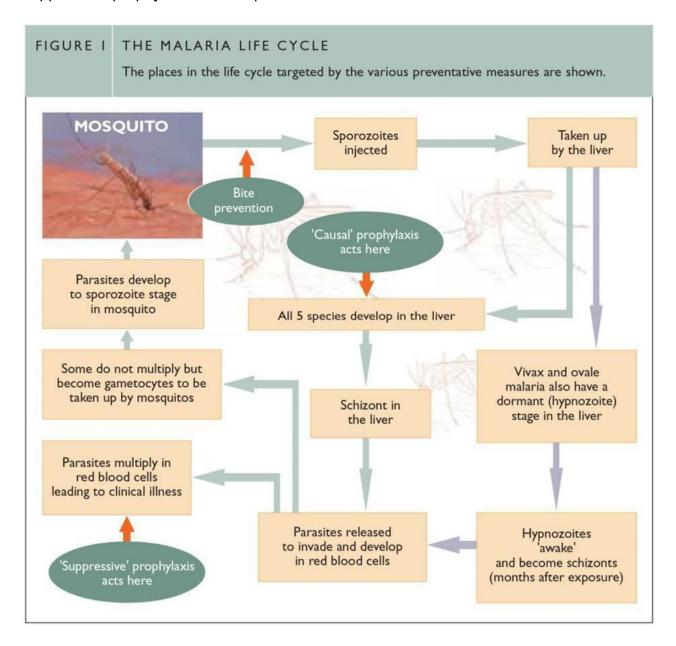
An infected mosquito inoculates 10 to 15 sporozoites when it bites. Each sporozoite introduced into a human that successfully enters a liver cell develops in 5 to 7 days (*P. falciparum*) into a schizont containing approximately 30,000 offspring (merozoites) which are released into the bloodstream when the schizont ruptures. Each merozoite has the potential to infect a red blood

¹ The annual UK malaria figures for the preceding January to December are released annually and can be found at <u>Malaria: guidance, data and analysis.</u>

cell. Once inside the red cell, the malaria parasite grows and divides over 24 hours (*P. knowlesi*), 48 hours (*P. falciparum*, *vivax* or *ovale*), or 72 hours (*P. malariae*) to form between 8 and 32 parasites, whereupon the red cell bursts to release them to infect new red cells. These cycles in the red cells continue, increasing the number of parasites in the infected person and leading to clinical illness. Some parasites in the red cells do not divide but form sexual stages (gametocytes) which mate if taken up by a biting female mosquito and thus complete the malaria life cycle. Figure 1 shows the points in the life cycle at which antimalarial preventive measures are targeted.

Figure 1. The malaria life cycle

This figure shows the life cycle described above in pictorial form, to indicate the points at which malaria preventative measures act. Bite prevention acts at the very start of the life cycle to prevent bites from infected mosquitoes; causal prophylaxis acts on the parasite in the liver suppressive prophylaxis acts on parasites in the red blood cells.



The malarial illness

Malaria can neither be confirmed nor excluded by clinical features alone. The common symptoms and signs are shown below. There may be no physical signs apart from fever, but it must be noted that even the absence of fever itself does not exclude the diagnosis in an ill patient. There is a risk of misdiagnosing malaria as influenza or other infectious illness: viral hepatitis (if jaundice is present), gastroenteritis (if diarrhoea is evident)or lower respiratory tract infection (cough can be a non-specific symptom).

Clinical symptoms and signs of malaria

(From the ACMP malaria treatment guidelines.)

Non-specific symptoms of malaria:

- fever, sweats or chills
- malaise (vague discomfort)
- myalgia (muscle pain, tenderness) headache
- diarrhoea
- cough

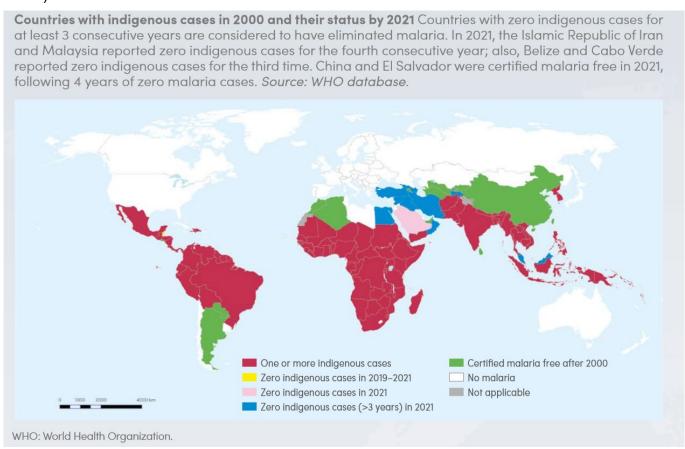
Major features of severe or complicated falciparum malaria in adults:

- impaired consciousness or seizures
- renal impairment (oliguria less than 0.4millilitre per kilogram (ml/kg) bodyweight per hour or creatinine more than 265 micromole per litre (µmol/l))
- acidosis (pH less than 7.3)
- hypoglycaemia (less than 2.2mmol/l)
- pulmonary oedema or acute respiratory distress syndrome (ARDS) haemoglobin less than or equal to 8g/dL
- spontaneous bleeding or disseminated intravascular coagulation shock (algid malaria)
- haemoglobinuria (without G6PD deficiency)

Major features of severe or complicated malaria in children:

- impaired consciousness or seizures, respiratory distress or acidosis (pH less than 7.3) hypoglycaemia
- severe anaemia
- prostration (inability to sit or stand) parasitaemia more than 2% red blood cells parasitised

Figure 2. Countries with indigenous cases in 2000 and their status by 2021 (Reproduced from the 2022 World Health Organization World Malaria Report, courtesy of the WHO)



Where malaria is found

Figure 2 shows the countries with indigenous cases of malaria as at 2021 courtesy of WHO (5). It is for illustration only and should not be used to advise individual travellers on chemoprophylaxis. Changes in malaria prevalence as a result of interrupted control efforts due to the COVID-19 pandemic may result in indigenous cases occurring in areas previously thought to be malaria free. Choice of preventive measures should be based on the information stated in Table 6, supported by the text of these guidelines.

In-country maps of prophylactic advice linked to malaria distribution are available for selected countries in these guidelines for use when advising individual travellers and can be printed for them. The likelihood of malaria transmission may vary considerably within one country.

Practitioners should be aware of the recognition of *P. knowlesi* as the fifth malaria parasite of humans. It is a parasite of macaques and a zoonosis in humans in the Asia-Pacific region. As its asexual cycle takes only 24 hours, it is possible for its parasitaemia to rise more rapidly than with the other malaria species. A further danger is its close morphological resemblance to *P. malariae* which is a much less severe infection.

Therefore, *P. knowlesi* should be urgently considered in any patient with malaria from the Asia-Pacific region with what appears to be *P. malariae*. Whilst *P. knowlesi* is a zoonosis and thus not amenable to control in the same way as those parasites which infect humans alone, prevention of human infection still relies on bite prevention, awareness of risk and chemoprophylaxis. *P. knowlesi* is sensitive to chloroquine.

Factors affecting risk of exposure to malaria

Exposure of individual travellers to malaria is influenced by the number of infectious bites received. Factors affecting the number of infectious bites received are given below.

Temperature, altitude and season

The optimum conditions for malaria transmission are high humidity and an ambient temperature in the range 20 to 30° C ($\underline{6}$).

Malaria transmission does not usually occur in regions with temperatures below the 16°C isotherm (line on a weather map joining all the places that have the same average temperature over a given time).

Parasite maturation in the mosquito usually cannot take place at altitudes greater than 2,000 metres. However, it has been reported at altitudes up to 2,500 metres in some countries.

Seasonal rainfall increases mosquito breeding and in some areas malaria is highly seasonal.

Climate change may influence the distribution of mosquitoes and malaria parasites and thus alter the areas where malaria is a risk, so the advice in the country tables is regularly reviewed.

Rural versus urban location

Malaria incidence is generally higher in rural than in urban areas, especially in Africa where the intensity of transmission is on average about 8 times higher in villages than towns $(\underline{7})$ but as Africa becomes increasingly urbanised, there is also a risk in certain cities and urban areas $(\underline{8})$.

Type of accommodation

An insecticide impregnated bed net should be used unless the accommodation is fitted with functioning air-conditioning which is switched on, and windows and doors which are sufficiently well sealed to prevent mosquito entry.

Backpackers and others staying in cheap accommodation have a higher risk of being bitten compared to tourists staying in air-conditioned hotels.

The traveller should embark on their journey already equipped with mosquito protection measures appropriate to their particular circumstances and carry their insect repellent in their hand luggage.

Patterns of activity

Anopheles mosquitoes can be active during the day, at dawn and dusk, and throughout the night depending on species and geographical location. Dawn and dusk are higher risk generally but it must be noted that the risk can occur at other times of the day; daytime biting in forested areas or overcast days for example. Both indoor and outdoor biting can occur, including inside vehicles. Biting at an airport on arrival whilst disembarking or awaiting luggage and onward ground transport should also be considered a risk area.

Length of stay

The longer the stay, the higher the risk of contracting malaria.

Distribution of drug-resistant malaria

Chloroquine-resistant falciparum malaria is now widespread (effectively universal). *P. falciparum* has also developed resistance to a variety of other agents in certain areas. Further comment on the extent and severity of drug resistance is given in the country table in Chemoprophylaxis.

Chloroquine remains effective against *P. ovale* and *P. malariae* (9).

Chloroquine-resistant *P. vivax* is found in the Indonesian archipelago, the Malay Peninsula, including Myanmar, and eastward to Southern Vietnam and may have spread further (10).

P. vivax with reduced susceptibility to primaquine is found in South-East Asia and Oceania and higher doses of primaquine are required to achieve radical cure of this parasite from those areas. A higher dose may also be required for *P. vivax* from India, Pakistan, Afghanistan and South America (10).

Bite prevention

Note: Effective bite prevention should be the first line of defence against malarial infection.

For some destinations, ACMP advises awareness of risk and bite prevention for malaria prevention and does not recommend chemoprophylaxis. Practitioners are strongly advised that for those destinations, and also for locations where chemoprophylaxis is also recommended, the benefits from using bite prevention measures, not only against malaria, but also in protecting against infection with other vector-borne diseases are emphasised to travellers.

When female Anopheles mosquitoes bite

Biting time varies between species, so travellers should assume they are at risk of being bitten mainly, but not only, from dusk to dawn inclusive. The biting of several major malaria vectors in Africa peaks at and just after midnight so protection in bed is especially important. However, in many parts of South America and South-East Asia, the greatest risk from being bitten by malaria vectors is in the evening, before the population retires indoors. Furthermore, as other species of mosquito – for example, those which transmit yellow fever, dengue fever and other arboviral infections, bite during the daytime – it is important to maintain bite precautions during daylight hours, both indoors and outdoors. See also <u>Patterns of activity</u>, above.

Measures to prevent mosquito bites

Repellents

As malaria prevention in travellers becomes reliant on bite avoidance and awareness of risk in more and more destinations, much greater attention to the correct use of insect repellents is required.

Debboun and Goodyer (11) have highlighted the fact that users decide whether or not to use an arthropod repellent for personal protection, what kind to use, and how much to apply. Therefore, the travel health advisor should emphasize the importance of adhering to the ACMP recommendations for their use, to achieve optimal protection, especially as repellents have an excellent safety profile.

In some circumstances, ACMP advice may differ from that in repellent manufacturers' product information. When this occurs, the recommendations in these guidelines (which are based on current expert advice from the ACMP) should be followed.

ACMP recommends a 50% DEET-based insect repellent as a first choice. If DEET is not tolerated (or is not available), an alternative preparation (see below) should be used.

Consult the instructions for use for individual products. Reapplication should be made when necessary, to ensure that mosquitoes are not biting, bearing in mind safe limits for the product concerned.

The 4 active ingredients described below are incorporated into repellent formulations available on the UK market (normally one active ingredient per product). If a product does not contain one of these active ingredients, it should not be used. They have excellent mosquito repellent properties, though DEET is supported by the strongest evidence base and its extensive use worldwide over the last 50 years.

In the field many factors will affect the perceived longevity of a repellent before reapplication is required including; the mosquito biting pressure (that is, the number of mosquitoes present), sweat and run off of the repellent, swimming, species of mosquito and 'attractants' produced by the individual. One of the most important factors, and one that can be controlled by the user, is the amount of repellent applied to exposed skin.. However, it has been demonstrated (13) that travellers will tend to apply almost half of the amount at which a product has been tested according to current protocols. Therefore, the stated longevity on manufacturers' packaging may not be achieved in the field and more frequent application will be required.

The general recommendations of the ACMP concerning repellent use are:

- 1. Use a 50% DEET-based repellent and if not tolerated or preferred by the traveller, the highest strength available of either an icaridin or eucalyptus citriodora oil, hydrated, cyclized or 3-ethlyaminopropionate-containing repellent. Long-acting formulations may increase longevity of the active ingredient but further evidence is required to demonstrate their advantages.
- 2. As a guide, users should reapply repellents when the mosquitoes begin to land, to ensure that they do not bite.
- 3. Some volatile oils from plant products, including citronella, do have repellent properties but they are usually short lasting. There is insufficient data to support the use of blends of such oils as reliable repellents.

DEET

DEET (N,N-diethyl-m-toluamide) has been in use as an insect repellent for more than 50 years and is reportedly used worldwide by approximately 200 million people each year (14). It is available in a variety of concentrations and in various preparations including sprays and a slow release preparation. A variety of studies has concluded that there is a low risk of adverse effects when DEET is applied according to product directions (14).

ACMP recommends using a 50% DEET-based insect repellent if available. There is no further increase in duration of protection beyond a concentration of 50% DEET (14).

Sweat-off time varies with activity (for example, sedentary activity versus vigorous exercise). The interval between applications depends on this as well as the DEET formulation and concentration used.

DEET and sunscreen

Several studies have evaluated the impact of co-application of sunscreen and DEET. DEET (33%) has been shown to decrease the protection from SPF 15 sunscreen 15 but there is no evidence that sunscreen reduces the efficacy of DEET when used at concentrations above 33% (15, 16). Frequent (every 2 hours) reapplication of sunscreen over DEET applied at below 20% (17%), was found to reduce the mean repellency rate and also mean protection time (by about one hour) compared with DEET alone (16).

Stanczyk and colleagues (<u>17</u>) recommended advising travellers to: apply repellent first and be aware that repellent may wear off more quickly if reapplying only sunscreen on top **or** use a combined repellent and sunscreen product

Note: In contrast to reference 17, ACMP's view is that as repellent activity will reduce more quickly than that of a sunscreen if reapplying only sunscreen on top, repellent will therefore usually need to be reapplied on top of a sunscreen. When both sunscreen and DEET are required, DEET should be applied after the sunscreen. Thirty to 50 SPF sunscreen should be applied to compensate for DEET-induced reduction in SPF. Sunscreen is not required from dusk to dawn.

DEET and infants

DEET is not recommended for infants below the age of 2 months. If a particular DEET manufacturer's product information recommends a higher age cut off for use in children, the ACMP guidance should be followed.

DEET and pregnancy

Use of 20% DEET in the second and third trimesters of pregnancy was not associated with adverse effects on infants from those pregnancies followed for up to 12 months after birth (18). Given the seriousness of malaria in pregnancy, ACMP recommends the use of DEET at a concentration of up to 50% as part of the malaria prevention regimen for pregnant women, including those in the first trimester. DEET may be used at a concentration of up to 50% in breast feeding and for infants and children aged over 2 months.

ACMP advice on use of DEET for protection from mosquito bites is that:

- DEET is suitable for all individuals over the age of 2 months (unless allergic), and furthermore, the United States Environmental Protection Agency states that <u>DEET</u> is <u>approved for use on children with no age restriction</u> (accessed 20 August 2023)
- there is no current evidence that any group (including pregnant women and small children) is at increased risk from using 50% DEET; the US Environmental Protection Agency (EPA) examined data on seizures potentially related to DEET exposure and concluded that observed incidence of recognized seizures is about one per 100 million users (19)
- DEET applications can damage some plastic watch straps, watch covers and plastic jewellery; these items should not be allowed to come into contact with DEET

- the user should ensure that repellents are not ingested or inhaled and do not come into contact with their eyes or mouth
- repellents should be used only on exposed areas of skin, though some products can be sprayed onto clothing. However, DEET may melt synthetic fibres

Eucalyptus citriodora oil, hydrated, cyclized (PMD)

Eucalyptus citriodora oil, hydrated, cyclized was previously known as p-menthane 3,8 diol or PMD – see the <u>European Chemicals Agency June 2016 minutes</u> (accessed 20 August 2023). Eucalyptus citriodora oil, hydrated, cyclized is a repellent that occurs naturally in the lemon eucalyptus plant and has structural similarities with the chemical menthol. This natural product can now be obtained synthetically.

Plant-based repellents have become more popular in recent years (11). For those travellers preferring plant-based repellents, Eucalyptus citriodora oil, hydrated, cyclized is the only active ingredient recommended by ACMP.

Eucalyptus citriodora oil, hydrated, cyclized is also an effective repellent (20, 21, 22). 15% DEET slightly outperformed 15% Eucalyptus citriodora oil, hydrated, cyclized as a repellent against *Anopheles stephensi* under laboratory conditions (23) but Eucalyptus citriodora oil, hydrated, cyclized remains a very useful repellent. If Eucalyptus citriodora oil, hydrated, cyclized is chosen by the traveller, more frequent application would be required than if DEET were used.

Eucalyptus citriodora oil, hydrated, cyclized is well tolerated with low toxicity when used according to the manufacturers' instructions. Accidental application to the eye can result in corneal damage, so the EPA concluded that product labels should clearly emphasize the hazard and first aid treatment for accidental eye exposure (24).

Icaridin (Picaridin)

Icaridin (KBR3023) (1piperidinecarboxylic acid, 2-(2hydroxyethyl)-,1-methyl-propylester) has repellent properties comparable to those of DEET (25, 26) with a comparable duration of protection (27, 28, 29) when both are used at 20%. Icaridin is available in various concentrations between 2% and 20% (30, 31). If a traveller elects to use icaridin for mosquito bite prevention, ACMP advises use of a 20% preparation.

Icaridin is well tolerated. Adverse events are uncommon and mild, with mostly cutaneous side effects (32) There have been some studies reporting fewer skin side effects when using icaridin versus DEET, albeit using lower concentrations of icaridin (33).

3-ethlyaminopropionate

In some studies 3-ethlyaminopropionate (IR3535) has shown a shorter duration of protection against mosquitoes than DEET when used at the same concentration (28, 34, 35) but is still a safe and effective repellent which has been in use for more than 25 years.

If IR3535 is chosen by the traveller, more frequent application may be required than if DEET were used.

Accidental application of IR3535 to the eye can result in moderate eye irritation (29) so appropriate warnings about avoiding accidental eye exposure and the need for first aid measures are required.

Oil of citronella

While oil of citronella-based products do have repellent properties, they provide short-lived protection (34) and are not recommended by ACMP. Citronella has been withdrawn in Europe.

Insecticides

Permethrin and other synthetic pyrethroids have a rapid knock-down effect on mosquitoes and are used to kill resting mosquitoes in a room. Permethrin can also be used to treat clothing.

Nets

Using multiple methods to prevent arthropod bites concurrently is more effective than using a single method, which underlies the use of insecticide-treated bed nets, which have become an important and cost-effective method of bite prevention globally (36).

All travellers to malaria-endemic areas should sleep under a mosquito net unless they are in a well screened room with mosquito netting on windows and doors into which mosquitoes cannot enter, or a room with switched on functioning air conditioning into which mosquitoes cannot enter. If the room door has been opened, the room should then be checked for mosquitoes.

Insecticide-treated mosquito nets should be used and kept in good condition. Protective efficacy against malaria for travellers has been estimated at 50% (37).

Mosquito bed nets must be free of tears, tucked in under the mattress and taut, not drooping. Insecticide (pyrethroid)-impregnated bed nets improve protection because they help to prevent (a) biting through the net on parts of the body touching the net, (b) mosquitoes surviving long enough near a net to find any tears in the net which may exist. (37).

Most of the nets now available are long-lasting impregnated nets (LLINs). In these products the pyrethroid is incorporated into the material of the net itself or bound to it with a resin (38). They have an expected useful life of at least 3 years. Impregnated nets other than LLINs will need to be re-impregnated every 6 to 12 months (depending on how frequently the net is washed) to remain effective (39). Follow the instructions for the product concerned.

Clothing

Within the limits of practicality, cover up with loosely fitting clothing with long sleeves, long trousers and socks if out of doors, to minimise accessibility to skin for biting mosquitoes. There is no evidence that the colour of clothing is relevant to mosquitoes.

Clothing may be sprayed or impregnated with an insecticide, for example, permethrin (39) or purchased pre-treated to reduce biting through the clothing. This can provide a high level of bite prevention (40) and is recommended by ACMP.

As an alternative to insecticides, WHO states that any of the repellents considered safe for skin application may be used to treat clothing (36) but be aware that DEET may melt synthetic fibres.

Cotton clothing (for example, socks) can be sprayed with DEET. DEET is useful as a clothing repellent but its duration on clothing is shortened due to its volatility (41). DEET preparations for use only on clothing are commercially available, but may ruin synthetic fabrics.

A repellent should still be applied to exposed skin even if the clothing has been treated.

Room protection

Room protection represents an important component of malaria prevention, but should never be relied upon on its own.

Air conditioning can reduce the likelihood of mosquito bites if it achieves substantial reduction in night time temperature and significantly increases air flow. Ceiling fans can reduce mosquito nuisance.

Doors, windows and other possible mosquito entry routes to sleeping accommodation should be screened with fine mesh netting which must be close-fitting and free from tears.

The room should be sprayed before dusk with a knockdown insecticide (usually a pyrethroid) to kill any mosquitoes which may have entered the accommodation during the day.

In addition, during the night, where electricity is available, use a plug-in proprietary heated liquid reservoir device containing insecticide or a plug-in electrically heated device to vapourise a 'mat' (tablet) containing a synthetic pyrethroid in the room.

Burning of a mosquito coil containing insecticide must not be undertaken indoors, but can be deployed outside to repel and kill mosquitoes (42).

Myths

Herbal remedies

The ACMP strongly advises against relying on any herbal remedies for the prevention of malaria. Herbal remedies have not been tested for their ability to prevent or treat malaria.

Homoeopathy

The ACMP strongly advises against relying on any homoeopathic remedies for the prevention of malaria. There is no scientific proof that homoeopathic remedies are effective in either preventing or treating malaria. In addition, the Faculty of Homoeopathy does not promote the use of homoeopathic remedies for malaria prevention.

Buzzers

Electronic buzzers (emitting high frequency sound waves) are completely ineffective as mosquito repellents. Companies selling them have been prosecuted and fined under the UK Trades Descriptions Act and ACMP advice is that they should not be used. The use of apps available on mobile phones to prevent mosquitoes biting is also strongly discouraged by ACMP. Heavy metal music is also ineffective as a mosquito repellent.

Vitamin B1

There is no evidence that vitamin B1 taken orally repels mosquitoes (41, 42).

Vitamin B12

There is no evidence that vitamin B12 taken orally has a repellent effect on mosquitoes.

Other vitamins and brewers yeast tablets

These are also ineffective as mosquito repellents.

