



Public Health
England

Protecting and improving the nation's health

Guidelines for malaria prevention in travellers from the UK 2015

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Executive summary

These practical guidelines from the Public Health England (PHE) 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.

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:

- **A**wareness of risk
- **B**ite prevention
- **C**hemoprophylaxis
- **D**iagnose 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 in Chapter 9.

This 2015 update of the guidelines includes the following key changes:

- updated guidance on the use of insect repellent and sun protection
- clarification on the use of hydroxychloroquine
- updated guidance on the use of anticoagulants with antimalarials
- updated guidance on the use of doxycycline in epilepsy
- changes to the country recommendations for Vietnam and Malaysian Borneo, and clarifications on the recommendations for India
- additional notes added at the beginning of the country recommendations table including information about vulnerable travellers
- new malaria maps for India and South Africa have been provided by NaTHNaC
- clarification of advice for travellers moving through areas where different antimalarials are recommended

- details about ACMP added (see [Appendices 1a-d](#)) including : membership, terms of reference and methodology used to make recommendations

These guidelines are available on the PHE website at <https://www.gov.uk/government/collections/malaria-guidance-data-and-analysis>. This site 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 PHE ACMP by Professor Peter Chiodini, Dr Dipti Patel, Professor Christopher Whitty and Professor David Lalloo (ACMP Chair).

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Abbreviations

AIDS Acquired Immune Deficiency Syndrome

ACMP Advisory Committee on Malaria Prevention for UK travellers

BIS British Infection Society

BNF British National Formulary

CDC Centers for Disease Control and Prevention

DEET N,N diethyl-m-toluamide (an insect repellent)

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 Hospital for Tropical Diseases

INR International Normalized Ratio

IPS International Passenger Survey

IPT Intermittent 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

PHE Public Health England

PI Protease Inhibitor

PCR Polymerase Chain Reaction

POM Prescription Only Medicine

RDT Rapid Diagnostic Test

RSTM&H Royal Society of Tropical Medicine and Hygiene

SP Sulfadoxine/pyrimethamine

SPC Summary of Product Characteristics or "data sheet"

TMHS Travel and Migrant Health Section

UK United Kingdom

VFR Visiting Friends and Relatives

WHO World Health Organization

1. 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.

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 risk assessment can be obtained from the Yellow Book, NaTHNaC and TRAVAX (see information resources, Chapter 9)

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. 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 exactly the same patterns of malaria exposure as permanent residents or visitors from other cultures.

1.1 How to give the advice

Emphasise to the traveller the ABCD of malaria prevention:

Awareness of risk

Bite prevention

Chemoprophylaxis

Dispose promptly and treat without delay

- emphasise that while no regimen is 100% effective, the **combination** of preventive measures advised will give significant protection against malaria
- 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. Public Health England has an information leaflet in Bengali, Gujarati, Punjabi and Urdu, in addition to English, which may be downloaded, photocopied and distributed free of charge (see Chapter 9)

1.2 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 (1) stated "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. (b) Inform the patient's general practitioner unless the patient objects."

ACMP suggests that 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.

2. Awareness of risk

2.1 What is malaria?

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 (21 in 2014).

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 (2).