Garlic

There is no evidence that garlic taken orally repels mosquitoes (43).

Savoury yeast extract spread

It is sometimes stated that Marmite® taken orally repels mosquitoes either by giving off a cutaneous odour repellent to mosquitoes or via its vitamin B1 content. There is no evidence that either assertion is true.

Tea tree oil

There is no evidence that tea tree oil is an effective mosquito repellent.

Bath oils and emollients

There is no evidence that proprietary bath oils provide effective protection against mosquito bites.

Alcohol

Alcoholic drinks do not protect against mosquito bites. Indeed, beer consumption is reported to increase human attractiveness to malaria mosquitoes (44).

Gin and tonic has no mosquito-repellent properties and the amount of quinine in tonic water has no effect on malaria parasites.

Chemoprophylaxis

Recommendations for antimalarials should be appropriate for the destination and tailored to the individual, taking into account possible risks and benefits to the traveller. As part of an individual stringent risk assessment it is essential that a full clinical history is obtained, detailing current medication, significant health problems and any known drug allergies. For a suggested risk assessment template see Appendix 2.

Given the possibility of antimalarials purchased in the tropics being fake or sub-standard (45), travellers should obtain the medication required for their chemoprophylaxis from a reputable source in the UK before they travel. ACMP advises those purchasing antimalarial drugs over the internet to ensure that they are dealing with a bona fide supplier or website.

Principles

Causal prophylaxis

Causal prophylaxis is directed against the liver stage of the malaria parasite, which takes approximately 7 days to develop (see life cycle in <u>Figure 1</u>). Successful drug activity at this stage prevents the parasite from progressing to infect red blood cells.

Causal prophylactics need to be continued for approximately 7 days after infection ($\underline{46}$), so ACMP recommends that they are continued for 7 days after leaving a malarious area (see $\underline{\text{Table 2}}$).

It is important not to confuse liver-stage schizonts with hypnozoites. All 5 species of human malaria have liver-stage schizonts, but only *P. vivax* and *P. ovale* have the hypnozoite stage, against which causal prophylaxis is **not** effective.

Suppressive prophylaxis

Suppressive prophylaxis is directed against the red blood cell stages of the malaria parasite. Therefore, to prevent infection, suppressive prophylactic drugs should be continued for 4 weeks after leaving a malarious area (47) (see drug regimens in <u>Table 2</u>).

Prophylaxis against hypnozoites

P. vivax and *P. ovale* have a dormant stage called the 'hypnozoite'. The hypnozoite remains dormant for months and then 'wakes up' to develop into a liver schizont. The dormant hypnozoite explains why attacks of vivax or ovale malaria can occur long after the end of chemoprophylaxis. This is not due to drug failure, as none of the prophylactic drugs currently advised by ACMP acts against the hypnozoite stage of *P. vivax* or *P. ovale*.

Primaquine is active against hypnozoites (present only in *P. vivax* and *P. ovale*) and is used in the treatment of these forms of malaria. It also has causal prophylactic activity against the liver stage schizonts of all malaria parasites of humans (48).

Primaquine is occasionally used for terminal prophylaxis, also known as presumptive antirelapse therapy (PART), to eradicate hypnozoites of *P. vivax* and *P. ovale*.

However, the routine use of primaquine for prophylaxis or terminal prophylaxis is not recommended by ACMP.

Primaquine is not licensed in the UK and practitioners considering the use of primaquine as a prophylactic agent should consult an expert centre (see <u>Information resources</u>).

Primaquine is an oxidant drug and can lead to significant haemolysis in G6PD-deficient individuals.

The drugs

The Summaries of Product Characteristics (SmPCs) for each antimalarial agent contain the full prescribing information. The British National Formulary (BNF) covers some of the major aspects of the full prescribing information. The SmPCs and the BNF should be consulted as required when recommending malaria chemoprophylaxis.

The **BNF** and **BNFC** are now available in one app.

This section on individual drugs is not as detailed as that provided for prescribers in the SmPCs and BNF. In the sections that follow, some of the ACMP's recommendations may not follow the SmPCs. In that situation we recommend following the ACMP recommendations.

This section should be read in conjunction with the chapters:

- Awareness of risk, which provides information on drug resistance
- Chemoprophylaxis, which provides details of recommended dose regimens
- Special groups and Special categories, which provide additional information on the
 use of antimalarial agents in special groups, including those with medical conditions
 (for example, pregnant and breastfeeding women and individuals with renal
 impairment) and those in special categories (for example, children and the elderly)

Note: Anybody from the UK, including members of the public, can report any suspected side effects from malaria medicines via the Yellow Card Scheme on the <u>Medicines and Healthcare products Regulatory Agency (MHRA)</u> website. Attacks of malaria that occur in individuals prescribed malaria prophylaxis should also be reported via this system.

Keep all medicines out of the sight and reach of children.

The following drugs are not listed in order of preference.

Chloroquine

Mode of action

Chloroquine is concentrated in the malaria parasite lysosome and is thought to act by interfering with malaria pigment formation, causing generation of a ferriprotoporphyrin IX-chloroquine complex which is highly toxic to the parasite.

Efficacy

Chloroquine-resistant falciparum malaria is now reported from all WHO regions except Central America north of the Panama Canal and the Island of Hispaniola (Haiti and the Dominican Republic). It remains effective against most *P. vivax*, *P. ovale*, *P. knowlesi* and virtually all *P. malariae*.

Formulations and method of administration

Tablets contain 155 milligrams (mg) chloroquine base; syrup contains chloroquine base 50 milligrams per millilitre (mg/5ml). To be taken orally with food. Antacids (aluminium, calcium and magnesium salts) and adsorbents (for example, kaolin) may reduce the absorption of chloroquine, so they should be taken at least 4 hours apart.

Prophylactic regimen

Adult dose 310mg (2 tablets) weekly, starting one week before entering a malarious area, continuing throughout the time in the area and for 4 weeks after leaving the area.

Contraindications

Allergy to chloroquine or to any other ingredients of the formulation (tablet or syrup). Concomitant use with amiodarone

Cautions

Chloroquine should not be used in those with a history of epilepsy. The risk of epilepsy is higher in first degree relatives of those in whom this condition has been diagnosed so it should be considered as part of risk assessment. Epilepsy in a first-degree relative may not contraindicate the use of an antimalarial, but may influence the choice of drug.

Chloroquine may exacerbate psoriasis and myasthenia gravis. Severe hypoglycaemia has occurred in diabetics and non-diabetics.

In long-term use, eye examinations every 6 to 12 months should be considered after 6 years' prophylactic usage, though the risk of retinopathy developing on prophylactic dosage is considered to be very low (49). See also long-term traveller section in <u>Special categories</u>.

Chloroquine is highly toxic in overdose and children are particularly susceptible.

Interactions

This section includes key interactions, but does not include all possible interactions. Practitioners should also consult the BNF and SmPC before prescribing.

Drugs: Use with amiodarone is contraindicated (increased risk of ventricular arrhythmias)

Other interactions include: ciclosporin (increased risk of ciclosporin toxicity); digoxin (possibly increases plasma concentration of digoxin); mefloquine (increased risk of convulsions); moxifloxacin (increased risk of ventricular arrhythmias).

Vaccines: Chloroquine may suppress the antibody response to pre-exposure intradermal human diploid cell rabies vaccine (50). This interaction is not seen when rabies vaccine is given intramuscularly (the currently recommended licensed mode of vaccination in the UK).

Side effects

Frequently reported side effects are gastrointestinal disturbances and headache. Convulsions and severe skin reactions have been reported. Chloroquine may cause itching, especially in persons of African descent.

Hydroxychloroquine

Hydroxychloroquine is usually used for the treatment of rheumatic diseases, in doses greater than those needed for malaria prevention. Individuals already taking hydroxychloroquine **and** for whom chloroquine would be an appropriate malaria chemoprophylactic agent, can remain on hydroxychloroquine and do not need to transfer to chloroquine. If doubt exists, seek expert advice.

Proguanil has been discontinued in the UK

Both Paludrine (proguanil hydrochloride) and Paludrine/Avloclor (proguanil hydrochloride, chloroquine phosphate) Anti-Malarial Travel Pack have been discontinued in the UK. Once current stocks are exhausted, no further supplies will be available. This means that proguanil will no longer be available in the UK and will impact on the malaria recommendations for a small number of countries where the combination of chloroquine and proguanil was recommended for malaria prevention.

Supplies of Avloclor (chloroquine phosphate) and atovaquone plus proguanil combination preparation are not affected.

If chloroquine plus proguanil was recommended previously, an alternative malaria chemoprophylaxis regimen (such as atovaquone plus proguanil combination preparation or doxycycline or mefloquine), may be selected.

Mefloquine

As with any antimalarial, stringent risk assessment is required before advising mefloquine use.

Mode of action

Mefloquine's mode of action has not been determined but is thought to be unrelated to that of chloroquine and not to involve an anti-folate action. It acts as a suppressive prophylactic.

Efficacy

The protective efficacy of mefloquine is 90% or more (52, 53). At the present time, significant resistance of *P. falciparum* to mefloquine is a problem only in some areas of South-East Asia (54), but is reported sporadically from the Amazon basin.

Formulation and method of administration

250mg tablets. Taken orally, preferably after a meal and with plenty of liquid.

Prophylactic regimen

Adult dose 250mg weekly, starting 2 to 3 weeks before entering a malarious area to assess tolerability, continuing throughout the time in the area and for 4 weeks after leaving the area.

Contraindications

- 1. Allergy to mefloquine or to any ingredient of the tablets.
- 2. Allergy to quinine or quinidine.
- 3. A current or previous history of depression, generalized anxiety disorder, psychosis, schizophrenia, suicide attempts, suicidal thoughts, self-endangering behaviour or any other psychiatric disorder, epilepsy or convulsions of any origin. The risk of epilepsy and serious mental health disorders is higher in first degree relatives of those in whom these conditions have been diagnosed so they should be considered as part of risk assessment. A condition in a first-degree relative may not contraindicate the use of an antimalarial but may influence the choice of drug. Please read in conjunction with the section on epilepsy in these quidelines.
- 4. A history of Blackwater fever.
- 5. Severe impairment of liver function.

Use with halofantrine. Also, halofantrine should not be given within 15 weeks after the last dose of mefloquine.

Use of a checklist should ensure that proper screening is undertaken prior to mefloquine administration and these contraindications are followed (<u>55</u>). See also the manufacturer's SmPC, Patient information leaflet and risk materials.

Cautions

Pregnancy and breast-feeding (see <u>Special groups (medical conditions)</u>), cardiac conduction disorders. Not recommended in infants under 5kg.

The SmPC points out that during clinical trials, mefloquine was not administered for longer than one year and states that periodic checks on liver function and eye assessments should be performed if mefloquine is used for a prolonged period. Any person taking mefloquine

presenting with a visual disorder should be referred to their treating physician as this may require stopping chemoprophylaxis.

In those who have suffered traumatic brain injury, the decision whether to advise mefloquine chemoprophylaxis should be made on an individual basis after a detailed risk assessment.

Diving and mefloquine

If the individual tolerates mefloquine prophylaxis, there is no evidence that they cannot physically perform underwater diving. However, mefloquine does lower the seizure threshold and its side effects could potentially be confused with decompression or narcosis events. It should also be noted that some sub-aqua centres do not permit those taking mefloquine to dive. Mefloquine might therefore be better avoided for those undertaking diving holidays but there is no contraindication to its use in occasional divers who have taken and tolerated the drug before, or those able to start taking it early to ensure that no adverse events occur.

Pilots

The UK Civil Aviation Authority advises that mefloquine should not be administered to pilots, although there is no evidence that mefloquine impairs function.

The Military

The ACMP recognises that malaria risk is different in military and civilian travellers. The Ministry of Defence has prepared guidelines for malaria prevention specific to military personnel. Civilian practitioners asked to provide malaria prevention advice for members of the Armed Forces should liaise with the Defence Medical Services via Defence Medical Services Public Health Unit at SG-DMed-Med-DPHU-GpMailbox@mod.gov.uk

Interactions

This section includes key interactions, but does not include all possible interactions. Practitioners should also consult the BNF and SmPC before prescribing.

Drugs: Use with halofantrine is contraindicated.

Mefloquine antagonises the anticonvulsant effect of antiepileptics and may enhance the effect of other drugs that reduce the epileptogenic threshold, increasing the risk of convulsions. Use of mefloquine with other drugs that affect cardiac conduction may enhance the risk of serious cardiac arrhythmias. Mefloquine is metabolised in the liver by CYP3A4. Caution if administered with drugs that inhibit this enzyme due to increased mefloquine levels (for example, itraconazole) (52). Drugs that induce metabolism of mefloquine may be expected to reduce mefloquine levels (for example, rifampicin).

Ritonavir levels are reduced by mefloquine due to decreased absorption, but the clinical significance of this interaction is unknown.

Side effects

Attention has focused on neuropsychiatric problems and vestibular disorders with mefloquine prophylaxis. Those taking mefloquine are more likely to have abnormal dreams, insomnia,

anxiety and depressed mood during travel than those who take atovaquone-proguanil or doxycycline (56).

Increased neuropsychiatric adverse events have been found, especially in women using mefloquine, when compared with those receiving doxycycline, or atovaquone plus proguanil, but not those taking chloroquine plus proguanil (52, 57, 58). No association between mefloquine prescriptions and hospitalisation has been demonstrated (59). Dizziness, balance disorder, tinnitus and vertigo may occur. In a small number of patients, it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuing the drug.

In February 2018 the SmPC added insomnia to the list of psychiatric symptoms that must be regarded as prodromal for a more serious event. The updated list is insomnia, abnormal dreams and/or nightmares, acute anxiety, depression, restlessness or confusion. Overall, mefloquine remains an important prophylactic agent which is tolerated by most travellers who take it (52, 56, 60).

Doxycycline

Mode of action

Doxycycline is lipophilic and acts intracellularly, binding to ribosomal mRNA and inhibiting protein synthesis. It acts as a suppressive prophylactic.

Efficacy

Doxycycline is of comparable prophylactic efficacy to mefloquine (61).

Formulations and method of administration

Capsules (50 or 100mg) or dispersible 100mg tablets.

The capsules and solution of dispersible tablets should be swallowed with plenty of fluid in either the resting or standing position and the recipient should not lie down for at least one hour after ingestion to reduce the likelihood of oesophageal irritation and ulceration. If gastric irritation occurs, it is recommended that doxycycline is taken with food or milk.

Studies indicate that the absorption of doxycycline is not notably influenced by simultaneous ingestion of food or milk.

The absorption of doxycycline may be impaired by concurrently administered antacids containing aluminium, calcium, magnesium or by oral zinc, iron salts or bismuth preparations. Intake of these substances should be separated from dosing with doxycycline as far as possible.

Prophylactic regimen

Dose 100mg daily, starting 1 to 2 days before entering a malarious area, continuing throughout the time in the area and for 4 weeks after leaving the area.

Contraindications

Allergy to tetracyclines or to any ingredients of the capsules or dispersible tablets. Children under 12 years of age.

Use during pregnancy is contraindicated in the SmPC.

The UK National Teratology Information Service states that doxycycline is best avoided for antimalarial prophylaxis during pregnancy. However, if required before 15 weeks' gestation it should not be withheld if other options are unsuitable (62). The course of doxycycline, including the 4 weeks after travel, must be completed before 15 weeks' gestation.

Use while breast feeding is contraindicated in the SmPC (63). A Centers for Disease Control Expert Meeting on malaria chemoprophylaxis stated that doxycycline is excreted at low concentrations in breast milk and that the American Academy of Pediatrics (AAP) assessed tetracycline as compatible with breast feeding (64).

ACMP's view is that doxycycline should not be used in breast feeding unless other options are unsuitable, and its use is felt to be essential.

Cautions

Hepatic impairment. Patients taking potentially hepatotoxic drugs. Renal impairment. Myasthenia gravis. Systemic lupus erythematosus. Candida infections may occur.

The prescriber should warn against excessive sun exposure (and advise on the correct use of a broad-spectrum sunscreen).

Interactions

This section includes key interactions, but does not include all possible interactions. Practitioners should also consult the BNF and SmPC before prescribing.

Drugs: The metabolism of doxycycline is accelerated by carbamazepine and phenytoin. In that situation try to advise another antimalarial. If not possible or acceptable to the traveller, increase the dose of doxycycline to 100mg twice daily and counsel regarding measures to minimise the risk of adverse events. Tetracyclines possibly enhance the anticoagulant effect of coumarins (for example, warfarin), and doxycycline may increase the plasma concentration of ciclosporin.

Doxycycline is a non-enzyme-inducing antibiotic. The Faculty of Sexual and Reproductive Healthcare and the BNF advise that for combined oral contraceptives and for progestogen only oral contraceptives additional precautions are not required when using non-enzyme-inducing antibiotics. However, if the traveller suffers vomiting or diarrhoea, the usual additional contraceptive precautions should be observed.

Vaccines: Possibly reduces the efficacy of oral typhoid vaccine if given simultaneously. Preferably should not be started within 3 days after the last dose of vaccine.

Side effects

Doxycycline hydrochloride preparations have a low pH and may produce oesophagitis and gastritis, especially if taken on an empty stomach and/or just before lying down.

Doxycycline may cause photosensitivity which is mostly mild and transient $(\underline{56}, \underline{65})$.

Doxycycline is a broad-spectrum antibiotic and may predispose to vaginal candidiasis (56, 64).

Atovaquone plus proguanil combination preparation

Mode of action

Atovaquone works by inhibiting electron transport in the mitochondrial cytochrome b-c1 complex, causing collapse in the mitochondrial membrane potential. This action is potentiated by proguanil and is not dependent upon conversion to its metabolite cycloguanil. Indeed, the combination remains effective in cycloguanil-resistant parasites (66). Atovaquone/proguanil prevents development of pre-erythrocytic (liver) schizonts (but not hypnozoites). It acts as a causal prophylactic agent, so needs to be continued for only 7 days after leaving a malarious area (67). It also has activity against the erythrocytic stages of malaria parasites and is useful for treatment.

Efficacy

Prophylactic efficacy against *P. falciparum* is 90% or more (<u>68 to 76</u>). There is less published data on protection against *P. vivax*, but data available indicate that atovaquone-proguanil is effective in the prevention of primary attacks of vivax malaria (<u>75</u>, <u>77</u>). However, like chloroquine, mefloquine and doxycycline, it will not protect against hypnozoite-induced episodes of *P. vivax* (or *P. ovale*) malaria.

Formulations and method of administration

Tablets containing proguanil 100mg and atovaquone 250mg. Paediatric tablets containing proguanil 25mg and atovaquone 62.5mg. To be taken orally with food or a milky drink.

Prophylactic regimen

Adult dose one tablet daily starting 1 to 2 days before entering a malarious area, continuing throughout the time in the area and for 7 days after leaving the area. ACMP does not support use of an abbreviated atovaquone-proguanil prophylaxis regimen in travellers after leaving malaria-endemic areas (78). Paediatric dose is given in <u>Table 6</u>.

Maloff Protect, a brand of atovaquone plus proguanil combination preparation is available to purchase from UK pharmacies, after previously only being available on prescription. They are available for adults aged over 18 weighing more than 40kg.

Contraindications

Allergy to proguanil or atovaquone or to any of the other ingredients in the tablets.

Renal impairment (avoid for malaria prophylaxis if eGFR less than 30 mL/minute/1.73m²).

Cautions

Atovaquone/proguanil should generally be avoided in pregnancy. The ACMP advises that if there are no other options, its use may be considered in the second and third trimesters after careful risk assessment. Inadvertent conception when using atovaquone/proguanil is not an indication to consider termination of the pregnancy, as no evidence of harm has emerged in data so far available (79, 92).

Atovaquone/proguanil should generally be avoided in breast feeding. The ACMP advises that atovaquone/proguanil can be used when breast-feeding if there is no suitable alternative antimalarial.

Diarrhoea or vomiting may reduce the absorption of atovaquone.

Interactions

This section includes key interactions, but does not include all possible interactions. Practitioners should also consult the BNF and SmPC before prescribing.

The proguanil component may enhance the anticoagulant effect of warfarin so monitoring. The antifolate effect of proguanil is increased when given with pyrimethamine.

Drugs: Plasma concentrations of atovaquone are reduced by rifabutin and rifampicin, most non-nucleoside reverse transcriptase inhibitors, boosted protease inhibitors of HIV, tetracycline and metoclopramide (possible therapeutic failure of atovaquone, avoid concomitant use).

Atovaquone interacts with some antiretroviral drugs. For up-to-date information and an interaction checker see the HIV Drug Interactions website.

Vaccines

None reported.

Side effects

The most frequent side effects are headache and gastrointestinal upsets.

Dosage tables

These drugs are not listed in order of preference. The preferred prophylaxis is determined by a full risk assessment for each individual traveller.

Table 2. Prophylactic regimens against malaria in adults in areas of chloroquine-resistant P. falciparum

Regimen	Dose for chemoprophylaxis	Usual amount for tablet (mg)
Mefloquine	One tablet weekly	250
For adults weighing 45kg or more. (For adults weighing less than 45kg please consult <u>Table 3</u>)		
Doxycycline	One tablet or capsule daily	100
Atovaquone plus proguanil combination preparation	One tablet daily	250 (atovaquone) plus 100 (proguanil)
For adults weighing 40kg or more. (For adults weighing less than 40kg please consult <u>Table 5</u>)		

Table 3. Doses of prophylactic antimalarials for children

Note: Weight is a better guide than age for children, so weight should be used for the purpose of children's dosage calculation including children who are over- or under-weight.

Weight in kilograms	Chloroquine base 155mg	Mefloquine 250mg	Doxycycline 100mg
Under 6.0	0.125 dose 1/4 tablet	See footnote ²	Not recommended
6.0 to 9.9	0.25 dose ½ tablet	0.25 dose 1/4 tablet	Not recommended
10.0 to 15.9	0.375 dose 3/4 tablet	0.25 dose ³ ½ tablet	Not recommended

² The SmPC for mefloquine indicates that it can be used for those weighing more than 5kgs. Therefore, mefloquine (0.25 dose, ¼ tablet) may be advised for children weighing 5 to 9.9kg.

³ For mefloquine at this weight, 0.375 dose would be preferable, but cannot be safely provided by breaking the adult tablet.

Weight in kilograms	Chloroquine base 155mg	Mefloquine 250mg	Doxycycline 100mg
16.0 to 24.9	0.5 dose One tablet	0.5 dose ½ tablet	Not recommended
25.0 to 44.9	0.75 dose 1 to 1/2 tablets	0.75 dose 3⁄4 tablet	The BNF for children advises 100mg once daily from 12 years (body weight 25kg and above). One tablet
45 and over	Adult dose Two tablets	Adult dose One tablet	Adult dose One tablet

Further important notes

Doxycycline is unsuitable for children under 12 years irrespective of their weight. Caution: In other countries tablet strength may vary. Atovaquone/proguanil paediatric dosage is given in <u>Table 5</u>.

Table 4. Table of doses by spoon or syringe⁴ measures for chloroquine syrup

Weight in kilograms	Number of 5ml measures (there is often a half size measure at the other end of the spoon)	Proportion of adult dose
Under 4.5	0.5 (2.5 ml)	0.08
4.5 to 7.9	1.0 (5.0 ml)	0.16
8.0 to 10.9	1.5 (2.5 ml plus 5 ml)	0.24
11.0 to 14.9	2.0 (2 x 5 ml)	0.32
15.0 to 16.5	2.5 (2.5 ml plus 2 x 5 ml)	0.40

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⁴ Chemists may dispense dosing syringes for child doses.

Note 1: These dose-steps are not the same as for chloroquine tablets, which differ from the syrup in chloroquine content. Chloroquine syrup contains 50mg chloroquine base in 5ml.

Note 2: If chloroquine syrup is required for a child weighing more than 16.5kg please follow the dosage regimen stated in the BNFC.

Table 5. Table of paediatric doses of atovaquone/proguanil

Weight in kg	Proportion of adult dose	Number of paediatric tablets
5 to 7.9	0.125	½ paediatric
8 to 9.9	0.188	¾ paediatric
10 to 19.9	0.25	1 paediatric
20 to 29.9	0.50	2 paediatric
30 to 39.9	0.75	3 paediatric
40 and over	1.00	4 paediatric (this dose is better given as one adult tablet)

See the section on <u>Children</u> for advice on how to administer antimalarials to children. NaTHNaC has produced <u>a useful summary table of children's dosage</u>.

Country recommendations

ACMP recommendations by country are summarised in Table 6, below.

Key to Table 6

Table 6 contains the following abbreviations:

A/P = atovaquone-proguanil combination preparation

BA only = bite avoidance plus awareness of risk

D = doxycycline

M = mefloquine

Notes

- 1. The role of ACMP is to provide high level general guidance to help practitioners give specific advice for individual travellers.
- 2. Bite avoidance is advised for travel to all areas, including the malaria-free areas of the countries listed in this table, as a preventive measure against other insect vector-borne diseases.
- Some countries not listed in this table may experience occasional instances of malaria transmission. Please check the <u>NaTHNaC</u> or <u>TRAVAX</u> websites regularly for clinical updates.
- 4. A recommendation for bite prevention plus awareness of risk does not mean there is no risk of malaria in the place in question but indicates that ACMP considers the level of risk to be below the threshold for routinely recommending chemoprophylaxis. Where bite avoidance is now the main preventive measure for a given area, rigorous adherence to the recommendations in Bite prevention is strongly advised. In all cases, whether or not chemoprophylaxis has been advised, special attention must be given to bite prevention and febrile illness must be taken seriously and investigated promptly.
- 5. Long-term VFR visitors run a higher risk of catching malaria than short term travellers to the same location. Furthermore, once infected, the risk of developing severe or complicated malaria is higher in certain groups, such as the elderly (over 70 years old), the immunosuppressed, those with complex co-morbidities and pregnant women.
- 6. Although such travellers at increased risk of developing complicated malaria should not be offered antimalarials routinely for malaria risk areas where bite avoidance only is recommended, this may be considered in exceptional circumstances. Expert advice to support the practitioner is available from the MRL, NaTHNaC and TRAVAX.
- 7. The final decision whether or not to advise chemoprophylaxis rests with the travel health advisor and the traveller after individual risk assessment has been performed.

Table 6. Country recommendations

Country name	ACMP recommendations 2022
Afghanistan (see <u>Figure</u> <u>4</u>)	There is a low risk of malaria below 2,000m from May to November (BA only). There is a very low risk of malaria in this part of the country during the rest of the year (BA only).
Andaman and Nicobar Islands (India)	There is a low risk of malaria in the Andaman and Nicobar Islands (BA only).
Angola (see Figure 5)	There is a high risk of malaria in Angola (A/P,D, M).
Argentina	In 2019 the WHO declared Argentina malaria-free. There is no risk of malaria (BA only)
Azerbaijan	In 2023 the WHO declared Azerbaijan malaria-free. There is no risk of malaria (BA only).
Bangladesh (see <u>Figure 6</u>)	There is a high risk of malaria in the Chittagong Hill Tract districts of Bangladesh (A/P,D, M). There is a very low risk in the rest of Bangladesh (including Chittagong city) (BA only). See the interactive malaria map for Bangladesh.
Belize	In 2023 the WHO declared Belize malaria free. There is no risk of malaria in Belize (BA only).
Benin (see Figure 7)	There is a <u>high risk of malaria in Benin</u> (A/P,D, M).
Bhutan	There is a low risk of malaria in the southern belt districts of Bhutan along the border with India: Chukha, Geyleg-phug, Samchi, Samdrup Jonkhar and Shemgang (BA only). There is no risk in the rest of Bhutan.
Bolivia (see <u>Figure 8</u>)	There is a low risk of malaria in the Amazon basin of Bolivia (BA only). There is a low risk of malaria in other rural areas below 2,500 m (BA only). There is no risk above 2,500m. See the interactive malaria map for Bolivia.
Botswana (see <u>Figure 9</u>)	There is a high risk of malaria, from November to June, in the northern half of Botswana, including the Okavango Delta area (A/P,D,M). There is a low risk of malaria in this part of the country during the rest of the year (BA only). There is very low risk in the southern half of the country (BA only).
Brazil(see <u>Figure 10</u>)	There is a low risk of malaria in the Amazon Basin of Brazil, including in the city of Manaus (BA only). There is a very low risk of malaria in the rest of Brazil (BA only). There is no risk of malaria in Iguaçu Falls. See the interactive malaria map for Brazil.
Brunei Darussalam	There is very low risk of malaria in Brunei Darussalam (BA only).
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Country name	ACMP recommendations 2022
Burundi	There is a high risk of malaria in Burundi (A/P, D, M).
Cambodia (see <u>Figure</u> <u>11</u>)	There is a low risk of malaria in Cambodia. (BA only). There is a very low risk of malaria in the temple complexes of Angkor Wat and around Lake Tonle Sap, including Siem Reap (BA only). There is no risk in Phnom Penh. Mefloquine resistance is widespread in the western provinces of Cambodia bordering Thailand.
Cameroon (see <u>Figure</u> <u>12</u>)	There is a high risk of malaria in Cameroon (A/P, D, M).
Cape Verde	There is no risk of malaria in Cape Verde (BA only).
Central African Republic	There is a high risk of malaria in the Central African Republic (A/P, D, M).
Chad	There is a high risk of malaria in Chad (A/P, D, M).
China	In 2021 the WHO declared China malaria free. There is no risk of malaria in China (BA only).
China (Hong Kong)	There is no risk of malaria in Hong Kong.
Colombia (see Figure 13)	There is a low risk of malaria in rural areas of Colombia below 1,600m (BA only). There is a very low risk in areas above 1,600m and in Cartagena (BA only).
Comoros	There is a high risk of malaria in the Comoros (A/P, D, M).
Congo (see Figure 14)	There is a high risk of malaria in the Congo (A/P, D, M).
Costa Rica (see <u>Figure</u> <u>15</u>)	There is a low risk of malaria in Limon Province (BA only) but not in the city of Limon (Puerto Limon). There is a very low risk in the rest of the country (BA only).
Côte d'Ivoire (see <u>Figure</u> <u>16</u>)	There is a high risk of malaria in the Cote d'Ivoire (A/P, D, M).
Democratic Republic of the Congo (see Figure 17)	There is a high risk of malaria in the Democratic Republic of the Congo (A/P, D, M).
Djibouti	There is a high risk of malaria in Djibouti (A/P, D, M).
Dominican Republic	There is a low risk of malaria in all areas of the Dominican Republic (BA only). There is no risk in the cities of Santiago and Santo Domingo.
East Timor (Timor-Leste)	There is a low risk of malaria in East Timor (BA only).
Ecuador (see Figure 18)	On mainland Ecuador, there is a low risk of malaria in areas below 1,500m, including the coastal provinces and Amazon basin (BA

Country name	ACMP recommendations 2022
	only). There is no risk of malaria in the Galapagos islands or the city of Guayaquil.
Egypt	There is no risk of malaria in Egypt. (BA only).
El Salvador	In 2021 the WHO declared El Salvador malaria free. There is no risk of malaria in El Salvador (BA only).
Equatorial Guinea	There is a high risk of malaria in Equatorial Guinea (A/P, D, M).
Eritrea (see Figure 19)	There is a high risk of malaria in Eritrea below 2,200m (A/P, D, M). There is no risk of malaria in Asmara or in areas above 2,200m.
Eswatini (see <u>Figure 20</u>)	There is a risk of malaria in the northern and eastern regions bordering Mozambique and South Africa, including all the Lubombo district and Big Bend, Mhlume, Simunye and Tshaneni regions (A/P, D, M).
	There is a very low risk of malaria in the rest of the country (BA only).
Ethiopia (see Figure 21)	There is a <u>high risk of malaria in Ethiopia below 2,000m</u> (A/P, D, M). There is no risk of malaria in Addis Ababa or in areas above 2,000m.
French Guiana	There is a risk of malaria in French Guiana, particularly in the border areas. Chemoprophylaxis is advised for visitors to border areas and for those travelling along the rivers (A/P, D, M). There is a low risk of malaria in the city of Cayenne or Devil's Island and environs (Ile du Diable) (BA only).
Gabon	There is a high risk of malaria in Gabon (A/P, D, M).
Gambia (see Figure 22)	There is a high risk of malaria in Gambia (A/P, D, M).
Georgia	There is a very low risk of malaria in the rural southeast of Georgia from June to October (BA only). There is no risk of malaria in this part of the country during the rest of the year.
Ghana (see <u>Figure 23</u>)	There is a high risk of malaria in Ghana (A/P, D, M).
Guatemala (see <u>Figure</u> <u>24</u>)	There is a low risk of malaria in Guatemala below 1,500m (BA only). There is no risk in Guatemala City, Antigua and Lake Atitlan and areas above 1,500m.
Guinea (see Figure 25)	There is a <u>high risk of malaria in Guinea</u> (A/P, D, M).
Guinea-Bissau	There is a high risk of malaria in Guinea-Bissau (A/P, D, M).
Guyana	There is a risk of malaria in all interior regions of Guyana (A/P, D,M). There is a very low risk of malaria in Georgetown and the coastal region (BA only).

Country name	ACMP recommendations 2022
Haiti	There is a risk of malaria in Haiti (C, A/P, D, M).
Honduras (see <u>Figure</u> <u>26</u>)	There is a low risk of malaria below 1,000m and in Roatán and other Bay Islands (BA only). There is no risk of malaria in San Pedro Sula and Tegucigalpa and areas above 1,000m.
India (see <u>Figure 27</u>)	There is a risk of malaria in the states of Assam and Orissa; the districts of East Godavari, Srikakulam, Vishakhapatnam and Vizianagaram in the state of Andhra Pradesh; and the districts of Balaghat, Dindori, Mandla and Seoni in the state of Madhya Pradesh (A/P, D, M).
	For the rest of India (including Goa and the Andaman and Nicobar Islands) there is a low risk of malaria (BA only). There is no risk of malaria in the Lakshadweep islands. See an interactive malaria map of India.
Indonesia (see <u>Figure 28</u>)	There is a high risk of malaria in Irian Jaya (Papua) (A/P, D, M). There is a low risk in Bali, Lombok and the islands of Java and Sumatra (BA only). There is no risk in the city of Jakarta.
Iran (see <u>Figure 29)</u>	There is a low risk of malaria from March to November in the rural south eastern provinces of Iran and in the north, along the Azerbaijan border in Ardabil and near the Turkmenistan border in North Khorasan (BA only). There is a very low risk in the rest of Iran. (BA only)
Iraq (see <u>Figure 30</u>)	There is a very low risk of malaria in the rural northern area of Iraq below 1,500m, from May to November (BA only). There is no risk in the rest of Iraq.
Kenya (see <u>Figure 31</u>)	There is a high risk of malaria in Kenya (A/P, D, M). There is very low risk in the city of Nairobi and in the highlands above 2,500m (BA only).
Lao People's Democratic Republic (Laos) (see <u>Figure 32</u>)	There is a low risk of malaria in Laos (BA only). There is a very low risk in the city of Vientiane (BA only).
Liberia	There is a high risk of malaria in Liberia (A/P, D, M).
Madagascar (see <u>Figure</u> 33)	There is a high risk of malaria in Madagascar (A/P, D, M).
Malawi (see <u>Figure 34</u>)	There is a <u>high risk of malaria in Malawi</u> (A/P, D, M).
Malaysia (see Figure 35)	There is a low risk of malaria in Mainland Malaysia (BA only).

Country name	ACMP recommendations 2022
Malaysia (Borneo) (see Figure 35)	There is a low risk of malaria in inland areas of Sabah and in the inland, forested areas of Sarawak (BA only). There is a very low risk of malaria in the rest of Malaysian Borneo including the coastal areas of Sabah and Sarawak (BA only)
Mali	There is a high risk of malaria in Mali (A/P, D, M).
Mauritania (see <u>Figure</u> <u>36</u>)	There is a high risk of malaria throughout the year in the southern provinces of Mauritania (A/P, D, M). There is a high risk of malaria in the northern provinces from July to October inclusive (A/P, D, M). There is a low risk of malaria in the northern provinces during the rest of the year (BA only).
Mauritius	There is no risk of malaria in Mauritius (BA only).
Mayotte	There is a low risk of malaria in Mayotte (BA only).
Mexico	There is a very low risk of malaria in Mexico (BA only).
Mozambique (see Figure 37)	There is a high risk of malaria in Mozambique (A/P, D, M).
Myanmar	There is an increase in the number of malaria cases reported on the border area with Thailand. A/P, D is recommended for this border area. The risk in the rest of Myanmar is difficult to assess and chemoprophylaxis (A/P, D) should be considered for travellers to all parts of Myanmar at altitudes below 1,000 metres.
Namibia (see <u>Figure 38)</u>	There is a high risk of malaria throughout the year in the Caprivi Strip, Kavango and Kunene river regions (A/P, D, M). There is a very low risk of malaria in the rest of Namibia (BA only).
Nepal (see <u>Figure 39</u>)	There is a low risk of malaria in areas of Nepal below 1,500m, including the Terai district (BA only). There is no risk of malaria in the city of Kathmandu and on typical Himalayan treks.
Nicaragua	There is a very low risk of malaria in Managua (BA only). There is a low risk of malaria in the rest of Nicaragua (BA only).
Niger	There is a high risk of malaria in Niger (A/P, D, M).
Nigeria (see Figure 40)	There is a high risk of malaria in Nigeria (A/P, D, M).
North Korea	There is a very low risk of malaria in some southern areas of North Korea (BA only).
Pakistan (see <u>Figure 41)</u>	There is normally a low risk of malaria in areas of Pakistan below 2,000m (BA only). There is a very low risk above 2,000m (BA only).

Country name	ACMP recommendations 2022
	However, due to the widespread flooding in Pakistan in 2022, there was a 4-fold increase in the number of malaria cases reported after the floods. Therefore, until the end of November 2024, antimalarial chemoprophylaxis is advised for travellers to the 2022 flood-affected areas; atovaquone-proguanil or doxycycline or mefloquine is recommended. Southern and central Pakistan were most affected, particularly Balochistan and Sindh provinces. See an interactive malaria map of Pakistan.
Panama (see <u>Figure 42</u>)	There is a low risk of malaria east of the Canal Zone in Panama (BA only). There is a very low risk of malaria west of the Canal Zone (BA only). There is no risk of malaria in Panama City or the Canal Zone itself.
Papua New Guinea (see <u>Figure 43</u>)	There is a high risk of malaria in Papua New Guinea below 1,800m (A/P, D, M). There is very low risk above 1,800m (BA only).
Peru (see <u>Figure 44)</u>	There is a low risk of malaria in the Amazon basin of Peru along the border with Brazil, particularly in Loreto province and in the other rural areas of Peru below 2,000m including that part of the Amazon Basin which borders Bolivia (BA only). There is no risk in the city of Lima and the coastal region south of Chiclayo.
Philippines (see <u>Figure</u> <u>45</u>)	There is a low risk of malaria in rural areas of the Philippines below 600m and on the islands of Luzon, Mindanao, Mindoro, and Palawan (BA only). There is no risk in cities or on the islands of Borocay, Bohol, Catanduanes, Cebu and Leyte.
Rwanda (see Figure 46)	There is a high risk of malaria in Rwanda (A/P, D, M).
Sao Tome and Principe	There is a high risk of malaria in São Tomé and Príncipe (A/P, D, M).
Saudi Arabia (see <u>Figure</u> <u>47</u>)	There is a low risk of malaria in the south western provinces of Saudi Arabia, along the border with Yemen including Asir province below 2,000m (BA only). There is no risk in the cities of Jeddah, Makkah (Mecca), Medina, Riyadh, and Ta'if, or in Asir province above 2,000m.
Senegal	There is a high risk of malaria in Senegal (A/P, D, M).
Sierra Leone (see Figure 48)	There is a <u>high risk of malaria in Sierra Leone</u> (A/P, D, M).
Singapore	There is no risk of malaria in Singapore (BA only).
Solomon Islands	There is a high risk of malaria in the Solomon Islands (A/P, D, M).
Somalia (see <u>Figure 49</u>)	There is a <u>high risk of malaria in Somalia</u> (A/P, D, M).

Country name	ACMP recommendations 2022
South Africa (see <u>Figure</u> <u>50</u>)	All travellers should take bite avoidance measures throughout the year in all risk areas. Transmission of malaria occurs typically between the months of September and May only.
	There is a risk of malaria in the low altitude areas of Mpumalanga and Limpopo particularly those bordering Mozambique, Eswatini and Zimbabwe; this includes the Kruger National Park: atovaquone/proguanil OR doxycycline OR mefloquine recommended during the transmission season, September to May only (see map provided by Department of Health, Republic of South Africa – marked as 'moderate risk').
	In June, July and August the risk in this area is considered to be very low: awareness of risk and bite avoidance recommended.
	There is a low risk of malaria in northeast KwaZulu-Natal and in designated areas of Mpumalanga, Limpopo (see map – marked as 'low risk') during the transmission season, September to May: awareness of risk and bite avoidance recommended.
	There is a very low risk of malaria in North West Province (adjacent to Molopo river) and Northern Cape Province (adjacent to Orange river): awareness of risk and bite avoidance recommended.
South Korea	There is a very low risk of malaria in the northern areas of South Korea, in Gangwon-do and Gyeonggi-do Provinces, and Incheon City (towards the Demilitarized Zone or DMZ) (BA only).
South Sudan	There is a high risk of malaria in South Sudan (A/P, D, M).
Sri Lanka	There is no risk of malaria in Sri Lanka (BA) only).
Sudan (see <u>Figure 51</u>)	Due to reported increases in malaria cases in Khartoum and the impact of civil unrest on health services there, antimalarial chemoprophylaxis is now advised for all travellers to Sudan, including Khartoum; atovaquone-proguanil or doxycycline or mefloquine is recommended. This change will be kept under review. Anyone returning from Sudan should be vigilant for the signs of malaria and seek immediate medical attention if they have a fever or flu-like illness.
Suriname	Mefloquine resistance has been reported. There is a low risk of malaria in Suriname (BA only). There is no risk in the city of Paramaribo.
Syria	There is thought to be a very low risk of malaria in small, remote foci of El Hasaka (BA only) but up-to-date data is not available, so the possibility of additional cases occurring cannot be excluded.

Country name	ACMP recommendations 2022
Tajikistan	In 2023 the WHO declared Tajikistan malaria-free. There is no risk of malaria (BA only).
Tanzania (see <u>Figure 52</u>)	There is a high risk of malaria in all areas below 1,800m (A/P, D, M). There is no risk of malaria above 1,800m. There is a risk of malaria in Zanzibar (A/P, D, M). See the interactive malaria map of Tanzania.
Thailand (see Figure 53)	There is mefloquine resistance in Thailand. There is a low risk of malaria in the rural, forested borders of Thailand with Cambodia, Laos and Myanmar (BA only). There is a very low risk of malaria in the remaining areas of Thailand including Kanchanaburi (Kwai Bridge) (BA only). There is no risk of malaria in the cities of Bangkok, Chiang Mai, Chiang Rai, Koh Phangan, Koh Samui, and Pattaya.
Togo	There is a high risk of malaria in Togo (A/P, D, M).
Turkey	There is a very low risk of malaria in Turkey (BA only).
Uganda (see <u>Figure 54</u>)	There is a <u>high risk of malaria in Uganda</u> (A/P, D, M).
Uzbekistan	The WHO certified Uzbekistan to be malaria-free in 2018. There is no risk of malaria (BA only).
Vanuatu	There is a risk of malaria in the whole of Vanuatu (A/P, D, M).
Venezuela	There is a risk of malaria in all areas of Venezuela, particularly in the Amazonas, Bolívar, Delta Amacuro and Sucre states: (A/P, D, M). There is no risk in the city of Caracas or on Margarita Island: (BA only).
Vietnam (see <u>Figure 55</u>)	There is a low risk of malaria in the southern part of the country in the provinces of Tay Ninh, Lam Dong, Dak Lak, Gia Lai, and Kon Tum, and other rural areas of Vietnam (BA only). There is no risk in large cities, including Hanoi and Ho Chi Minh City (Saigon), the Red River delta, coastal areas north of Nha Trang and Phu Quoc Island (BA only).
Western Sahara	There is no risk of malaria in this country (BA only).
Yemen (see <u>Figure 56</u>)	There is a risk of malaria in Yemen below 2,000m (A/P, D, M). There is very low risk of malaria on Socrota Island (BA only). There is no risk of malaria above 2,000m including Sana'a city (BA only).
Zambia (see Figure 57)	There is a high risk of malaria in Zambia (A/P, D, M).

Country name	ACMP recommendations 2022
Zimbabwe (see <u>Figure</u> <u>58</u>)	There is a high risk of malaria in Zimbabwe below 1,200m from November to June (A/P, D, M). There is a low risk of malaria in this part of the country during the rest of the year (BA only). In the Zambezi valley the risk is throughout the year (A/P, D, M). There is very low risk in Harare and Bulawayo (BA only).

Emergency standby treatment

Emergency standby treatment should be recommended for those taking chemoprophylaxis and visiting remote areas where they are unlikely to be within 24 hours of medical attention.

It is intended for those travellers who believe that they may have malaria and is not a replacement for chemoprophylaxis.

It is particularly important that the individual traveller is sufficiently well briefed to be able to use standby emergency treatment appropriately, as studies have shown that a significant proportion of travellers did not follow the pre-travel recommendations on administration of Emergency Standby Treatment, especially regarding the response to fever (80). Therefore, written instructions for its use are required (81).

Standby emergency treatment should be started if it is impossible to consult a doctor and/or reach a diagnosis within 24 hours of the onset of fever.

Medical attention should be sought as soon as possible for full assessment and to exclude other serious causes of fever. This is particularly important as many illnesses other than malaria may present with fever.

The traveller should complete the standby treatment course and recommence their antimalarial chemoprophylaxis one week after taking the first treatment dose. If quinine is used for standby treatment, mefloquine prophylaxis should be resumed at least 12 hours after the last treatment dose. Antipyretics should be used to treat fever. A second full treatment dose of the antimalarial should be taken if vomiting occurs within 30 minutes of taking it (half-dose if vomiting occurs after 30 to 60 minutes) (82).

The agent used for emergency standby treatment should be different from the drugs used for chemoprophylaxis, both to minimise drug toxicity and due to concerns over drug resistance (83).

Individuals for whom emergency standby treatment is advised must be provided with written instructions for its use. In particular, they must be informed about symptoms suggesting possible malaria, including fever of 38°C and above, indications for starting the standby

treatment, how to take it, expected side effects and the possibility of drug failure (83). ACMP recommended regimens for emergency standby treatment are given in <u>Table 7</u>.

Dihydroartemisinin-piperaquine has only recently been licensed in the EU and there are limited data on its use in travellers, so it cannot currently be recommended for this indication. Sulfadoxine/pyrimethamine (SP) is **not** recommended due to reports of widespread resistance to this agent among *P. falciparum* strains. Halofantrine is no longer recommended due to concerns over its association with sometimes fatal cardiac arrhythmias (83).

Antimalarials purchased in the tropics may be fake (45) and travellers should obtain the medication required for their emergency standby treatment from a reputable source in the UK before they travel. ACMP also advises those purchasing antimalarial drugs over the internet to ensure that they are dealing with a bona fide supplier or website.

Table 7. Emergency standby treatment for adults

Situation for use	Standby treatment regimen	Usual amount per tablet	Adult dose
Chloroquine or multi-drug resistant falciparum malaria	Regimen 1: Artemether plus lumefantrine combination preparation	20mg artemether plus 120mg lumefantrine	4 tablets initially, followed by 5 further doses of 4 tablets each given at 8, 24, 36, 48 and 60 hours. Total 24 tablets over a period of 60 hours. Tablets should be taken with food to enhance drug absorption
Chloroquine or multi-drug resistant falciparum malaria	Regimen 2: Atovaquone plus proguanil combination preparation	250mg atovaquone plus 100mg proguanil	4 tablets as a single dose on each of 3 consecutive days
Chloroquine or multi-drug resistant falciparum malaria	Quinine plus doxycycline	300mg quinine 100mg doxycycline	Quinine 2 tablets 3 times a day for 3 days, accompanied by one tablet of doxycycline twice daily for 7 days
First, second or third trimester of pregnancy*	Regimen 1 (see above) is preferred. Regimen 3 (see below) is an alternative		
First, second or third trimester of pregnancy*	Regimen 3: Quinine plus clindamycin	300mg quinine 150mg clindamycin	Quinine 2 tablets 3 times a day for 5 to 7 days Clindamycin 3 tablets (450mg) 3 times a day for 5 days

^{*} Pregnant travellers should avoid malarious areas. If that is not possible, artemether plus lumefantrine combination preparation can be used in first, second and third trimesters (WHO Guidelines for Malaria, 14 March 2023).

See Appendix 3 for an emergency standby medication traveller information leaflet which can be copied and pasted for use.

Diagnosis

Suspected malaria is a medical emergency.

Consider malaria in every ill patient who has returned from the tropics in the previous year, especially in the previous 3 months.

Fever on return from the tropics should be considered to be malaria until proven otherwise.

Malaria cannot be diagnosed with certainty by clinical criteria alone. Suspected cases should be investigated by obtaining a blood film diagnosis as a matter of urgency.

There is no need to wait for fever spikes before taking blood; this only delays diagnosis and the fever pattern seldom conforms to text book periodicity, especially in the case of *Plasmodium falciparum*.

Blood tests and how to request them in the UK

A synopsis is given here. Full details are contained in the latest British Society for Haematology guidelines for the laboratory diagnosis of malaria, published in March 2022 (134)

An EDTA-anticoagulated venous blood sample should be taken.

The test request form should include the phrase 'Urgent, suspected malaria' and the form and the blood sample should be received in the laboratory within one hour of being taken as falciparum malaria may increase in severity over a few hours and the morphology of malaria parasites in EDTA deteriorates over time, rendering accurate laboratory diagnosis more difficult.

Finger-prick samples smeared directly onto microscope slides at the bedside are sub-optimal for modern diagnosis as the laboratory then has no additional material to make and stain further smears, undertake rapid diagnostic tests (RDTs) or refer for PCR testing.

Laboratories in England, Wales and Northern Ireland making a diagnosis of malaria should send blood films and a portion of the blood sample on which the diagnosis was made to the <a href="https://www.ukman.com/ww

Rapid diagnostic tests (RDTs)

RDTs (sometimes known as 'dipsticks') can be used successfully in trained, selected high-risk groups (84) but ACMP does not recommend routine use of RDTs for self-diagnosis by travellers.

RDTs permit the detection of malaria parasites in human blood without microscopy. Used correctly, they can confirm the clinical diagnosis of malaria in places remote from medical attention (85). However travellers may use them incorrectly and thus fail to detect parasites (86).

RDTs do have a place in the medical kit carried by a doctor or nurse accompanying an expedition to remote malarious regions. Performance of RDTs may be impaired if they are stored at temperatures outside the recommended range (87). Therefore, care must be taken to transport and store them correctly and thus prevent deterioration in their performance in the field.

Furthermore, a study of self-diagnosis by travellers and expatriates using RDTs available on the internet showed the particular RDTs used had variable diagnostic accuracy. Only 4 of 8 RDT products for self-diagnosis were judged reliable for the diagnosis of *P. falciparum* and *P. vivax* and none for *P. ovale* and *P. malariae* (88).

Appropriate choice of RDT product is therefore crucial and the <u>WHO has an extensive product</u> testing programme for RDTs. Prospective purchasers should consult the WHO web site for information to inform their decision.

Blood film and/or RDT negative malaria

One negative blood film or RDT does not exclude a diagnosis of malaria. RDTs are not a substitute for microscopy in UK practice, but have a useful role alongside blood films as additional tests.

Where malaria is suspected blood films should be examined daily for 3 days whilst other diagnoses are also considered. If all these films are negative and malaria is still considered a possible diagnosis, expert advice should be sought from a specialist in tropical or infectious diseases. It is particularly important to seek such advice early in the care of pregnant patients with suspected malaria, as most parasites may be sequestered in the placenta such that peripheral blood films are negative despite the patient having malaria (see Information resources for expert advice listing).

Resources for treatment advice

The treatment of malaria is outside the scope of this document and is addressed in the <u>ACMP</u> malaria treatment guidelines.

Expert advice on malaria treatment may be obtained from:

- Hospital for Tropical Diseases
- Liverpool School of Tropical Medicine
- Your local infectious diseases unit

Notification

Malaria is a statutorily notifiable disease in England, Northern Ireland, and Wales and the clinician caring for the patient must complete a notification form (89). In Scotland, malaria is not on the list of notifiable diseases, but *Plasmodium* is on the list of notifiable organisms. UK laboratories outwith Scotland are also required to notify organisms they have diagnosed. The legislation for notifiable organisms places duties on directors of diagnostic laboratories to report organisms named in the list.

In England, Northern Ireland, and Wales, the <u>Malaria Reference Laboratory (MRL)</u> reporting form should also be completed and sent to the MRL separately or along with referred specimens.

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Special groups (medical conditions)

Smoking cessation

Chloroquine or mefloquine should not be used in those taking Zyban® (bupropion hydrochloride SR) as the chances of seizure may be increased.

Pregnancy

Pregnant women are advised to avoid travel to malarious areas.

Pregnant women have an increased risk of developing severe malaria and a higher risk of fatality compared to non-pregnant women.

If travel is unavoidable, the pregnant traveller must be informed of the risks which malaria presents and the risks and benefits of antimalarial chemoprophylaxis.

Diagnosis of falciparum malaria in pregnancy can be particularly difficult, as parasites may not be detectable in blood films due to sequestration in the placenta.

Expert advice is required at an early stage if malaria is suspected in a pregnant woman. Complications, including severe anaemia, hypoglycaemia, jaundice, renal failure, hyperpyrexia and pulmonary oedema, may ensue. The result may be miscarriage, premature delivery, maternal and/or neonatal death.

Congenital malaria is rare but occurs more commonly with *P. vivax* than with the other malaria parasites of humans.

Avoidance of mosquito bites is extremely important in pregnancy as pregnant women are particularly attractive to mosquitoes. Ideally, pregnant women should remain indoors between dusk and dawn. If they must be outdoors at night they should adhere rigorously to bite precautions (see Bite prevention).

DEET should be used in a concentration of not more than 50%. DEET has a good safety record in children and pregnancy (35) but ingestion should be avoided. Nursing mothers should wash repellents off their hands and breast skin prior to handling infants. See <u>Bite prevention</u> for further details on DEET.

Chloroquine

Safe in all trimesters of pregnancy. Its major disadvantage is the relatively poor protection it gives in many geographical areas due to the presence of drug-resistant *P. falciparum*.

Mefloquine

Caution in first trimester but can be used in all trimesters for travellers to high risk areas. It seems unlikely that mefloquine is associated with adverse foetal outcomes (86, 87, 85).

A review of the manufacturer's global drug safety database covering 1986 to 2010 showed that for mefloquine exposure in pregnancy, the birth defect prevalence and foetal loss in maternal, prospectively monitored cases were comparable to background rates (90).

The decision whether to advise mefloquine prophylaxis in pregnancy always requires a careful harm-benefit analysis. Where the levels of transmission and drug resistance (see country tables in Chemoprophylaxis) make mefloquine an agent of first choice, it is generally agreed that mefloquine may be advised in the second and third trimesters of pregnancy.

Given the potential severity of falciparum malaria in a pregnant woman, its use is also justified in the first trimester in areas of high risk of acquiring falciparum malaria such as sub-Saharan Africa (see <u>Information resources</u>).

Women who have taken mefloquine inadvertently just prior to or during the first trimester should be advised that this does not constitute an indication to terminate the pregnancy (91).

Doxycycline

Contraindicated in pregnancy. However, under special circumstances, if required before 15 weeks' gestation it should not be withheld if other options are unsuitable. The course of doxycycline, including the 4 weeks after travel, must be completed before 15 weeks' gestation.

Atovaquone/proguanil

Lack of evidence on safety in pregnancy. Animal studies showed no evidence for teratogenicity of the combination. The individual components have shown no effects on parturition or pre and post-natal development (Malarone SmPC).

A registry-based study of the inadvertent use of atovaquone-proguanil in weeks 3 to 8 after conception identified 149 pregnancies and found no significant association between exposure to atovaquone-proguanil in early pregnancy and the risk of a major birth defect (79).

An anonymous, internet-based survey to describe outcomes of pregnancies accidentally exposed to atovaquone-prognanil identified 10 who had atovaquone-prognanil exposure in the first trimester. All resulted in term births with no birth defects (92).

A study of 198 women who received atovaquone-proguanil in pregnancy or breastfeeding, 79.8% of them in the first trimester, did not show a specific signal to suggest a teratogenic effect, but numbers were too small confidently to determine safety of this combination in pregnancy (93).

A systematic review of the safety of atovaquone-proguanil for malaria prevention and treatment in pregnancy suggested that the rates of adverse events are not higher than the expected rates in similar populations (94).

A retrospective analysis of risk for adverse fetal and infant outcomes after atovaquone-proguanil exposure in pregnancy was unable to reach a definitive conclusion, but highlighted a clear need for further research (95).

ACMP does not currently advise the use of atovaquone/proguanil for antimalarial chemoprophylaxis in pregnancy due to sparse data. However, if there are no other appropriate options, its use may be considered in the second and third trimesters after careful risk assessment.

Folic acid 5mg daily should be taken for the length of time that atovaquone/proguanil is taken in pregnancy and also by those taking atovaquone/proguanil who are seeking to become pregnant.

Women who have taken atovaquone/proguanil inadvertently just prior to or during the first trimester should be advised that this does not constitute an indication to terminate the pregnancy.

For a useful recent review of malaria in the pregnant traveller (96).

Chemoprophylaxis prior to conception

If a female traveller is planning to conceive during a visit to a destination with a high risk of contracting chloroquine-resistant falciparum malaria, expert advice should be sought. Use of mefloquine may be considered after careful risk assessment.

Those travellers who plan to become pregnant after taking antimalarials and who wish to do so with minimal antimalarial drug present, may elect to observe the following time intervals after completing the course, before attempting to conceive:

- Mefloquine 3 months
- Doxycycline 1 week
- Atovaquone/proguanil 2 weeks

Breastfeeding

Mefloquine

Experience suggests safe to use during lactation.

Doxycycline

The British National Formulary states that tetracyclines should not be given to women who are breast feeding (63). A Centers for Disease Control Expert Meeting on malaria

chemoprophylaxis stated that doxycycline is excreted at low concentrations in breast milk and that the American Academy of Pediatrics assessed tetracycline as compatible with breast feeding (64). ACMP's view is that doxycycline should not be used in breast feeding unless there is no alternative agent and its use is felt to be essential.

Atovaquone/proguanil

Not recommended because of the absence of data however, can be used when breast-feeding if there is no suitable alternative antimalarial

Breast-feeding mothers should be advised to take the usual adult dose of antimalarial appropriate for the country to be visited.

The amount of medication in breast milk will not protect the infant from malaria. Therefore, the breastfeeding child needs his or her own prophylaxis. See <u>tables 3 to 5</u> for paediatric doses.

Anticoagulants

The coumarins, including warfarin

Travellers should ensure their INR (International Normalised Ratio) is stable and within the therapeutic range prior to departure and they have adequate supplies of their anticoagulant for the whole trip. Changes in diet and alcohol intake can affect the INR.

Patients on warfarin may have underlying cardiovascular disease and may be on cardiovascular medication. Interactions with other medication together with the individuals' medical history should be taken into account when deciding on appropriate malaria chemoprophylaxis.

Chloroquine

No interaction between warfarin and chloroquine documented in the BNF.

Mefloquine

Not considered to be a problem for those taking warfarin. The manufacturer states that: "although no drug interaction is known with anticoagulants, effects of mefloquine on travellers should be checked before departure." See below for how this can be monitored.

Doxycycline

The anticoagulant effect of coumarins (including warfarin) is possibly enhanced by tetracyclines (63).

Atovaquone/proguanil

Unknown whether there are interactions between atovaquone/proguanil and warfarin, although there has been an isolated report of an enhanced effect of warfarin when taken together with proguanil (97).

Advice for travellers needing malaria chemoprophylaxis who are taking warfarin

Travellers should inform their anticoagulant clinic and start taking their malaria tablets 2 to 3 weeks prior to their departure.

A baseline INR should be checked prior to starting chemoprophylaxis and re-checked after one week of taking chemoprophylaxis to determine whether the warfarin dosage needs to be adjusted. The traveller must check with their anticoagulant clinic to see if their INR is appropriate for travel. If a traveller is away for a long period of time the INR should be checked at intervals at the destination. However, the sensitivity of thromboplastin reagent used by some laboratories in different countries may vary (98). Self-monitoring of the INR may be suitable for some travellers, but must be under the supervision of an anticoagulant clinic (99). INR self-testing devices are readily available and can be used safely by experienced patients. Expert patients, defined as such by their anticoagulant clinic, can undertake self-management. Other patients may perform INR self-testing and stay in contact with their home anticoagulant clinic for dosage recommendations (99). Given modern communication methods it should be possible to keep-in touch from many malaria-endemic areas.

Once chemoprophylaxis has been completed, the INR should be checked again to re-stabilise anticoagulant therapy.

Direct oral anticoagulants (DOAC)

Dabigatran etexilate, rivaroxaban, apixaban and edoxaban are the most commonly available DOAC. They do not interact with food, do not require laboratory monitoring and have a lower potential for drug interactions than the coumarins (see below) (100).

There is relatively limited experience of antimalarial chemoprophylactic use by those taking DOAC.

Apixaban and rivaroxaban are substrates of CYP3A4 and p-glycoprotein. Dabigatran is a substrate of p-glycoprotein.

Mefloquine inhibits CYP3A4 and p-glycoprotein, so could increase DOAC plasma concentrations which might lead to an increased bleeding tendency (100).

Atovaquone may produce minor inhibition of CYP3A4. The effect of proguanil on this enzyme is unknown.

Neither atovaquone nor proguanil inhibits p-glycoprotein (100).

In addition to following this guideline, please consult the drug interactions section of the latest edition of the BNF. If doubt exists after taking these steps, seek expert advice from a haematologist.

Epilepsy

Note: A history of febrile convulsions only does **not** contraindicate use of any of the currently available malaria chemoprophylactic drugs. The following advice applies to travellers with epilepsy where restrictions **do** apply.

In epilepsy:

- doxycycline or atovaquone/proguanil can be used
- chloroquine is unsuitable
- mefloquine is unsuitable

Doxycycline

Half-life may be reduced by phenytoin, carbamazepine, and barbiturates. Try to advise another antimalarial. If not possible or acceptable to the traveller, increase the dose of doxycycline to 100mg twice daily and counsel regarding measures to minimise the risk of adverse events.

Glucose 6-phosphate dehydrogenase deficiency

Glucose 6-phosphate dehydrogenase (G6PD) is an enzyme that helps protect the red cell against oxidative damage. Absence of G6PD renders the red cell liable to haemolysis in the presence of some drugs.

All G6PD-deficient travellers to malarious areas should take appropriate chemoprophylaxis despite some protection against infection being conferred by the most common G6PD deficiency allele in Africa (G6PD A-) (101).

Chloroquine

Theoretical risk of haemolysis in some G6PD-deficient individuals. Haemolysis does not appear to be a problem when chloroquine is given in the dose recommended for malaria chemoprophylaxis so there is no need to withhold chloroquine prophylaxis from those known to be G6PD-deficient. This risk is acceptable in acute malaria (63) and G6PD levels are not usually checked before using chloroquine in treatment doses.

Atovaquone-proguanil, doxycycline, or mefloquine

There is no need to withhold any of these agents from those known to be G6PD-deficient.

Primaquine

Not currently recommended as a first line agent for malaria prevention in UK travellers, but may be considered in special circumstances on expert advice (48). There is a definite risk of

haemolysis in G6PD-deficient individuals. The traveller's G6PD level must be checked before primaquine is prescribed: G6PD deficiency contraindicates its use for prophylaxis.

Sickle cell disease and thalassaemia (102)

Presence of the sickle cell trait confers some protection against malaria, though individuals with the sickle cell trait still require antimalarial prophylaxis.

For those with homozygous sickle-cell disease, malaria is regarded as a significant cause of morbidity and mortality, producing further haemolysis against the background of that due to sickle cell disease itself. Therefore, it is essential that individuals with sickle cell disease travelling to malaria-endemic areas receive rigorous antimalarial protection.

Thalassaemia may provide protection against severe malaria, but there is currently no evidence it prevents uncomplicated malaria.

Immunocompromised travellers

Risks for transplant patients

A review on the prevention of infection in adult travellers after organ transplantation (103) recommended that ciclosporin levels should be monitored if chloroquine is co-administered.

Risks for those living with HIV

Co-infection with malaria and human immunodeficiency virus (HIV) increases both the severity and mortality rates of those diseases. Most reported studies of malaria and HIV co-infection have been done in those living in endemic areas where HIV infection increases the risks for contracting and developing severe malaria and increasing immunosuppression reduces treatment success (104) although this varies by area (105). A meta-analysis of the co-infection literature covering the years 1991 to 2018 showed a pooled prevalence of severe malaria of 43% in co-infected patients. The odds of severe malaria were significantly higher in HIV and malaria co-infected patients than in malaria mono-infected patients, and significantly higher in children than adults. Furthermore, parasite densities were higher in co-infected patients with severe malaria than those with malaria mono-infection (106). Twenty-eight of the 29 studies in that meta-analysis were conducted in malaria-endemic areas, but one was performed on imported malaria in France, also showing that severe malaria in those living with HIV was associated with decreased CD4 cell counts (107).

Mirzohreh and colleagues ($\underline{108}$) reported a systematic review and meta-analysis of malaria prevalence studies in children, pregnant women, and adults living with HIV conducted predominantly in Africa in the period 1983 to 2020. In adult patients living with HIV, CD4+ counts less than 200 cells per microlitre (μ I) were associated with a significant increase in the

odds of malaria infection, whilst antiretroviral therapy was associated with a significant decrease in the chance of malaria infection in adults living with HIV.

In pregnant women living with HIV, CD4+ count less than 200 cells/µI is related to a higher risk of malaria infection (108).

Co-infected pregnant women are at risk from higher parasite density, anaemia and malarial infection of the placenta and children born to women living with HIV and malaria infection have low birth weight and are more likely to die during infancy. Data on the effect of malaria during pregnancy on the risk of mother to child transmission of HIV in the pre-ART era were conflicting and have been limited since the widespread use of ART to prevent vertical transmission (109).

In almost all studies on co-infection with HIV, the malaria parasite has been *Plasmodium falciparum*, so data on the interaction with other malarias has been limited. A study from the Brazilian Amazon (110) stated that individuals living with HIV had a significantly greater chance of acquiring *Plasmodium vivax* malaria than those who were not. Given the widespread distribution of *P. vivax*, much more work is required to understand the interaction, especially as it has the capacity to produce hypnozoite-based relapses.

The recommended malaria chemoprophylactic agents are the same for those living with HIV and those who are not infected. Whilst co-trimoxazole has been shown to reduce malaria in adults living with HIV in Africa, it is not as effective as antimalarial chemoprophylactic drugs, so travellers living with HIV should not rely on co-trimoxazole alone for prophylaxis against malaria (109).

The main issue with antimalarial chemoprophylaxis in those living with HIV is the possibility of drug interaction with antiretroviral agents. HIV protease inhibitors (PIs) as well as the non-nucleoside reverse transcriptase inhibitors (NNRTIs) can either inhibit or induce the same liver enzymes which metabolise most drugs used for malaria prophylaxis and treatment. Potentially this could result in altered metabolism of some antimalarials, though the extent of this and the clinical significance is often unclear, as data is limited. Doxycycline is the simplest chemoprophylaxis against malaria for most people on antiretrovirals.

Nevertheless, the travel health advisers should check the manufacturer's summary of product characteristics and the BNF on an individual agent basis and should discuss and agree their recommendation for chemoprophylaxis with the traveller's own HIV physician.

Up-to-date information can also be obtained from the University of Liverpool site where it is possible to look up specific antiretroviral compounds against malaria prophylactic drugs in readily-accessible tables.

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However, information in this area is accumulating rapidly and the travel health adviser should check the manufacturer's SmPC and the BNF on an individual agent basis and should discuss and agree their recommendation for chemoprophylaxis with the traveller's own HIV physician.

Up-to-date information can also be obtained from the <u>University of Liverpool</u> site where it is possible to look up specific antiretroviral compounds against malaria prophylactic drugs in readily-accessible tables.

Liver disease

Most antimalarial drugs are excreted or metabolised by the liver. Thus, there is a risk of drug accumulation in severe liver impairment.

Severe liver disease

A CDC expert meeting concluded that the dose of doxycycline does not have to be adjusted in patients with impaired hepatic function since it is excreted as an inactive chelated product via a process of back diffusion in the small bowel (64). Note to prescribers: The BNF states that tetracyclines should be avoided or used with caution in patients with hepatic impairment. The manufacturer of atovaquone-proguanil combination preparation states that although no pharmacokinetic studies have been conducted in severe hepatic impairment, no special precautions or dosage adjustment are anticipated (SmPC).

Mefloquine is contraindicated in severe hepatic impairment (SmPC).

Moderate impairment

Doxycycline, or atovaquone-proguanil combination preparation, or mefloquine may be used.

Mild impairment

Chloroquine, or atovaquone-proguanil combination preparation, or mefloquine, or doxycycline may be used.

The choice of chemoprophylaxis should be made after discussion with the patient's specialist, who will be able to assess their degree of hepatic impairment.

The Child-Pugh classification is often used for grading liver function and can be found at the <u>Liverpool Medics</u> website or the <u>US Department of Veteran Affairs</u> website.

Renal impairment

Chloroquine is partially excreted via the kidneys.

Chloroquine

Dose reduction for prophylaxis is required only in severe renal impairment.

Atovaquone/proguanil

Not recommended for patients with an eGFR of less than 30mL/minute (63). Not to be used in patients receiving renal dialysis

Doxycycline or mefloquine

May be used in severe renal failure. There is no need to reduce the dose of mefloquine in renal dialysis (63).

Splenectomy

Those who have no spleen or whose splenic function is severely impaired are at particular risk of severe malaria and, where possible, should avoid travel to malarious areas.

If travel is essential, every effort should be made to avoid infection by rigorous use of antimosquito precautions and strict adherence to appropriate chemoprophyaxis, even in BA only malarious areas, apart from those areas regarded as very low to no malaria risk, where BA only would still apply. If the traveller becomes unwell during or after their visit, medical attention is required as a matter of urgency, as malarial parasitaemia in asplenic individuals may rise rapidly to very high levels (for example, greater than 50% with *P. falciparum*).

Acute porphyrias

Doxycycline is unsafe in porphyria (63) so should not be used for antimalarial chemoprophylaxis in patients with acute porphyria.

Special categories

Children

Children are at particular risk of severe and fatal malaria; therefore, parents are advised against taking infants and young children to malarious areas without adequate precautions.

If travel is unavoidable, infants and children should be well protected against mosquito bites and receive appropriate malaria chemoprophylaxis.

It is important that the child's carers understand the importance of trying to ensure that the child properly completes the full course of prophylactic medication.

Parents should supervise children's chemoprophylaxis, as some regimens can be difficult even for adults to follow.

Parents must be cautious not to exceed maximum recommended doses, since antimalarials can be particularly toxic to children.

Paediatric doses of antimalarials for prophylaxis are shown in <u>tables 3 to 5</u> in <u>Chemoprophylaxis</u>.

Chloroquine

Take care to ensure that tablets are swallowed, as they have a bitter taste. Sweetened chloroquine syrup is available. Store safely away from children since an overdose can be fatal.

Mefloquine

Problem in administering correct dosage because there is currently no suspension available and adult-dose tablets must be broken.

Doxycycline

Only licensed in the UK for children over the age of 12 years due to its potential to cause bone damage and discolouration of teeth. This age limit varies between countries; tablets or capsules should be swallowed whole and must not be crushed. Doxycycline is also available in the UK as 100mg dispersible tablets. See <u>Table 3</u> for paediatric dosage recommendations.

Atovaquone-proguanil combination preparation

Paediatric tablets are licensed in the UK for malaria prophylaxis in children from 11kg upwards. For children weighing less than 11kg, ACMP recommends a dosage regimen of:

- weight 5 to 7.9kg half a paediatric tablet daily
- weight 8 to 9.9kg three-quarters of a paediatric tablet daily

Whilst it is preferable to avoid breaking and crushing tablets, and in the absence of syrup preparations, the appropriate dose of mefloquine or atovaquone-proguanil combination preparation may be broken if dosing requires it and the drugs crushed if necessary and mixed with condensed milk, butter, oily spreads, full fat pasteurised yoghurt, jam, honey, or similar food to mask the bitter taste, to aid administration to young children.

Goodyer (personal communication) assessed the dosing accuracy obtained when cutting Malarone paediatric tablets. When carers or pharmacists were asked to cut tablets into quarters, the results suggested that only 25% of quarters would be within 10% of the expected weight. Furthermore, there was evidence of an uneven distribution of atovaquone through the tablet mass.

To minimise dose variation, when quarter tablets are required, each quarter from the same tablet should be taken on consecutive days; when half tablets are required, each half from the same tablet should be taken on consecutive days; and if the dose is three-quarters of a tablet, cutting 3 tablets into quarters in advance (total 12) and then giving 3 of the quarter tablets a day can provide 4 days' dosage and ensure that the correct dose is achieved as smoothly as practicable over that time period.

Tablet-cutters can be purchased from some pharmacies or travel shops. If further advice is required a pharmacist should be consulted.

Children with malaria may deteriorate very rapidly to become critically ill. Those looking after children on their return from malarious areas including: family members, friends, professional carers, or school nursing and medical staff should be made aware that such children need medical attention and a blood test for malaria without delay if they become unwell within a year of leaving a malarious area.

Healthcare professionals should strive to improve access to advice on malaria prevention for families with children, especially travellers <u>visiting friends and relatives</u> (111).

Elderly travellers

The elderly are at particular risk of dying from malaria once acquired (82). No reduction in antimalarial dosage is required on the basis of advanced age. However, elderly travellers are more likely to have underlying disorders, for example, renal impairment, which may necessitate antimalarial dose reduction. Furthermore, the increased likelihood of elderly travellers taking additional medication, for example, for cardiac conditions, will influence the choice of chemoprophylactic agent in their particular case.

Of concern, a recent systematic review of malaria prevention in the older traveller concluded that older travellers seem less likely to comply with bite-prevention measures (115). Given the good safety profile of such measures, every effort should be made to improve their uptake by elderly travellers.

As the UK population ages yet further, the number of individuals suffering from cognitive decline will increase. Travel health practitioners need to be aware of this possibility when conducting pre-travel malaria risk-assessments for the elderly. Much more work is needed in this area across the whole of travel medicine practice.

Multi-trip travel

Some travellers – for example, business persons or expatriate contract employees – may make several short visits to malarious areas in the same year. For instance, someone working in the tropics 4 weeks on, 4 weeks off, might be taking chemoprophylaxis for most or all the year when including the periods before and after travel that prophylaxis is required.

The strategy for chemoprophylaxis will then be mainly influenced by the level of malaria risk in the areas to be visited. For example, in the highly malarious regions of West Africa, the risk-benefit assessment is strongly in favour of taking chemoprophylaxis, even if it means year-round administration. For less frequent trips, the regions visited should determine the chemoprophylactic agents from which to choose.

When the choice lies between mefloquine or doxycycline or atovaquone-proguanil combination preparation and the traveller wishes tablet-free periods between visits, the shorter period of 7 days post exposure for atovaquone-proguanil combination preparation prophylaxis versus the alternatives may be helpful.

Cruises

All travellers on cruises should use insect bite avoidance measures.

Cruises are a growing part of the holiday market. Most travellers on cruises are only ashore during daylight hours when *Anopheles* bites rarely occur, and therefore do not require malaria chemoprophylaxis. However, the cruise itinerary must be reviewed carefully to determine the risk of exposure to malaria.

For example, cruises along the East African coast may include a stop for a night or more in the port of Mombasa in Kenya and passengers may be ashore or on deck after dusk. These itineraries will require malaria chemoprophylaxis.

In addition, cruises that have an overnight stay in any other malaria-endemic region of the world may require malaria chemoprophylaxis.

Oil rigs

Many staff are employed in the oil industry, predominantly based around West Africa. Employees commonly travel to these areas every 4 to 6 weeks, followed by a similar period of leave back in the UK. Oil rigs may be based in river estuaries or many miles offshore. Thus, the level of risk may be difficult to assess until one period of work has been completed, so antimalarial chemoprophylaxis should be taken for the whole of this first trip, by when the situation will be known, and then be reviewed for subsequent trips.

Antimalarial chemoprophylaxis is advised for workers on oil rigs based in river estuaries.

Offshore rigs pose little risk and antimalarial chemoprophylaxis may only be needed if staying overnight onshore during transit.

Visits to national parks

Travellers visiting countries where malaria is restricted in distribution may plan to make day trips to national parks in malarious regions of the country. They should be advised on awareness of risk, bite precautions and the need for prompt attention in the event of fever during the succeeding year. If they plan to stay overnight in the malarious area – for example, in a safari lodge – they should also take chemoprophylaxis.

Stopovers

Many stopovers are in urban or tourist areas (particularly in Asia) and have minimal malaria risk. They are often situated in countries which may have malaria transmission in parts. Therefore, to assess risk, it is essential to establish where overnight accommodation will be.

Stopovers after dark in most of sub-Saharan Africa, including main cities, present a risk of malaria and antimalarial prophylaxis should be recommended.

Stops to change or refuel aircraft do not usually require chemoprophylaxis, but it may be considered if the trip entails an overnight stop away from the airfield (assessed as above).

Last-minute travellers

Last-minute visits to malarious regions, whether for vacation, business or family reasons, are now commonplace. This may leave the traveller little time to seek and act on travel advice.

Maloff Protect, a brand of atovaquone plus proguanil combination preparation is available to purchase from pharmacies, whereas atovaquone plus proguanil was previously only available on prescription. Maloff Protect is available for adults aged over 18 weighing 40kg and above. Retail pharmacy outlets can also supply chloroquine as an over-the-counter antimalarial but there are very few geographical locations where it would provide protection, as well as antimosquito products.

Mefloquine and doxycycline and for those less than 18 years old, atovaquone-proguanil combination preparation, are currently prescription-only medicines (POMs), but some pharmacists are now prescribers and thus able to prescribe these POMs. Some retail pharmacy outlets also supply these POMs under PGDs.

If the traveller cannot obtain a GP appointment at short notice, some commercial travel clinics cater for walk-in attendees.

Doxycycline or atovaquone-proguanil combination preparation should be started 2 days before travel to a malarious area. Chloroquine one week before, and mefloquine 2 to 3 weeks before (to ensure tolerance).

Nevertheless, it is better to start chemoprophylaxis late than not to take it at all, as suppressive prophylactics will begin to work by the end of the malaria incubation period.

Where the recommended choice for the region to be visited is mefloquine or doxycycline or atovaquone-proguanil combination preparation, it would be sensible to avoid mefloquine for last-minute prophylaxis as it takes time to reach steady state, and especially if the traveller has not taken and tolerated mefloquine in the past.

ACMP does not recommend loading doses of any prophylactic antimalarial. The dosages recommended in these guidelines should be followed.

Visiting friends and relatives

See Visiting friends and relatives abroad: health advice.

(Adapted from the HPA Migrant Health Report 2006 (<u>113</u>) updated 2011 (<u>114</u>). See also the Office for Health Improvement and Disparities Migrant Health Guide (<u>115</u>))

In the UK, malaria predominantly affects the non-UK born population and their families, particularly those from Africa and south Asia, largely due to their high rates of travel to malarious areas. Much greater effort is needed to convey health prevention advice to this key group. Data suggest that people visiting friends and relatives (VFR travellers) are significantly less likely to take antimalarial prophylaxis than other travellers to Africa. Reasons for this may be that those visiting friends and relatives in Africa substantially underestimate the risk of acquiring malaria and overestimate the amount of protection that having been brought up in Africa may give them.

Awareness needs to be raised that malaria is not a trivial disease. Those born in malarious countries need to be aware that any immunity they may have acquired is rapidly lost after migration to the UK. The view that this group is relatively protected is a dangerous myth.

Migrants from malarious areas also need to be made aware that second-generation members of their families have no clinically relevant immunity to malaria, and that their children are particularly vulnerable.

Effective chemoprophylaxis taken correctly reduces the risk of malaria by around 90%, especially if combined with sleeping under insecticide-treated nets.

Appropriately tailored health information should be targeted to migrant communities, especially of African descent, to stress the importance of chemoprophylaxis. Community-based participatory work can identify barriers to malaria prevention in VFR travellers and help implement suitable interventions (116). Health advisers for this group, including primary care practitioners working in areas with large numbers of migrants, can have a major role to play via opportunistic discussions during visits to the practice undertaken for other reasons

Those who feel unwell following any trip to tropical areas should be encouraged to present to their doctors early, and to inform the doctors that they are at risk of malaria. Patients of African origin, and occasionally doctors, can underestimate the severity of malaria in this group.

Students and children at boarding school

Many people from malaria-endemic areas come to the UK for secondary or higher education.

Those who stay in Britain for a year or more will lose a significant degree of any malarial immunity they had acquired and become more susceptible to clinical malaria. When they return home, they should be advised as for the section The long-term traveller to the UK returning to live in malarious parts of the world

Those who are making short visits home (for example, in school or college vacations) should be considered as VFR travellers and should be advised to use chemoprophylaxis in addition to personal protective measures against mosquito bites.

Students may become infected during their school or college vacations, but the first symptoms of clinical malaria may occur in term time whilst they are in the UK. Therefore, it is essential that school and/or college nursing and medical staff consider malaria from the outset in any pupil from, or with a history of travel to, a malarious region and arrange a blood test for malaria without delay.

Adherence to antimalarial chemoprophylaxis is reported as poor in children who return home to malarious areas. This may be due to a lack of understanding that children who reside in the UK are at increased risk of acquiring malaria when they return home to malarious areas, compared to those who live there permanently.

Provision of specific written instruction and advice for the parents may be helpful and could include the following:

- children who reside in the UK lose natural immunity to malaria and are at increased risk of acquiring malaria compared to those who live permanently in malarious areas
- antimalarial chemoprophylaxis is recommended for children in UK boarding schools in accordance with UK ACMP guidance
- where chemoprophylaxis is taken correctly, along with all other malaria prevention measures, the risk of a child acquiring malaria will be significantly reduced
- parents should support advice given to children in the UK and should encourage adherence to the recommended antimalarial chemoprophylaxis
- where possible, the course of tablets supplied in the UK should be completed and not substituted with different tablets at the destination
- where tablets provided in the UK must be replaced with different tablets at the
 destination (for example, if they are lost or side effects occur) information on the
 replacement medication should be supplied to the nurse in writing when the child
 returns to the UK. This is important especially if the child becomes unwell after return
 and requires treatment with other medication

The long-term traveller

Risk assessment

The long-term traveller is defined here as those travelling through or visiting malaria-endemic countries for over 6 months.

One major problem for the long-term traveller is the variable access to and quality of medical care available overseas (117). The provision of details of healthcare facilities or points of information could be crucial.

The main issues influencing the choice of malaria chemoprophylaxis on a long-term basis are the same as for short-term use, that is malaria risk, adverse events profile, compliance and efficacy. However, the licensing criteria for antimalarial drugs often restrict the recommended periods of administration (usually due to a lack of formal trials of long-term administration, rather than from evidence of adverse effects). This leads to uncertainly about the safety of long-term prescribing.

A decision on whether chemoprophylaxis is continued on a long-term basis may be influenced by the overall length of stay, seasonal risk in the area, and access to medical facilities.

Travellers living or backpacking in rural areas may be far from appropriate medical attention and the need for standby emergency medication should also be considered. The continued use of chemoprophylaxis will also depend on current personal health, current medication, previous medical history and relevant family medical history. However, long-term travellers are at high risk from malaria, and should not neglect necessary prophylaxis.

Health risks for the long-term traveller will vary considerably, depending in part on the reasons for travel including:

Visiting friends and relatives (VFR)

Individuals who originate from countries where malaria is transmitted, but who have settled in the UK. They may later visit their country of origin and remain there for long periods of time while working or visiting friends and relatives. They may perceive little risk from malaria infection or believe they are immune. This is not true (see the section on <u>Visiting friends and relatives</u>).

Expatriates

Usually based at a single location where the risk of malaria is known, they often have access to medical care, a good standard of accommodation and are usually more aware of the malaria risks. However, up to 30% of some expatriates develop malaria within 2 years and many cases can be attributed to poor adherence to prophylaxis (118).

Backpackers

Often younger than expatriates, they may be less careful of their personal safety and less adherent to medical advice, in addition to having less experience of overseas travel in general. They have less control over their environment as they are constantly moving on.

Chemoprophylaxis for long-term travellers

Adverse events

The cumulative risk of contracting malaria is roughly proportional to the length of stay in a malarious area over the first few months. A 3-month visit carries a risk around 6 times greater than a visit of 2 weeks.

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 (see <u>Figure 3</u>). Thus, chemoprophylaxis in highly malarious areas is even more important for long-term visitors than it is for short-term travellers. Indeed, long-term travellers may wish to consider using malaria prophylaxis, or have standby medication, when short-term travellers might not, because of their sustained exposure to a small risk of infection.

Adherence to chemoprophylaxis

Compliance has been shown to decrease with the duration of travel (<u>119</u>), except where military-style discipline tends to support adherence. There is also evidence of weekly regimens having increased adherence over daily regimens (<u>119</u>). Long-term adherence decreases for both daily and weekly prophylactic regimens (<u>64</u>).

Possible reasons for reduced compliance in long-term travellers may include:

- fear of long-term side effects
- actual adverse events on one or more regimens

- conflicting advice
- complex regimen or daily tablets
- reduced confidence if intercurrent fever misdiagnosed as malaria
- perception from anecdotal evidence that chemoprophylaxis is unnecessary (<u>120</u>)

In addition, long-term travellers may overlook personal protective measures against mosquitoes (121).

Number of adverse events and of Malaria risk Fewer new events of adverse events and risk of malaria

Most new events

Figure 3. Cumulative risk of adverse events and malaria

Efficacy of regimens

It is important to stress that no chemoprophylactic regimen is 100% effective and that antimosquito measures should also be used. Travellers should be encouraged to continue chemoprophylaxis despite suffering what they believe to be a malarial illness. Many febrile episodes in long-term travellers or expatriates are incorrectly diagnosed as malaria.

Time

Licensing restrictions

The specific problem relating to prophylaxis advice for long-term travellers is that long-term use of some of the currently advised antimalarial drugs falls outside the terms of their current Marketing Authorisation (Licence). Approaches in response to this time limit are:

- switching from one chemoprophylactic regimen to another as the time limit is reached
- discontinuing prophylaxis in favour of access to local advice and standby or physicianquided treatment
- continuing with one prophylactic regimen beyond its licensed length of use

General advice for all regimens

Once an individual is compliant on one prophylactic regimen and is tolerating it well, transfer to another regimen increases the likelihood of the development of side effects due to the introduction of a different drug.

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, see below.

Evidence for safety in long-term use comes more from an accumulating lack of evidence of harm than from scientific evidence of safety.

Individual risk assessments are important when deciding what advice should be given. In particular, advice on prophylaxis may be influenced by other measures that might be used by those staying in areas where the risk is seasonally variable.

Simplicity in regimen can, as always, be expected to improve adherence. The safest option is compliance with one of the most effective regimens.

Minimising exposure to infection is important, especially taking precautions against being bitten while asleep.

It is essential to seek medical advice promptly if symptoms develop.

ACMP advice on long-term use of specific antimalarials is summarised in <u>Table 8</u>.

Specific considerations for pregnant and breastfeeding women See section on pregnancy and breastfeeding in <u>Special groups (medical conditions)</u>, which includes advice on chemoprophylaxis prior to conception.

Specific considerations for infants and older children

Refer to the section on Children, above.

Evidence in support of long-term use of antimalarials in infants and older children is limited. Advice for long-term use in these age groups is the same as for adults.

Chloroquine

Safe for both infants and young children.

Mefloquine

Well tolerated (<u>13</u>). Long-term use of mefloquine is reported to be safe, well tolerated and not associated with an increase in adverse effects (<u>124</u>, <u>125</u>, <u>126</u>).

Doxycycline

Not for use in those under 12 years of age. No data available on the long-term use of doxycycline. However, long-term use of other tetracyclines for other indications is generally well tolerated (127).

Atovaquone-proguanil combination preparation

Both agents highly effective and safe (72).

Long-term visitors to the UK returning to live in malarious parts of the world

Persons returning to their original homes in malarious regions after prolonged residence in the UK are likely to have suffered a decline in the partial immunity to malaria that develops during childhood and is maintained by repeated exposure in endemic regions. They may therefore be at increased risk of suffering an acute attack of malaria after returning home.

Pregnant women and small children are at higher risk than others of suffering severe disease.

Risk assessment and personal counselling is essential to warn individuals of the risk of suffering from malaria, emphasising avoidance measures, and the need for immediate diagnosis and treatment of acute feverish illnesses.

Preventive measures appropriate to an endemic setting (128)

Bed nets

Bed nets and other personal barrier protective measures (for example, suitable clothing) are very low-cost, are effective long-term, have virtually no side effects and will also help to protect from other mosquito-borne infections.

Intermittent Preventive Therapy (IPT)

If IPT is local policy in their destination country to prevent malaria in pregnancy and childhood, the returning visitor should be advised to seek medical advice on this immediately on arrival.

Case management of illness

People should be advised to seek medical attention immediately if either they or their children become feverish after repatriation in the endemic country. They should be warned that a malaria attack may be more serious because of diminished immunity.

Guidance

See the WHO and/or national country guidance on the appropriate measures in endemic settings which include IPT, insecticide-treated bed nets and case-management of illness with drug therapy.

Prophylaxis

Intended use

The ACMP prophylaxis guidance is for temporary protection for the UK traveller. This is not appropriate for individuals who are returning to permanent residence in their country of origin.

Exception for pregnant women and young children

A limited period of prophylaxis of 4 to 6 weeks for pregnant women and young children may be appropriate in some circumstances, to allow them to settle and arrange for future healthcare after arrival in the endemic country.

Standby treatment

Offering standby treatment is inappropriate where there are likely to be health services able to diagnose and manage malaria.

Table 8. Long-term chemoprophylaxis for adults

Malaria chemoprophylaxis	ACMP advice on long-term use
Chloroquine	Considered safe for long-term use. ⁵ Consider ophthalmic examination for retinopathy 6 to 12 monthly, commencing at 6 years' cumulative prophylactic usage.
Mefloquine	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 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.
Doxycycline	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.
Atovaquone/Proguanil	No evidence of harm in long-term use. Can be used confidently for travel up to one year. Longer term use possible if justified by the risk of exposure to malaria.

Table 9. Half-lives of selected antimalarial drugs

Drug	Half-life	
Chloroquine	Can extend from 6 to 60 days	
Mefloquine	2 to 3 weeks	
Doxycycline	12 to 24 hours	
Atovaquone	2 to 3 days	

⁵ Considered safe for long-term use but considerable concern regarding level of protective efficacy of chloroquine in the geographical areas where the regimen used to be useful.

Frequently asked questions

Malaria prevention advice for travellers going on cruises

Cruises are a significant part of the holiday market. Most travellers on cruises are only ashore during daylight hours when the *Anopheles* vector of malaria is not feeding, and therefore do not require malaria chemoprophylaxis. Occasionally this is not the case and therefore the cruise itinerary must be reviewed to determine if there will be exposure to malaria.

For example, cruises along the East African coast may include a stop for a night or more in the port of Mombasa, Kenya and passengers may be ashore or on deck after dusk. These itineraries will require malaria chemoprophylaxis.

In addition, cruises that have an overnight stay in any other malaria-endemic region of the world may require malaria chemoprophylaxis. Risks in specific destinations can be determined by referring to the country table in Chemoprophylaxis. Based on the destination, duration of exposure, and health of the traveller, the choice of malaria chemoprophylaxis can be made using the advice in these guidelines. All travellers on cruises should use insect bite avoidance measures (see Bite prevention).

'Once you get malaria, it keeps coming back'

Hypnozoite-induced relapses occur in vivax and ovale malaria but can be treated successfully and further relapses prevented. If the patient has received a full course of treatment with modern antimalarial drugs and has not been re-exposed to malaria, it is extremely unlikely that a history of recurrent febrile illness over a number of years is the result of chronic malaria.

Which antimalarial to give to a traveller with a history of psoriasis

Atovaquone/proguanil, doxycycline and mefloquine do not cause problems in those with psoriasis. Chloroquine and chloroquine-related drugs can exacerbate psoriasis and should be avoided in those with generalised psoriasis or a history of such. Travellers with mild psoriasis can consider chloroquine if they are aware of the possible risks. The benefit of chemoprophylaxis with chloroquine may outweigh the risk of exacerbation of psoriasis, but each case should be considered on an individual basis. However, chloroquine chemoprophylaxis is now appropriate in only a few geographical areas.

Which antimalarial to give a traveller who is taking anticoagulants

The coumarins, including warfarin

Travellers should ensure their INR (International Normalised Ratio) is stable and within the therapeutic range prior to departure and they have adequate supplies of their anticoagulant for the whole trip.

Changes in diet and alcohol intake can affect the INR.

Patients on warfarin may have underlying cardiovascular disease and may be on cardiovascular medication. Interactions with other medication together with the individuals' medical history should be taken into account when deciding on appropriate malaria chemoprophylaxis:

Chloroquine

No interaction between warfarin and chloroquine documented in the BNF.

Mefloquine

Not considered to be a problem for those taking warfarin. The manufacturer states that 'although no drug interaction is known with anticoagulants, effects of mefloquine on travellers should be checked before departure.' Please see below for how this can be monitored.

Doxycycline

The anticoagulant effect of coumarins (including warfarin) is possibly enhanced by tetracyclines (63).

Atovaquone/proguanil

Unknown whether there are interactions between atovaquone/proguanil and warfarin, although there have been isolated reports of an enhanced effect of warfarin when taken together with proguanil, a component of this combination preparation (97).

Advice for travellers needing malaria chemoprophylaxis who are taking warfarin

Travellers should inform their anticoagulant clinic and start taking their malaria tablets 2 to 3 weeks prior to their departure.

A baseline INR should be checked prior to starting chemoprophylaxis and re-checked after one week of taking chemoprophylaxis to determine whether the warfarin dosage needs to be adjusted. The traveller must check with their anticoagulant clinic to see if their INR is appropriate for travel. If a traveller is away for a long period of time the INR should be checked at intervals at the destination. However, the sensitivity of thromboplastin reagent used by some laboratories in different countries may vary (98). Self-monitoring of the INR may be suitable for some travellers, but must be under the supervision of an anticoagulant clinic, see Ringwald and others (99). INR self-testing devices are readily available and can be used safely by experienced patients. Expert patients, defined as such by their anticoagulant clinic, can undertake self- management. Other patients may perform INR self-testing and stay in contact with their home anticoagulant clinic for dosage recommendations (99). Given modern communication methods it should be possible to keep-in touch from many malaria-endemic areas.

Once chemoprophylaxis has been completed, the INR should be checked again to re-stabilise anticoagulant therapy.

Direct oral anticoagulants (DOAC)

Dabigatran etexilate, rivaroxaban, apixaban and edoxaban are the most commonly available DOAC. They do not interact with food, do not require laboratory monitoring and have a lower potential for drug interactions than the coumarins (see below) (100).

There is relatively limited experience of antimalarial chemoprophylactic use by those taking DOAC.

Apixaban and rivaroxaban are substrates of CYP3A4 and p-glycoprotein. Dabigatran is a substrate of p-glycoprotein.

Mefloquine inhibits CYP3A4 and p-glycoprotein, so could increase DOAC plasma concentrations which might lead to an increased bleeding tendency (100).

Atovaquone may produce minor inhibition of CYP3A4. The effect of proguanil on this enzyme is unknown.

Neither atovaquone nor proguanil inhibits p-glycoprotein (100).

In addition to following this guideline, please consult the drug interactions section of the latest edition of the BNF. If doubt exists after taking these steps, seek expert advice from a haematologist.

How long a traveller can take different antimalarial drugs

Guidelines for the long-term traveller are summarised in <u>Special categories</u>. Further detail is available in reference (<u>129</u>).

The main issues influencing the choice of malaria chemoprophylaxis on a long-term basis are the same as for short-term, that is adverse event profile, ease of compliance and efficacy. However, the specific issue relating to advice on chemoprophylaxis for the long-term traveller relates to current licensing restrictions. Long-term use of malaria chemoprophylaxis outside licensing restrictions is based on the cumulative evidence of lack of harm rather than positive evidence of safety. This situation is unlikely to change.

Chloroquine

Chloroquine has been taken safely for periods of many years at doses used for malaria chemoprophylaxis. However, there has been concern expressed about the possible development of retinal toxicity with long-term use of chloroquine (or hydroxychloroquine, often used to treat rheumatological disorders). Retinal toxicity has been described in those on daily chloroquine dosage for rheumatic disorders. As a result, 2 thresholds for the risk of retinopathy have been suggested, which are:

- a total cumulative dose of 100g of chloroquine base
- a daily dose of 250mg base (4mg/kg) (<u>130</u>)

The first threshold would require an adult to take chloroquine continuously, weekly, for a period of 6 years. The second threshold is far more than the prophylactic dosage. It has been concluded that the risk of retinopathy from prophylactic dosage alone is negligible (49). Further reassurance can be gained from the fact that retinopathy has only rarely been reported in patients taking weekly prophylactic dosages (130, 131).

ACMP advice suggests that chloroquine can be taken on a long-term basis. However, physicians should consider an ophthalmological examination every 6 to 12 months, beginning at 6 years' cumulative use for those on long-term chloroquine.

Mefloquine

There are few data on the use of mefloquine for periods exceeding 2 years, although there is no evidence of cumulative toxicity, and mefloquine taken for over one year is well tolerated. The SmPC states the maximum recommended duration of administration of mefloquine is 12 months. However, advice from the ACMP indicates that there is no evidence of harm in long-term use if the drug is tolerated in the short term and suggests that mefloquine can be used safely for up to 3 years and beyond in the absence of significant side effects.

Doxycycline

The ACMP have concluded that there is no evidence of harm in long-term use of doxycycline and it may be taken safely for periods of at least up to 2 years and beyond in the absence of significant side effects. Longer term use possible if justified by the risk of exposure to malaria.

Atovaquone/proguanil

Both components of this combination preparation have been used individually on a long-term basis, although there is little experience of long-term use of the combination.

In a study of 154 travellers, 50% travelled for between 9 and 34 weeks with no excess of adverse effects and no appearance of unexpected adverse effects (132). The ACMP concludes that there is no evidence of harm in long-term use and suggests that it can be taken confidently for travel up to one year and beyond in the absence of significant side effects.

Antimalarial drugs which are suitable for women during pregnancy

Malaria during pregnancy is a serious illness for both the mother and the fetus. Pregnant women should be advised against travel to an area with malaria, particularly if there is chloroquine-resistant *P. falciparum*.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy (SmPC).

The <u>UK National Teratology Information Service</u> states that doxycycline is best avoided for antimalarial prophylaxis during pregnancy. However, if required before 15 weeks' gestation it should not be withheld if other options are unsuitable. The course of doxycycline, including the 4 weeks after travel, must be completed before 15 weeks' gestation.

The safety of atovaquone and proguanil hydrochloride when administered concurrently for use in human pregnancy has not been established and the potential risk is unknown. Animal studies showed no evidence for teratogenicity of the combination. The individual components have shown no adverse effects on parturition or pre- and post-natal development (SmPC).

ACMP advises against the use of atovaquone/proguanil for antimalarial chemoprophylaxis in pregnancy. However, if there are no other options, its use may be considered in the second and third trimesters after careful risk assessment. Folic acid 5mg daily is required for the length of time that proguanil is taken in pregnancy and also by those taking proguanil who are seeking to become pregnant. A registry-based study of the inadvertent use of atovaquone-proguanil in weeks 3 to 8 after conception identified 149 pregnancies and found no significant association between exposure to atovaquone-proguanil in early pregnancy and the risk of a major birth defect (79). An anonymous, internet-based survey to describe outcomes of pregnancies accidentally exposed to atovaquone-proguanil identified 10 who had atovaquone-proguanil exposure in the first trimester. All resulted in term births with no birth defects (92). Women should be reassured that taking atovaquone-proguanil combination preparation inadvertently prior to or during the first trimester is not an indication to terminate a pregnancy.

The data available from studies on the prophylactic use of mefloquine in pregnancy are generally reassuring. Mefloquine can be offered to pregnant women during the second and third trimesters and in the first trimester where travel to a high-risk area for *P. falciparum* is unavoidable. The risk of adverse effects of mefloquine use in pregnancy should be balanced against the risk of contracting malaria and the complications that can result. The decision on whether to recommend mefloquine should be carefully discussed with the traveller.

Women should be reassured that taking mefloquine inadvertently prior to or during the first trimester is not an indication to terminate a pregnancy. Chloroquine has been taken safely during pregnancy for many years although it offers insufficient protection in areas with chloroquine-resistant *P. falciparum*.

Antimalarial drugs which can be taken by women breastfeeding

Chloroquine can be used during breastfeeding. However, it provides suboptimal protection for the mother in areas of chloroquine-resistant *P. falciparum* malaria and should not be used except in the very rare areas where it is known to be effective.

Although mefloquine is excreted in breast milk in small amounts experience suggests that it is safe to use in breast feeding.

The small amounts of antimalarials that pass into breast milk are not enough to protect the baby. Breastfeeding infants therefore need to take their own prophylaxis. If both mother and infant are taking mefloquine there is a possible concern that the amount of mefloquine the infant may receive will exceed the recommended maximum, particularly in infants in the lower weight range. However, this possible effect is likely to be short lasting as the weight of the child increases and the contribution of mefloquine in breast milk to the total prophylactic dose becomes relatively small.

Atovaquone/proguanil should generally be avoided in breast feeding, but ACMP advises that atovaquone/proguanil can be used when breast-feeding if there is no suitable alternative antimalarial.

The BNF states that tetracyclines should not be given to women who are breast feeding. Doxycycline is excreted in low concentrations in breast milk and is noted to be compatible with breast feeding by the American Academy of Pediatrics (64).

Antimalarial drugs which can be given to babies and young children

Chloroquine can be given from birth and is available as syrup.

Mefloquine can be given to infants weighing 5kg or more (see summary of product characteristics). Atovaquone/proguanil can be given to infants weighing 5kg or more. Paediatric tablets are available.

Doxycycline is unsuitable for children under 12 years.

One of the main challenges in giving malaria tablets to babies and young children will be the practical aspects of administration.

All dosages for malaria chemoprophylaxis in children are found in Tables $\underline{4}$, $\underline{5}$ and $\underline{6}$, and in the British National Formulary for Children (BNFC). The dose for children will be dependent on the weight and age of the infant or child. Weight is a better guide than age.

Mosquito bite avoidance is extremely important for this age group.

The easiest way to calculate the correct dose of chloroquine for babies and young children

The dose steps for chloroquine syrup are not the same as for chloroquine tablets and a child may be prescribed a different dose of chloroquine depending on whether they take tablets or syrup (see <u>Table 3</u> and <u>Table 4</u>). The main reason for any differences is due to the different amount of chloroquine base within the syrup and the tablets. The chloroquine syrup formulation contains 50mg chloroquine base/5mls syrup. The amount of chloroquine base contained within the tablets is 155mg.

The ACMP guidelines and BNFC dosages should be used.

While there is an optimum dose of chloroquine base for children of every weight, the final dosage given to the child will depend, in part, on the practicality of administering the formulation of chloroquine available (that is either tablet or syrup). For example, when dividing tablets for children, it is not possible to break a tablet into thirds, so the dosages will involve either a half or a quarter of a tablet.

The tables in <u>Chemoprophylaxis</u> have been calculated based on weight and surface area and the most accurate dose according to the weight is recommended. Although differences occur, all recommended dosages in the tables fall within accepted limits of toxicity. It is important not to overdose children with chloroquine as severe toxicity can occur.

A practical approach when calculating children's dosages for chloroquine is to decide on the most appropriate preparation (either tablet or syrup) for the child and calculate the dose appropriate to that preparation, according to <u>tables 3 to 5</u>.

Weight is a better guide than age for children, so they should be weighed for dosage calculation.

Antimalarial drugs for a traveller who has epilepsy

Both chloroquine and mefloquine are unsuitable for those with epilepsy. For areas with a high risk of chloroquine-resistant P. falciparum, doxycycline or atovaquone-proguanil can be used. However, for children under the age of 12 the only suitable antimalarial under these circumstances will be atovaquone-proguanil combination preparation.

Doxycycline half-life is reduced by phenytoin, carbamazepine, and barbiturates. Try to advise another antimalarial. If not possible or acceptable to the traveller, increase the dose of doxycycline to 100mg twice daily and counsel regarding measures to minimise the risk of adverse events.

Advice for a traveller with glucose 6- phosphate dehydrogenase deficiency

Glucose 6-phosphate dehydrogenase (G6PD) is an enzyme in the hexose monophosphate shunt of the glycolytic pathway. This shunt supports the red cell's protection against oxidative damage. Absence of G6PD renders the red cell liable to haemolysis in the presence of some drugs.

The most common G6PD deficiency allele in Africa (G6PD A-) has been shown to confer some resistance to malaria in both hemizygous males and heterozygous females (101). Nevertheless, all G6PD-deficient travellers to malarious areas still require appropriate chemoprophylaxis.

Chloroquine

There is a theoretical risk of haemolysis in some G6PD-deficient individuals who receive chloroquine. This risk is acceptable in acute malaria (63) and G6PD levels are not usually checked before using chloroquine in treatment doses. Haemolysis does not appear to be a problem when chloroquine is given in the dose recommended for malaria chemoprophylaxis, so there is no need to withhold chloroquine prophylaxis from those known to be G6PD-deficient.

Atovaquone-proguanil, doxycycline, or mefloquine prophylaxis

There is no need to withhold any of these agents from those known to be G6PD-deficient.

Primaquine

This drug is not currently recommended as a first line agent for malaria prevention in UK travellers, but may be considered in special circumstances on expert advice (48). There is a definite risk of haemolysis in G6PD-deficient individuals. The traveller's G6PD level must be checked before primaquine is prescribed and G6PD deficiency contraindicates its use for prophylaxis.

Advice for people working on oil rigs

There are many staff employed in the oil industry predominantly based around West Africa. Employees commonly travel to these areas every 4 to 6 weeks, followed by a similar period of leave back in the UK. Oil rigs may be based in river estuaries or many miles offshore. Therefore, the level of risk may be difficult to assess until one period of work has been completed and antimalarial chemoprophylaxis should be taken for the whole of this first trip.

Antimalarial chemoprophylaxis is advised for those workers on oil rigs based in river estuaries. Offshore rigs pose little risk and antimalarial chemoprophylaxis may only be needed if staying overnight onshore during transit.

Advice for the traveller on a stopover

Many stopovers are in urban or tourist areas (particularly in Asia) and have minimal malaria risk. They are often situated in countries which may have malaria transmission in parts. Therefore, to assess risk it is essential to establish where overnight accommodation will be.

Stopovers in most of sub-Saharan Africa, including main cities, present a risk of malaria and antimalarial prophylaxis should be recommended. Stops to change or refuel aircraft do not usually require chemoprophylaxis, but it may be considered if the trip entails an overnight stop away from the airfield (assessed as above).

Doxycycline's affect on oral contraception

Doxycycline is a non-enzyme-inducing antibiotic. The <u>Faculty of Sexual and Reproductive</u> Healthcare and the BNF advise that for combined oral contraceptives and for progestogen only

oral contraceptives, additional precautions are not required when using non enzyme-inducing antibiotics. However, if the traveller suffers vomiting or diarrhoea, the usual additional precautions relating to these conditions should be observed.

Advice for travellers who discontinue chemoprophylaxis on or after return to the UK due to drug side effects; or who lost their supply; or whose trip has been extended beyond their supply of antimalarials

Atovaquone-proguanil combination preparation

If atovaquone-proguanil is discontinued before completing 7 days' dosage post-return, no additional prophylactic drug need be recommended but the traveller must be warned of the increased risk of malaria compared with those who take the full dosage regimen. Increased vigilance is required and if the traveller becomes unwell in the first year after return, a blood test for malaria should be obtained without delay.

Suppressive prophylaxis (chloroquine, doxycycline, mefloquine)

If suppressive prophylaxis is discontinued before completing 4 weeks' dosage post-return, no additional prophylactic drug need be recommended, but the traveller must be warned of the increased risk of malaria compared with those who take the full dosage regimen. Increased vigilance is required and if the traveller becomes unwell in the first year after return, a blood test for malaria should be obtained without delay.

Information resources

Expert centres

Prophylaxis advice

National Travel Health Network and Centre (NaTHNaC)

Advice line for healthcare professionals: 0845 602 6712

Malaria Reference Laboratory (MRL)

Download a malaria risk assessment form and email the form to phe.malproph@nhs.net

TRAVAX (Public Health Scotland)

Advice line for healthcare professionals: 0141 300 1130

Diagnostic advice

Malaria Reference Laboratory (MRL)

Diagnostic advice for healthcare professionals: 020 7927 2427

The Hospital for Tropical Diseases (HTD)

The Liverpool School of Tropical Medicine (LSTM)

Treatment advice

The treatment of malaria is outside the scope of this document and is addressed in the <u>ACMP</u> malaria treatment guidelines.

Expert advice on malaria treatment may be obtained from:

Hospital for Tropical Diseases (HTD)

Requests for emergency admission or very urgent clinic attendance should be made to the duty doctor, who is contacted via switchboard. Call 0845 155 5000 and ask for the duty doctor for tropical medicine.

Liverpool School of Tropical Medicine (LSTM)

Advice line for healthcare professionals: 0151 705 3100 Monday to Friday 9 am to 5pm. Via Royal Liverpool Hospital switchboard at all other times: 0151 706 2000.

Your local infectious diseases unit.

Useful websites

- British National Formulary (BNF)
- BNF for children app
- British Infection Association (BIA)
- Department of Health
- Electronic Medicines Compendium (for Summaries of Product Characteristics)
- Liverpool School of Tropical Medicine (LSTM)
- London School of Hygiene and Tropical Medicine (LSHTM)
- Malaria Reference Laboratory (MRL)
- Medicines and Healthcare products Regulatory Agency (MHRA)
- National Travel Health Network and Centre (NaTHNaC)
- UK Health Security Agency Malaria: guidance, data and analysis
- Royal Society of Tropical Medicine and Hygiene (RSTM&H)
- TRAVAX (Public Health Scotland)
- WHO International Travel and Health

Information leaflets

- UKHSA. Mosquito bite avoidance: advice for travellers
- UKHSA. Visiting friends and relatives abroad: health advice

Appendices

Appendix 1a. Terms of reference 2023

Background

The Advisory Committee on Malaria Prevention (ACMP) was established in 1998 to formulate guidelines on malaria prevention in the UK. The guidelines are used by medical professionals and other travel medicine advisors based in the UK and many other countries. The guidelines are also the basis for recommendations from the National Travel Health Network and Centre (NaTHNaC). Today, the ACMP is overseen by UKHSA.

Purpose

To provide guidelines for health professionals on the prevention of malaria for travellers from the UK, updated annually or soon as there is a significant change in the distribution or behaviour of malaria, or the need to consider new advice on drugs and anti-insect measures. The Advisory Committee on Malaria Prevention will do this in light of data from the UKHSA Malaria Reference Laboratory, London (MRL), the Medicines and Healthcare Products Regulatory Agency (MHRA), World Health Organization Global Malaria Programme and other sources by:

- assessing new information on methods of malaria prevention for travellers, in relation to both efficacy and any unwanted effects
- reviewing patterns of malaria and of resistance to anti-malarial agents and anti-vector measures as determinants of malaria risk to travellers
- formulating practical advice on protection against malaria for UK travellers and making this available to those who advise travellers
- formulating advice on the treatment of malaria cases imported to the UK

Membership

Membership is open to medical and non-medical professionals who have expertise in:

- antimalarial drug resistance
- the use of antimalarial drugs
- malaria prevention and/or treatment methods
- the behaviour of UK travellers

The ACMP will be chaired by a leading international expert in malaria and tropical medicine or malaria and infectious diseases.

There are no strict restrictions on the number of members able to join the committee however; the number should be beneficial and not detrimental to the ACMP purpose. Membership will be

reviewed every 3 years, after which membership may be renewed. Members of sub-groups associated with the ACMP may not always be direct members of the ACMP.

Accountability

Individual ACMP members and associated sub-groups are responsible for reporting back on activities tasked to them, either directly to the committee or via the secretariat when necessary.

Review process

The Terms of Reference (ToR) will be reviewed annually by the ACMP committee and proposed changes will be mutually agreed prior to being finalised by the Chair. The relevance and value of any subgroups will be reviewed on a regular basis.

Working methods

Sub-groups will be convened as necessary to take forward different aspects of the work of the ACMP. Essential meeting papers will be circulated electronically to all members no later than 5 days prior to the next meeting whenever possible.

Meeting arrangements

Prevention Guidelines meeting will be held twice a year, face to face.

The Country Recommendations meeting and the Treatment Guidelines meeting will be held once a year, face to face.

Meetings will be chaired by the ACMP Chair. If the Chair is not available, the Deputy Chair will take this role.

Non-ACMP members may be invited to meetings to contribute specialist skills, experience and knowledge when necessary.

A UKHSA scientific secretariat will coordinate and provide scientific secretariat support to the ACMP.

Confidentiality or conflicts of interest

Members of ACMP may have access to, see or hear information of a confidential nature with respect to the business of the ACMP and must not disclose such data to a third party unless expressly authorised to do so by the Chair. It is the individual responsibility of ACMP members to declare conflicts of interest annually, or when their conflicts of interest status changes, to the UKHSA scientific secretariat who will inform the committee.

Funding

ACMP is supported by UKHSA.

Equality and diversity

The ACMP will treat all members equally with respect to the business of the committee and will encourage member diversity.

Appendix 1b. ACMP member list

Member	Representation and expertise
Brian Angus	Chair, lead author for Treatment Guidelines
	Malaria expert, Nuffield Department of Medicine, Oxford University
Anna Checkley	Malaria expert. Hospital for Tropical Diseases
Christopher Williams	Consultant Epidemiologist. Public Health Wales
David Ross	Travel medicine expert. Ministry of Defence
Delane Shingadia	Paediatric infectious diseases expert. Institute of Child Health
Diana Ayoola Mabayoje	Infectious Diseases and Microbiology Consultant, Barts Health NHS Trust
Dinesh Aggarwal	Infectious disease and microbiology expert. Wellcome Clinical PhD Fellow, University of Cambridge
Dipti Patel	Travel medicine expert. National Travel Health Network and Centre (NaTHNaC)
Helena Bond	Infectious diseases consultant, Royal Victoria Hospital Belfast
Hilary Kirkbride	Consultant Epidemiologist and Head of Travel Health and IHR Team, UKHSA
James Logan	Vector borne diseases and medical entomology expert, London School of Hygiene and Tropical Medicine
Jan Jones	Travel Health Specialist Pharmacist
Jane Chiodini	Travel Health Specialist Nurse, Primary Care
Larry Goodyer	Pharmacy expert. De Montfort University
Mahinaz Harrison	Pharmacy expert. Royal Pharmaceutical Society and British National Formulary
Oliver Koch	Infectious Diseases expert. NHS Lothian
Richard Dawood	Travel medicine expert. Fleet Street Clinic
Steve Green	Infectious disease and tropical medicine consultant, Public Health Scotland
Swati Bhat	Clinical pharmacology expert, Medicines and Healthcare products Regulatory Agency
Tania Thomas	Travel Medicine Specialist Nurse, Royal Air Force
Xin Hui Chan	Malaria and emerging infectious diseases expert. Pandemic Sciences Institute, University of Oxford

Appendix 1c. ACMP conflict of interest statements

Both personal and non-personal interests are relevant within the last 4 years.

ACMP member	Personal interests: name of organisation	Personal interests: nature of interest	Non-personal interests: name of organisation	Non-personal interests: nature of interest
Professor Brian Angus	None	None	None	None
Professor Peter Chiodini	Parasitology Services Limited Institute of Tropical Medicine, Antwerp	Director, private practice Scientific Advisory Council	Travel Health Training Limited Intellectual Ventures, Global Good	Spouse, Jane Chiodini is Director Research funding and consultancy
Christopher Williams	None	None	None	None
Colonel David Ross	MASTA	Consultant Medical Advisor	Faculty of Travel Medicine, RCPSG	Vice Dean
Dr Anna Checkley	None	None	None	None
Dr Delane Shingadia	None	None	None	None
Dr Diana Ayoola Mabayoje	None	None	None	None
Dr Dinesh Aggarwal	None	None	None	None
Dr Dipti Patel	None	None	None	None
Dr Hilary Kirkbride	None	None	None	None
Dr Oliver Koch	None	None	None	None
Dr Richard Dawood	Fleet Street Clinic	Medical Director, private practice	None	None

ACMP member	Personal interests: name of organisation	Personal interests: nature of interest	Non-personal interests: name of organisation	Non-personal interests: nature of interest
Dr Xin Hui Chan	None	None	None	None
Mrs Jane Chiodini	Travel Health Training Limited	Director	Faculty of Travel Medicine, Royal College of Physicians and Surgeons of Glasgow	Dean 2028 to 2021 (now immediate past-Dean)
Ms Helena Bond	None	None	None	None
Ms Jan Jones	Boots UK	Employee	None	None
Ms Mahinaz Harrison	None	None	None	None
Ms Swati Bhat	None	None	None	None
Professor James Logan	Arctech Innovation	CEO, Co-Founder	Various companies (including pharma, biochemical, agritech, and so on)	Advisor to various companies via Arctech Innovation or LSHTM
Professor Larry Goodyer	Nomad Travel Store and Clinics British Global and Travel Health Association	 Superintendent pharmacist and advisor of a National network of Travel Clinics Chair of the association 	Sigma Tau Advisory Board (till 2013)	Antimalarial manufacturer
Professor Steve Green	None	None	None	None
Squadron Leader Tania Thomas	None	None	None	None

Appendix 1d. ACMP methodology

Purpose

To provide guidelines for health professionals on the prevention of malaria for travellers from the UK, updated annually or soon as there is a significant change in the distribution or behaviour of malaria, or the need to consider new advice on drugs and anti-insect measures.

Assessing in-country risk

The location, level of endemicity (parasite rate, entomological inoculation rate) and species of malaria parasites present are evaluated using data from:

- WHO Global Malaria Programme
- World Malaria Report
- estimates of the *P. falciparum* parasite rate and entomological inoculation rate published by the <u>Oxford University Malaria Atlas project</u>
- the number of cases and deaths in-country from published and unpublished sources
- Centers for Disease Control and Prevention information for Central and South America, a region where the CDC has local knowledge
- local, expert contacts of the London School of Hygiene and Tropical Medicine Malaria Centre as necessary

Returned traveller data

The UKHSA Malaria Reference Laboratory, London (MRL) database captures 56% of cases (66% for *P. falciparum*) (133).

Numbers of cases are also converted to attack rates where good denominator data is available.

Details of the data requested on all imported malarias can be seen in the MRL case report form.

Enhanced surveillance of malaria cases from a country or region is undertaken following a major change in ACMP recommendations for travellers to that location.

Information on case numbers, species of parasite and special groups (for example, pregnant travellers) is sought.

Deaths are all subject to a detailed confidential audit.

MRL data on molecular markers of resistance to anti-malarial agents is reviewed.

Available preventive measures

New information on methods of malaria prevention for travellers, in relation to both efficacy and any unwanted effects is reviewed. Information on efficacy, adverse events and interactions with concomitant medication is reviewed for:

- 1. Bite prevention products using data from the published literature and the WHO Pesticide Evaluation Scheme (WHOPES).
- 2. Chemoprophylaxis and Standby Emergency Medication, using data from:
- Medicines and Healthcare Products Regulatory Agency (MHRA) literature on chemoprophylaxis and stand-by treatment
- efficacy and tolerance reports
- specific drug trials
- comparative studies
- surveillance data and case/control studies
- post-marketing surveillance
- systematic reviews (Cochrane)
- adherence and use

Other jurisdictions

Guidelines produced by WHO, CDC, Health Canada, Switzerland, Germany and Austria and Italy are compared with the conclusions reached by ACMP. The actual malaria situation in a particular country is the same whoever looks at it, yet published guidelines for malaria prevention written for travellers from non-endemic countries can and do differ (133). When malaria data is least good or limited, recommendations are extremely dependent on subjective expert opinion which results in different recommendations for chemoprophylaxis. This reflects the different health systems present in those countries, their experts' tolerance of malaria risk versus the side effect profile of antimalarial chemoprophylactic drugs and the medicolegal climate in which they practice.

Reaching a decision

These sources are assessed by the country recommendations sub-group then submitted for discussion and decision by the full ACMP as the basis for malaria prevention policy for each country. Data quality may not be uniform for the countries considered, so a single formula to decide policy is not possible and different weighting may need to be applied to the information sources used.

The future

Large-scale field diagnostics are likely to be widely used, especially in those countries moving to the pre-elimination phase of malaria eradication. Data generated both on species present and on drug-resistance markers, will give a much closer picture of the true in-country malaria situation and strengthen the evidence base for the ACMP guidelines.

Appendix 2. Template for risk assessment and summary of advice given

A risk assessment should be performed when an antimalarial is prescribed and this also applies to an over-the-counter sale of a Pharmacy only medicine. For the recently reclassified atovaquone plus proguanil product, the manufacturers provide a pharmacist checklist which can usefully be used as part of such an assessment. ACMP advises that a risk assessment for malaria chemoprophylaxis should be performed or checked by the pharmacist, is described specifically in the pharmacy standard operating procedures and a record be kept of the outcome of such an assessment. These principles should also apply to sales over the internet through registered e-pharmacies where an appropriate on-line risk assessment is conducted.

This template is suggested for use in gathering information required for risk assessment when advising on malaria prevention. It may be adapted for the particular circumstances of individual clinics.

Note: The information needed to complete this template and thus make a full risk assessment should be used in any consultation for malaria prevention, whether conducted face-to-face or via e-prescribing.

Guidance is available from the General Medical Council on remote prescribing.

Traveller details

Name of traveller	
Age	
Sex assigned at birth (male / female / prefer not to say)	
Dates of travel	

Underlying condition

Condition	Yes or no
Pregnancy	Actual number of weeks
	Planned while on trip
Sickle cell	Disease
	Carrier
Thalassaemia	Disease
	Carrier

Condition	Yes or no	
Epilepsy	Patient	
	First degree relative	
History of depression requiring treatment		
Severe mental health disorder	Patient	
	First degree relative ⁶	
Asplenic		
Liver disease		
Renal failure (state eGFR)		
Diabetes mellitus		
Cardiovascular	Ischaemic heart disease	
	Arrythmias	
	Other	
Immunocompromised		

Allergies

Give details of allergies to drugs or other below		

Medication

Current medication	Yes or no	Comments
Antiarrhythmics		
Anticonvulsants		
Anticoagulants		
Antiretrovirals		
Corticosteroids or other immunosuppressive agents		
Bupropion (Zyban ®)		

⁶ First degree relatives are included in risk assessment as a precaution since risk of epilepsy and major depression is higher in first degree relatives of those in whom these conditions have been diagnosed. A condition in a first-degree relative may not contraindicate the use of an antimalarial but may influence the choice of drug.

Current medication	Yes or no	Comments
Other, please state		

Previous antimalarial chemoprophylactic agent taken	Describe any problems	

Area to be visited

See country table and maps in **Chemoprophylaxis**.

Destination	Length of stay	Risk of malaria	Urban, rural or both	Prophylaxis advised from country table ⁷

Purpose of visit and type of accommodation: tick all those that apply

Purpose of visit or accommodation	Tick if applies	
Visiting friends and relatives		
Safari		
Backpacking		
Business or work		
Study more than 6 months		
Study less than 6 months		
House		
Hotel		
Hostel		
Tent		
Oil rig		

⁷ If the recommended regimens differ between the countries to be visited, see note on multi-trips in Chemoprophylaxis.

Purpose of visit or accommodation	Tick if applies
Cruise ship	
Urban	
Rural	
Other (please give details below)	

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1. Bite prevention: please tick measures advised.

Measures advised	Tick if applies
Repellent	
Clothing spray	
Bed net	
Coils or electric vapourisers	
Insecticide sprays	
Suitable clothing	

2. Chemoprophylaxis.

Warning: do **not** rely on homoeopathic or 'natural' antimalarial prophylaxis.

Antimalarial	Tick the regimen advised	Dose	Duration
Chloroquine			
Mefloquine			
Doxycycline			
Atovaquone/Proguanil			
Other (please specify)			
No chemoprophylaxis			Awareness of risk including bite prevention must still be recommended. Give advice to seek medical attention for any fever (up to about a year later).

Standby emergency medication

For the vast majority of travellers, standby emergency antimalarial medication is neither required nor recommended. Please undertake a risk assessment including information on the distance and time away from medical facilities which apply in each case.

Standby emergency medicine advised? Yes or no (please circle).

If standby emergency medication is recommended, please tick the regimen advised.

Standby regimen advised	Tick if applies
Atovaquone with proguanil combination preparation	
Artemether with lumefantrine combination preparation	
Quinine plus doxycycline	
Quinine plus clindamycin	

Standby emergency medication advice leaflet given? Yes or no (please circle).

Appendix 3. Emergency standby medication: traveller information leaflet

[Free to copy and paste for use]

You have been advised to carry emergency standby antimalarial medication with you on your forthcoming trip. This leaflet provides you with advice on when and how to use it. Please keep it safely with your medication. If you are travelling with a companion, please ask them to read this leaflet as they may be able to assist you in following its advice in the event of your becoming ill.

Incubation period of malaria

The minimum period between being bitten by an infected mosquito and developing symptoms of malaria is 8 days, so an illness with fever starting within the first week of your arrival in a malarious area is not likely to be due to malaria.

Symptoms and signs of malaria

Malaria usually begins with a fever. You may then feel cold, shivery, shaky and very sweaty. Headache, feeling sick and vomiting are common with malaria and you are also likely to experience aching muscles. Some people develop jaundice (yellowness of the whites of the eyes and the skin). It is not necessary for all these symptoms to be present before suspecting malaria as fever alone may be present at first.

When to take your emergency standby medication

If you develop a fever of 38°C/100°F or more, more than one week after being in a malarious area, seek medical attention straight away.

If you will not be able to get medical attention within 24 hours of your fever starting, start your standby medication and set off to find and consult a doctor.

How to take your emergency standby medication

First, take medication (usually paracetamol) to lower your fever. If your fever is controlled, it makes it less likely that you will vomit your antimalarial drugs then, without delay, take the first dose of your emergency standby antimalarial medication.

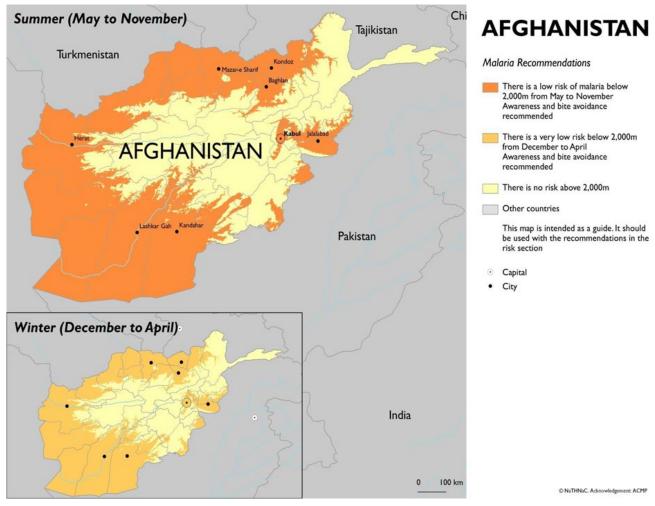
If you do vomit and it is within 30 minutes of taking the antimalarial drugs, repeat the first dose of them (but do not repeat the paracetamol). If you vomit 30 to 60 minutes after taking the first dose of the antimalarial drugs, repeat the treatment, but take only **half** the first dose.

Continue the treatment as instructed for the particular drugs prescribed for you. Please remember that this emergency standby medication has been prescribed based on your particular medical history and should be taken only by you as it may not be suitable for others.

Once you have completed your emergency standby medication you should restart your malaria prevention drugs one week after you took the first treatment dose of emergency standby medication. If your preventive medication consists of mefloquine and your standby treatment included quinine, you should wait at least 12 hours after completing the course of quinine before you restart mefloquine.

Appendix 4. Destinations: maps showing the areas with appropriate malaria prevention measures recommended

Figure 4. Map of Afghanistan showing the areas with appropriate malaria prevention measures recommended



Information about malaria in Afghanistan on the Travel Health Pro website.

Congo **ANGOLA** Malaria Recommendations There is a high risk of malaria in Angola Democratic Republic of the Congo Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Other countries This map is intended as a guide. It should be used with the recommendations in the Capital ATLANTIC OCEAN City ▼ Point of interest **ANGOLA** Zambia Namibia Botswana @ NaTHNaC. Advnowledgement: ACMP

Figure 5. Map of Angola showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Angola on the Travel Health Pro website.

Bhutan **BANGLADESH** Nepal Malaria Recommendations India There is a high risk of malaria in Chittagong Hill Tract districts Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine There is a very low risk in the rest of Bangladesh Awareness and bite avoidance Sylhet recommended Other countries BANGLADESH This map is intended as a guide. It should be used with the recommendations in the risk section Capital ▼ Point of interest lessore Cox's Bazar Myanmar 100 km © NaTHNaC. Acknowledgement ACMP

Figure 6. Map of Bangladesh showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Bangladesh on the Travel Health Pro website.

BENIN Niger Burkina Faso Malaria Recommendations There is a high risk of malaria in Benin Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Other countries BENIN This map is intended as a guide. It should be used with the recommendations in the Capital City ▼ Point of interest Togo Ghana Nigeria @ NaTHNaC. Adknowledgement: ACMP

Figure 7. Map of Benin showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Benin on the Travel Health Pro website.

BOLIVIA Malaria Recommendations Brazil There is a low risk of malaria in the Amazon Basin and in rural areas below 2,500m Awareness and bite avoidance Peru recommended There is no risk above 2,500m Other countries **BOLIVIA** This map is intended as a guide. It should be used with the recommendations in the risk section Capital City ▼ Point of interest Uyuni Salt Flat
▼ IC OCEAN Paraguay Chile Argentina 0 100 km © NaTHNaC, Adknowledgement ACMP

Figure 8. Map of Bolivia showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Bolivia on the Travel Health Pro website.

Summer (November to June) **BOTSWANA** Zambia Malaria Recommendations There is a high risk of malaria from Zimbabwe November to June in the northern half of Botswana Antimalarials recommended: atovaquone-Nixai Pan N.P. proguanil or doxycycline or mefloquine Makgadikgadi Pans N.P. There is a low risk from July to October in the northern half Namibia Awareness and bite avoidance recommended There is a very low risk in the southern half of the country Awareness and bite avoidance recommended Other countries Winter (July to October) This map is intended as a guide. It should be used with the recommendations in the Gaborone risk section Kgalagadi N.P. Capital City Point of interest South Africa 100 km © NaTHNaC. Acknowledgement: ACMP

Figure 9. Map of Botswana showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Botswana on the Travel Health Pro website.

Guyana Venezuela **BRAZIL** F.G. Colombia NORTH ATLANTIC OCEAN Suriname Malaria Recommendations There is a low risk of malaria in the Amazon Basin Awareness and bite avoidance recommended There is a very low risk in the rest of Brazil and no risk at Iguazu Falls Awareness and bite avoidance recommended BRAZIL Other countries This map is intended as a guide. It should be used with the recommendations in the risk section Peru Capital City Point of interest Bolivia Belo Horizonte Paraguay SOUTH ATLANTIC OCEAN Chile IC OCEAN Argentina Uruguay 200 km © NaTHNaC. Advowledgement ACHP

Figure 10. Map of Brazil showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Brazil on the Travel Health Pro website.

CAMBODIA Laos Thailand Malaria Recommendations There is a low risk of malaria in Cambodia Awareness and bite avoidance recommended There is a very low risk around Lake Tonle Sap and Angkor Wat Awareness and bite avoidance recommended Angkor Wat There is no risk in Phnom Penh CAMBODIA Mefloquine resistance is widespread in the western provinces Other countries This map is intended as a guide. It should be used with the recommendations in the risk section 0 Capital City ▼ Point of interest Vietnam MEKONG RIVER 100 km © NaTHNaC. Adknowledgement: ACMP

Figure 11. Map of Cambodia showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Cambodia on the Travel Health Pro website.

Niger **CAMEROON** Malaria Recommendations There is a high risk of malaria in Cameroon Chad Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Other countries Nigeria This map is intended as a guide. It should be used with the recommendations in the risk section Capital City Point of interest Central African Republic ATLANTIC OCEAN Equatorial Gabon Congo Guinea © NaTHNaC. Adknowledgement: ACMP

Figure 12. Map of Cameroon showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Cameroon on the Travel Health Pro website.

ragua San Andres **COLOMBIA** CARIBBEAN SEA Barranquilla Malaria Recommendations There is a low risk of malaria in rural areas below 1,600m osta Rica Awareness and bite avoidance recommended Panama City Venezuela There is very low risk in areas above Panama 1,600m and in Cartagena Awareness and bite avoidance Bucaramanga recommended Other countries Medellin This map is intended as a guide. It should be used with the recommendations in the risk section Capital NORTH PACIFIC OCEAN COLOMBIA City Quito Ecuador SOUTH PACIFIC OCEAN Brazil Peru 0 100 km © NaTHNaC. Adknowledgement: ACMP

Figure 13. Map of Colombia showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Colombia on the Travel Health Pro website.

Central African Republic **CONGO** Cameroon Malaria Recommendations There is a high risk of malaria in Congo Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Equatorial Guinea Other countries This map is intended as a guide. It should be used with the recommendations in the risk section Capital City ▼ Point of interest Gabon CONGO Democratic Republic of the Congo Pointe-Noire Angola © NaTHNaC. Adknowledgement: ACMP

Figure 14. Map of Congo showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Congo on the Travel Health Pro website.

COSTA RICA Nicaragua Malaria Recommendations There is a low risk of malaria in Limon Province CARIBBEAN SEA Awareness and bite avoidance COSTA recommended RICA There is very low risk in the rest of Volcan Arenal Tortuguero N.P. Costa Rica including Puerto Limon (City of Limon) Awareness and bite avoidance _Volcan Poas recommended Other countries Puerto Limon Puntarenas This map is intended as a guide. It should Playa Samara be used with the recommendations in the risk section LIMON Montezuma PROVINCE Capital City Cerro Chirripo ▼ Point of interest Manuel Antonio N.P. Panama NORTH PACIFIC OCEAN Corcovado N.P. 0 100 km © NaTHNaC. Adknowledgement: ACMP

Figure 15. Map of Costa Rica showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Costa Rica on the Travel Health Pro website.

CÔTE Mali Burkina Faso **D'IVOIRE** Malaria Recommendations There is a high risk of malaria in Ivory Coast Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Guinea Other countries CÔTE D'IVOIRE This map is intended as a guide. It should be used with the recommendations in the risk section Capital City Point of interest Ghana Liberia ATLANTIC OCEAN © NaTHNaC. Adknowledgement: ACMP

Figure 16. Map of Cote D'Ivoire showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Cote D'Ivoire on the Travel Health Pro website.

Central African Republic **DEMOCRATIC** South Sudan REPUBLIC OF Cameroon THE CONGO Malaria Recommendations There is a high risk of malaria in DRC Congo Uganda Antimalarials recommended: atovaquone-Gabon proguanil or doxycycline or mefloquine Rwanda DRC Other countries This map is intended as a guide. It should be used with the recommendations in the Burundi risk section (Capital City ▼ Point of interest Tanzania Zambia Angola © NaTHNaC. Adknowledgement: ACMP

Figure 17. Map of Democratic Republic of Congo showing the areas with appropriate malaria prevention measures recommended

Information about malaria in the Democratic Republic of Congo on the Travel Health Pro website.

ECUADOR Malaria Recommendations Colombia GALAPAGOS ISLANDS There is a low risk of malaria in areas below 1,500m Awareness and bite avoidance recommended There is no risk in the Galapagos Islands and in the city of Guayaquil Other countries Cotobax This map is intended as a guide. It should be used with the recommendations in the **ECUADOR** risk section Ambato Capital City ▼ Point of interest Peru 0 100 km © NaTHNaC. Adknowledgement: ACMP

Figure 18. Map of Ecuador showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Ecuador on the Travel Health Pro website.

ERITREA Saudi Arabia Sudan Malaria Recommendations There is a high risk of malaria in Eritrea below 2,200m Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine ERITREA There is no risk in Asmara and in areas above 2,200m RED SEA Other countries This map is intended as a guide. It should be used with the recommendations in the Yemen risk section Capital City ▼ Point of interest Ethiopia Djibouti 100 km © NaTHNaC. Adknowledgement: ACMP

Figure 19. Map of Eritrea showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Eritrea on the Travel Health Pro website.

ESWATINI Mozambique Malaria Recommendations Piggs Peak There is a risk of malaria in the northern and eastern regions Antimalarials recommended: atovaquone-Malolotja N.R. proguanil or doxycycline or mefloquine There is a very low risk in other parts Hlane N.P. **Mbabane ⊙** Awareness and bite avoidance recommended Other countries This map is intended as a guide. It should Siteki be used with the recommendations in the Manzini risk section Lobamba Capital **▼**Mkhaya Game Reserve City ▼ Point of Interest **ESWATINI** Hlatikulu South Africa Golela © NaTHNaC. Acknowledgement ACMP

Figure 20. Map of Eswatini showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Eswatini on the Travel Health Pro website.

Saudi Arabia **ETHIOPIA** Eritrea RED SEA Malaria Recommendations Yemen There is a high risk of malaria below Sudan Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine There is no risk above 2,000m and in Addis Ababa Other countries Djibouti **⊙**Djibouti This map is intended as a guide. It should be used with the recommendations in the risk section Capital City ▼ Point of interest ETHIOPIA S. Sudan Somalia Kenya INDIAN OCE Uganda 100 km © NaTHNaC. Adknowledgement ACMP

Figure 21. Map of Ethiopia showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Ethiopia on the Travel Health Pro website.

GAMBIA Malaria Recommendations There is a high risk of malaria in Gambia Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Senegal recommended Other countries This map is intended as a guide. It should be used with the recommendations in the risk section Capital Gambia N.P. • City Point of interest Guinea-Bissau Guinea

Figure 22. Map of Gambia showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Gambia on the Travel Health Pro website.

© NaTHNaC. Adknowledgement: ACMP

GHANA Burkina Faso Malaria Recommendations Benin There is a high risk of malaria in Ghana Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Other countries This map is intended as a guide. It should Togo be used with the recommendations in the risk section Côte d'Ivoire Capital ▼ Point of interest -ATLANTIC OCEAN @ NaTHNaC. Advnowledgement: ACMP

Figure 23. Map of Ghana showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Ghana on the Travel Health Pro website.

GUATEMALA Malaria Recommendations Belmopan ⊙ There is a low risk of malaria below ▼Tikal Awareness and bite avoidance only Flores There is no risk in Antigua, Guatemala City, by Lake Atitlan, and in areas above 1,500m Mexico Belize Other countries This map is intended as a guide. It should be used with the recommendations in the San Luis risk section Capital City ▼ Point of interest **GUATEMALA** Honduras El Salvador NORTH PACIFIC OCEAN 50 km © NaTHNaC. Acknowledgement: ACMP

Figure 24. Map of Guatemala showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Guatamala on the Travel Health Pro website.

GUINEA Gambia Senegal Malaria Recommendations Mali There is a high risk of malaria in Guinea Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Guinea-Bissau Other countries This map is intended as a guide. It should be used with the recommendations in the risk section GUINEA Capital City Point of interest Sierra Leone Côte d'Ivoire ATLANTIC OCEAN Liberia © NaTHNaC. Adknowledgement: ACMP

Figure 25. Map of Guinea showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Guinea on the Travel Health Pro website.

HONDURAS Belize CARIBBEAN SEA Malaria Recommendations There is a low risk of malaria below 1,000m and in Islas de Bahia (Bay Islands) San Pedro Sula Awareness and bite avoidance only Guatemala **HONDURAS** There is no risk in Tegucigalpa, San Pedro Sula, and areas above 1,000m Cerro Azul Meambar N.P. Other countries Santa Rosa de Copan Comayagua This map is intended as a guide. It should be used with the recommendations in the risk section Tegucigalpa Capital S. Salvador City Nicaragua Nacaome El Salvador Choluteca NORTH PACIFIC OCEAN 100 km © NaTHNaC. Acknowledgement: ACMP

Figure 26. Map of Honduras showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Honduras on the Travel Health Pro website.

Tajikistan anistan **INDIA** Malaria Recommendations China There is a risk of malaria in the states **Pakistan** of Assam and Orissa and in the districts of East Godavari, Srikakulam, Vishakhapatnam, and Vizianagaram in the state of Andhra Pradesh; and Balaghat, Dindori, Nepal Mandla and Seoni in the state of Madhya Pradesh Bhutan Lucknow Antimalarials recommended: atovaquone-INDIA proguanil or doxycycline or mefloquine Dispur There is a low risk in other parts MADHYA Bangladesh PRADESH Awareness and bite avoidance recommended Myanmar There is no risk in the Lakshadweep ORISSA Islands Other countries Thaila This map is intended as a guide. It should be used with the recommendations in the Vishakhapatnam risk section ANDHRA PRADESH Capital ARABIAN SEA City Point of interest Chennai ANDAMAN SEA LAKSHADWEEP ISLANDS LACCADIVE SEA Sri Lanka 0 100 km **Maldives** INDIAN OCEAN © NaTHNaC. Adknowledgement: ACMP

Figure 27. Map of India showing the areas with appropriate malaria prevention measures recommended

Information about malaria in India on the Travel Health Pro website.

Figure 28. Map of Indonesia and Indonesia (Borneo) showing the areas with appropriate malaria prevention measures recommended



Information about malaria in Indonesia and Indonesia (Borneo) on the Travel Health Pro website.

Summer (March to November) **IRAN** Azerbaijan Turkmenistan CASPIAN SEA Malaria Recommendations There is a low risk of malaria from March to November in the rural southeastern NORTH provinces and along the Azerbaijan border KHORASAN in Ardabil and the Turkmenistan border in North Khorosan Mashhad Awareness and bite avoidance recommended IRAN There is very low risk in the rest of Iran Awareness and bite avoidance recommended Isfahan Afghanistan SOUTH Other countries Yazd KHORASAN Ahvaz This map is intended as a guide. It should Iraq be used with the recommendations in the risk section Kerman Persepolis Zahedan Capital Kuwait City Point of interest SISTAN AND BALUCHESTAN Winter (December to February) Pakistan United Arab Emirates ARABIAN SEA Oman 0 100 km © NaTHNaC. Acknowledgement: ACMP

Figure 29. Map of Iran showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Iran on the Travel Health Pro website.

Summer (May to November) **IRAQ** Turkey Dahuk Malaria Recommendations There is a very low risk of malaria from May to November in the rural northern areas below 1,500m Awareness and bite avoidance recommended Syria There is no risk in the rest of Iraq Iran Other countries This map is intended as a guide. It should be used with the recommendations in the risk section Capital Jordan City An Nasiriyah Kuwait Winter (December to April) 100 km © NaTHNaC. Adknowledgement: ACMP

Figure 30. Map of Iraq showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Iraq on the Travel Health Pro website.

KENYA S. Sudan Ethiopia Malaria Recommendations There is a high risk of malaria in Kenya Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine There is very low risk in the city of Nairobi and above 2,500m Awareness and bite avoidance recommended Uganda Other countries This map is intended as a guide. It should be used with the recommendations in the risk section Somalia Capital City ▼ Point of interest LVICTORIA Nairobi INDIAN OCEAN Tanzania 0 100 km © NaTHNaC. Adknowledgement ACMP

Figure 31. Map of Kenya showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Kenya on the Travel Health Pro website.

LAOS China Malaria Recommendations Vietnam There is a low risk of malaria in Laos Myanmar Awareness of risk and bite avoidance recommended There is a very low risk in the city of Awareness of risk and bite avoidance recommended Other countries LAOS This map is intended as a guide. It should be used with the recommendations in the risk section Phou Hin Poun National Biodiversity Conservation Area Capital Thakhek City ▼ Point of interest Thailand Pakse _ Wat Phu Si Phan Don Archipelago Cambodia © NaTHNaC. Adknowledgement: ACMP

Figure 32. Map of Laos showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Laos on the Travel Health Pro website.

MADAGASCAR Malaria Recommendations There is a high risk of malaria in Madagascar Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Other countries This map is intended as a guide. It should be used with the recommendations in the risk section MADAGASCAR Capital Toamasina City ▼ Point of interest @ NaTHNaC. Adknowledgement: ACMP

Figure 33. Map of Madagascar showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Madagascar on the Travel Health Pro website.

MALAWI Malaria Recommendations Tanzania There is a high risk of malaria in Malawi Zambia Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Other countries This map is intended as a guide. It should be used with the recommendations in the risk section Capital City ▼ Point of interest MALAWI Mozambique Zimbabwe © NaTHNaC. Advnowledgement: ACMP

Figure 34. Map of Malawi showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Malawi on the Travel Health Pro website.

Vietnam **MALAYSIA** N SEA Thailand SULU SEA Philippin Malaria Recommendations Kota Kinabalu Sepilok Orangutan Centre There is a low risk of malaria in mainland Malaysia, inland forested areas of Sarawak SOUTH CHINA SEA and inland areas of Sabah Taman Negara N.P. Brunei Awareness and bite avoidance recommended **MALAYSIA** CELEBES SEA Kuala Lumpur There is a very low risk in unforested SARAWAK areas of Sarawak and in coastal areas of Sabah and Sarawak Awareness and bite avoidance Singapore Kuching recommended Other countries This map is intended as a guide. It should Indonesia be used with the recommendations in the risk section INDIAN OCEAN Capital City Point of interest IAVA SEA 0 100 km © NaTHNaC. Acknowledgement: ACMP

Figure 35. Map of Malaysia and Malaysia (Borneo) showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Malaysia and Malaysia (Borneo) on the Travel Health Pro website.

Summer (July to October) **MAURITANIA** Algeria Malaria Recommendations Morocco There is a high risk of malaria throughout the year in southern provinces and in northern provinces from July to October Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine There is a low risk in northern provinces from November to June Awareness and bite avoidance recommended MAURITANIA Other countries NORTH ATLANTIC OCEAN This map is intended as a guide. It should be used with the recommendations in the risk section Capital City Senegal Dakar Winter (November to June) Bissau Guinea Bissau Guinea 0 100 km © NaTHNaC. Acknowledgement: ACMP

Figure 36. Map of Mauritania showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Mauretania on the Travel Health Pro website.

MOZAMBIQUE Tanzania DRC Zambia Malaria Recommendations MOZAMBIQUE There is a high risk of malaria in Mozambique Malawi Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Other countries This map is intended as a guide. It should be used with the recommendations in the risk section Capital Point of interest Zimbabwe Bazaruto Archipelago Botswana South Africa _Inhaca Island Eswatin © NaTHNaC. Advnowledgement: ACMP

Figure 37. Map of Mozambique showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Mozambique on the Travel Health Pro website.

Zambia **NAMIBIA** Angola KUNENE Malaria Recommendations CAPRIVL Katima Mulilo There is a high risk of malaria throughout the year in the Caprivi Strip, Kavango and Kunene river regions: atovoquone/proguanil OR doxycycline OR mefloquine recommended. Etosha N.P. There is a very low risk of malaria in the rest Grootfontein of Namibia: Skeleton Coast V Awareness of risk and bite avoidance recommended. KAVANGO Other countries This map is intended as a guide. It should be used with the recommendations in Gobabis the risk section. Swakopmund 9 Walvis Bay Botswana Rehoboth Capital City ▼ Point of interest NAMIBIA Lüderitz South Africa Fish River Canyon © NaTHNaC. Acknowledgement: ACMP

Figure 38. Map of Namibia showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Namibia on the Travel Health Pro website.



Figure 39. Map of Nepal showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Nepal on the Travel Health Pro website.

NIGERIA Niger Malaria Recommendations Chad There is a high risk of malaria in Nigeria Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Other countries This map is intended as a guide. It should be used with the recommendations in the risk section Benin Capital NIGERIA City ▼ Point of interest ATLANTIC OCEAN Cameroon © NaTHNaC. Adknowledgement: ACMP

Figure 40. Map of Nigeria showing the areas with appropriate malaria prevention measures recommended

<u>Information about malaria in Nigeria</u> on the Travel Health Pro website.

Figure 41. Map of Pakistan showing the areas with appropriate malaria prevention measures recommended For temporary measures advised for travellers to flood-affected areas of Pakistan consult <u>Table 6</u>.



Information about malaria in Pakistan on the Travel Health Pro website.

PANAMA CARIBBEAN SEA Costa Rica Islas de San Blas Portobelo N.P. Malaria Recommendations Bocas del Toro Almirante There is a low risk of malaria east of the Canal Zone PANAMA CANAL Awareness and bite avoidance Volcan Baru recommended There is a very low risk west of the PANAMA Canal Zone Penonome Awareness and bite avoidance recommended Puerto Armuelles Chitre There is no risk in Panama City and the Las Tablas Canal Zone itself Darien N.P. Other countries ▼Isla de Coiba This map is intended as a guide. It should Colombia be used with the recommendations in the risk section 0 Capital City ▼ Point of interest NORTH PACIFIC OCEAN 100 km © NaTHNaC. Adknowledgement: ACMP

Figure 42. Map of Panama showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Panama on the Travel Health Pro website.

PAPUA NEW SOUTH PACIFIC OCEAN **GUINEA** BISMARCK SEA Malaria Recommendations There is a high risk of malaria below Indonesia Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine There is a very low risk above 1,800m Solomon Is Awareness and bite avoidance recommended SOLOMON SEA Other countries This map is intended as a guide. It should be used with the recommendations in the **Port Moresby** risk section ARAFURA SEA Capital City CORAL SEA Point of interest 100 km 0 © NaTHNaC. Acknowledgement: ACMP

Figure 43. Map of Papua New Guinea showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Papua New Guinea on the Travel Health Pro website.

Quito NORTH PACIFIC OCEAN **PERU** Colombia Ecuador Malaria Recommendations There is a low risk of malaria below 2,000m including the Amazon Basin Awareness and bite avoidance recommended There is no risk in the city of Lima and coastal regions south of Chiclayo Other countries Brazil This map is intended as a guide. It should be used with the recommendations in the risk section Capital Cordillero Blanca PERU City ▼ Point of interest Huancayo Manu N.P. Lima Puerto Maldonado SOUTH PACIFIC OCEAN Bolivia Colga Canyon_▼ La Paz 200 km Chile © NaTHNaC. Adknowledgement: ACMP

Figure 44. Map of Peru showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Peru on the Travel Health Pro website.

PHILIPPINES Malaria Recommendations There is a low risk of malaria in rural areas below 600m and on the islands of Luzon, LUZON Mindanao, Mindoro, and Palawan Awareness and bite avoidance recommended **PHILIPPINES** There is no risk in cities or on the islands of Borocay, Bohol, Cantaduanes, Cebu and Other countries CATANDUANES This map is intended as a guide. It should be used with the recommendations in the risk section Capital City BOHOL

Figure 45. Map of Philippines showing the areas with appropriate malaria prevention measures recommended

Information about malaria in the Philippines on the Travel Health Pro website.

Malaysia

100 km

© NaTHNaC. Acknowledgement: ACMP

RWANDA Malaria Recommendations Uganda There is a high risk of malaria in Rwanda DRC Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Other countries This map is intended as a guide. It should be used with the recommendations in the risk section Capital • City Point of interest Tanzania Burundi © NaTHNaC. Adknowledgement: ACMP

Figure 46. Map of Rwanda showing the areas with appropriate malaria prevention measures recommended

<u>Information about malaria in Rwanda</u> on the Travel Health Pro website.

yprus Lebanon Syria **SAUDI** RANEAN SEA Iraq **ARABIA Palestine** Iran Israel Jordan Malaria Recommendations Kuwait There is a low risk of malaria in the south √Jubbah western provinces below 2,000m Awareness and bite avoidance recommended Madain Saleh There is no risk in the cities of Jeddah, Makkah (Mecca), and Ta'if, or in the SAUDI province of Asir above 2,000m Other countries **ARABIA** Al Hillah United Arab Emirate This map is intended as a guide. It should Egypt be used with the recommendations in the risk section Makkah (Mecca) \odot Capital City RED SEA ▼ Point of interest ASIR Sudan NAJRAN Oman Eritrea Yemen ARABIAN SEA Ethiopia 100 km Djibouti 1 Sudan © NaTHNaC. Adknowledgement: ACMP

Figure 47. Map of Saudi Arabia showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Saudi Arabia on the Travel Health Pro website.

SIERRA LEONE Guinea Malaria Recommendations There is a high risk of malaria in Sierra Leone Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Other countries This map is intended as a guide. It should be used with the recommendations in the risk section SIERRA LEONE Capital City Point of interest Banana Islands ATLANTIC OCEAN Liberia © NaTHNaC. Adknowledgement: ACMP

Figure 48. Map of Sierra Leone showing the areas with appropriate malaria prevention measures recommended

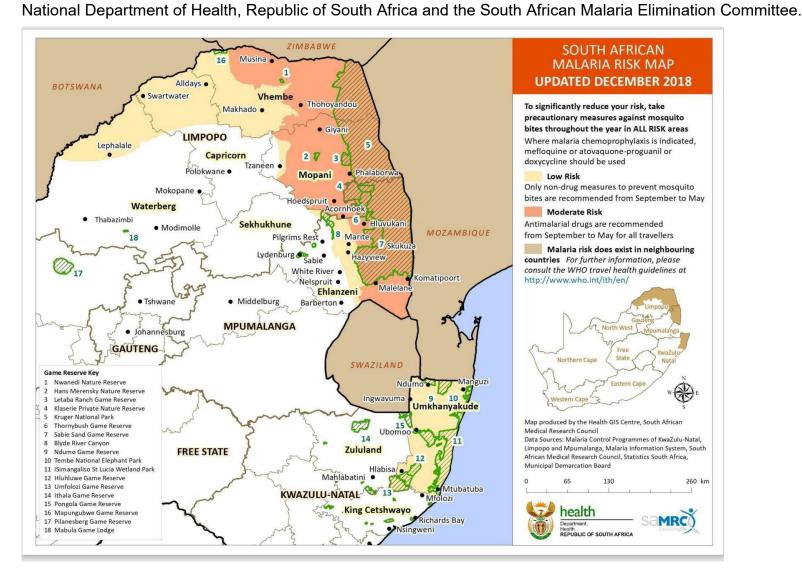
Information about malaria in Sierra Leone on the Travel Health Pro website.

Eritrea Yemen **SOMALIA** Djibouti _Sa'ad ad-Din Islands Malaria Recommendations There is a high risk of malaria in Somalia Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Other countries This map is intended as a guide. It should be used with the recommendations in the risk section Ethiopia Capital City Point of interest SOMALIA Kenya Mogadishu ana-Bushbush N.P. @ NaTHNaC. Adknowledgement: ACMP

Figure 49. Map of Somalia showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Somalia on the Travel Health Pro website.

Figure 50. Map of South Africa showing the areas with appropriate malaria prevention measures recommended See the Republic of South Africa Department of Health Malaria page (accessed 3 September 2023). Reproduced with permission of the



Guidelines for the prevention of malaria on the South African National Travel Health Network website.

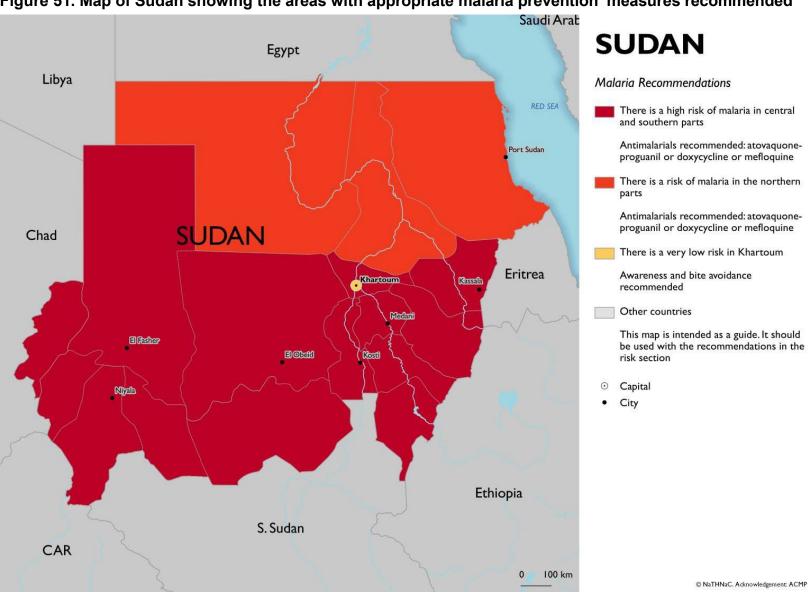


Figure 51. Map of Sudan showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Sudan on the Travel Health Pro website.

Somali **TANZANIA** Uganda LVICTORIA Malaria Recommendations Kenya Rwanda There is a high risk of malaria below 1,800m (including Zanzibar and other islands) Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Burundi There is no risk above 1,800m Other countries This map is intended as a guide. It should be used with the recommendations in the risk section TANZANIA Capital City INDIAN OCEAN ▼ Point of interest Dar es Salaam Morogoro DRC Selous N.P. Zambia Malawi Mozambique 100 km © NaTHNaC. Acknowledgement: ACMP

Figure 52. Map of Tanzania showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Tanzania on the Travel Health Pro website.

THAILAND Myanmar Laos China Malaria Recommendations There is a low risk of malaria in rural, forested borders with Myanmar, Laos, and Cambodia Awareness and bite avoidance recommended There is a very low risk in other parts Awareness and bite avoidance recommended There is a no risk in Bangkok, Chiang Mai, Chiang Rai, Koh Phangan, Koh Samui, and Pattaya Vietnam There is mefloquine resistance in Thailand Other countries Cambodia This map is intended as a guide. It should be used with the recommendations in the risk section ANDAMAN SEA Capital City SOUTH CHINA SEA Nakhon Si Thammarat 100 km © NaTHNaC. Acknowledgement: ACMP onesia

Figure 53. Map of Thailand showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Thailand on the Travel Health Pro website.

UGANDA South Sudan Malaria Recommendations There is a high risk of malaria in Uganda Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Other countries This map is intended as a guide. It should be used with the recommendations in the DRC risk section Capital LAKE ALBERT City ▼ Point of interest **UGANDA** Kenya LAKE VICTORIA Tanzania Rwanda ◎ NaTHNaC. Adknowledgement: ACMP

Figure 54. Map of Uganda showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Uganda on the Travel Health Pro website.

VIETNAM China Hong Kong S.A.R. Malaria Recommendations There is a low risk of malaria in Vietnam Awareness and bite avoidance recommended There is no risk in Hanoi, Ho Chi Minh Laos City, the Red River Delta, coastal areas north of Nha Trang, and the island of Phu Quoc Other countries This map is intended as a guide. It should be used with the recommendations in the risk section **Thailand** Capital City VIETNAM SOUTH CHINA SEA Cambodia PHU QUOC MEKONG RIVER 0 100 km © NaTHNaC. Adknowledgement: ACMP

Figure 55. Map of Vietnam showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Vietnam on the Travel Health Pro website.

YEMEN Saudi Arabia Oman Malaria Recommendations There is a risk of malaria below 2,000m Antimalarials recommended: YEMEN chloroquine and proguanil There is very low risk on Socrota Island Awareness and bite avoidance recommended RED SEA There is no risk above 2,000m including in Sanaa City Al Mukalla Other countries This map is intended as a guide. It should be used with the recommendations in the trea ARABIAN SEA risk section Capital City Djibouti Ethiopia 100 km © NaTHNaC. Acknowledgement: ACMP

Figure 56. Map of Yemen showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Yemen on the Travel Health Pro website.

ZAMBIA Malaria Recommendations There is a high risk of malaria in Zambia Tanzania DRC Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine Other countries This map is intended as a guide. It should be used with the recommendations in the risk section Capital Angola City ▼ Point of interest Malawi ZAMBIA Mozambique Namibia Zimbabwe Victoria Falls Botswana @ NaTHNaC. Adknowledgement: ACMP

Figure 57. Map of Zambia showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Zambia on the Travel Health Pro website.

Summer (November-June) **ZIMBABWE** Malaria Recommendations There is a high risk of malaria in Zambezi Valley throughout the year and in areas of Zimbabwe below 1,200m from November to June Antimalarials recommended: atovaquoneproguanil or doxycycline or mefloquine There is a low risk of malaria above 1,200m throughout the year and in lowlands outside Zambezi Valley from July to October Awareness and bite avoidance recommended There is a very low risk of malaria in Harare and Bulawayo Awareness and bite avoidance recommended Winter (July-October) Other countries This map is intended as a guide. It should be used with the recommendations in the risk section Capital Point of interest 100 km © NaTHNaC. Acknowledgement: ACMP

Figure 58. Map of Zimbabwe showing the areas with appropriate malaria prevention measures recommended

Information about malaria in Zimbabwe on the Travel Health Pro website.

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