Table 1 *Plasmodium* species that infect humans

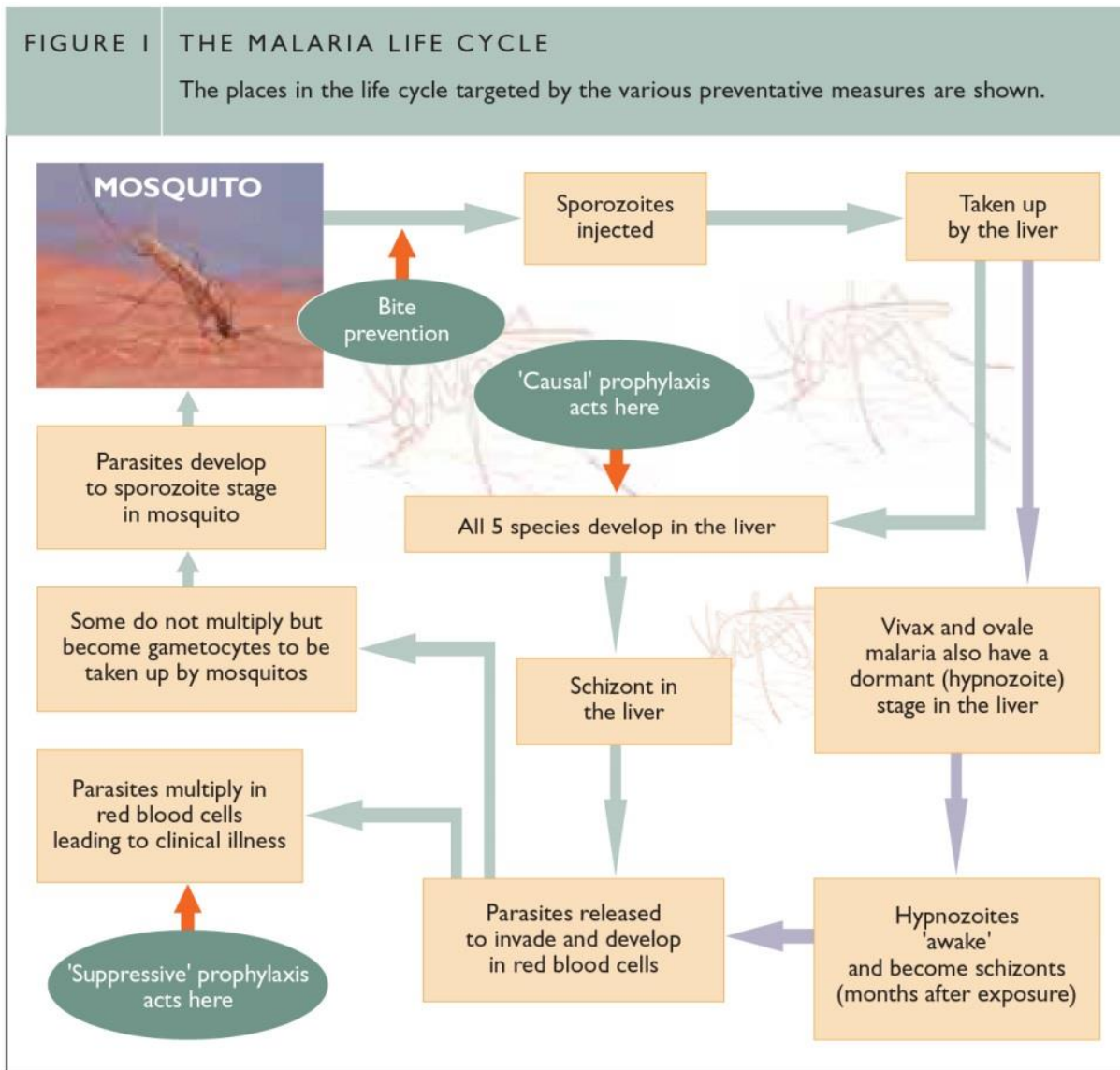
Species	Comment	Number of cases reported in the UK in 2014 out of 1586 ¹
<i>Plasmodium falciparum</i>	The most dangerous, responsible for the vast majority of malaria deaths worldwide	1169 (74%)
<i>Plasmodium vivax</i>	A relapsing malaria See life cycle	225 (14%)
<i>Plasmodium ovale</i>	A relapsing malaria See life cycle	130 (8%)
<i>Plasmodium malariae</i>	May present with late recrudescence after many years	41 (3%)
<i>Plasmodium knowlesi</i>	Very rarely imported at present, but capable of producing severe illness	0

2.2 Life cycle

An infected mosquito inoculates 10 to 15 sporozoites when it bites. Each sporozoite introduced into a human and successfully entering a liver cell develops in five to seven 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 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 numbers 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.

¹ The UK malaria figures for the preceding January to December are released annually on World Malaria Day (25th April) and can be accessed at <https://www.gov.uk/government/collections/malaria-guidance-data-and-analysis#epidemiology>

Figure 1 The malaria life cycle



2.3 The malarial illness

Malaria can neither be confirmed nor excluded by clinical features alone. The common symptoms and signs are shown in Table 2. 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 viral illness: viral hepatitis (if jaundice is present), gastroenteritis (if diarrhoea is evident) or lower respiratory tract infection (cough can be a non-specific symptom).

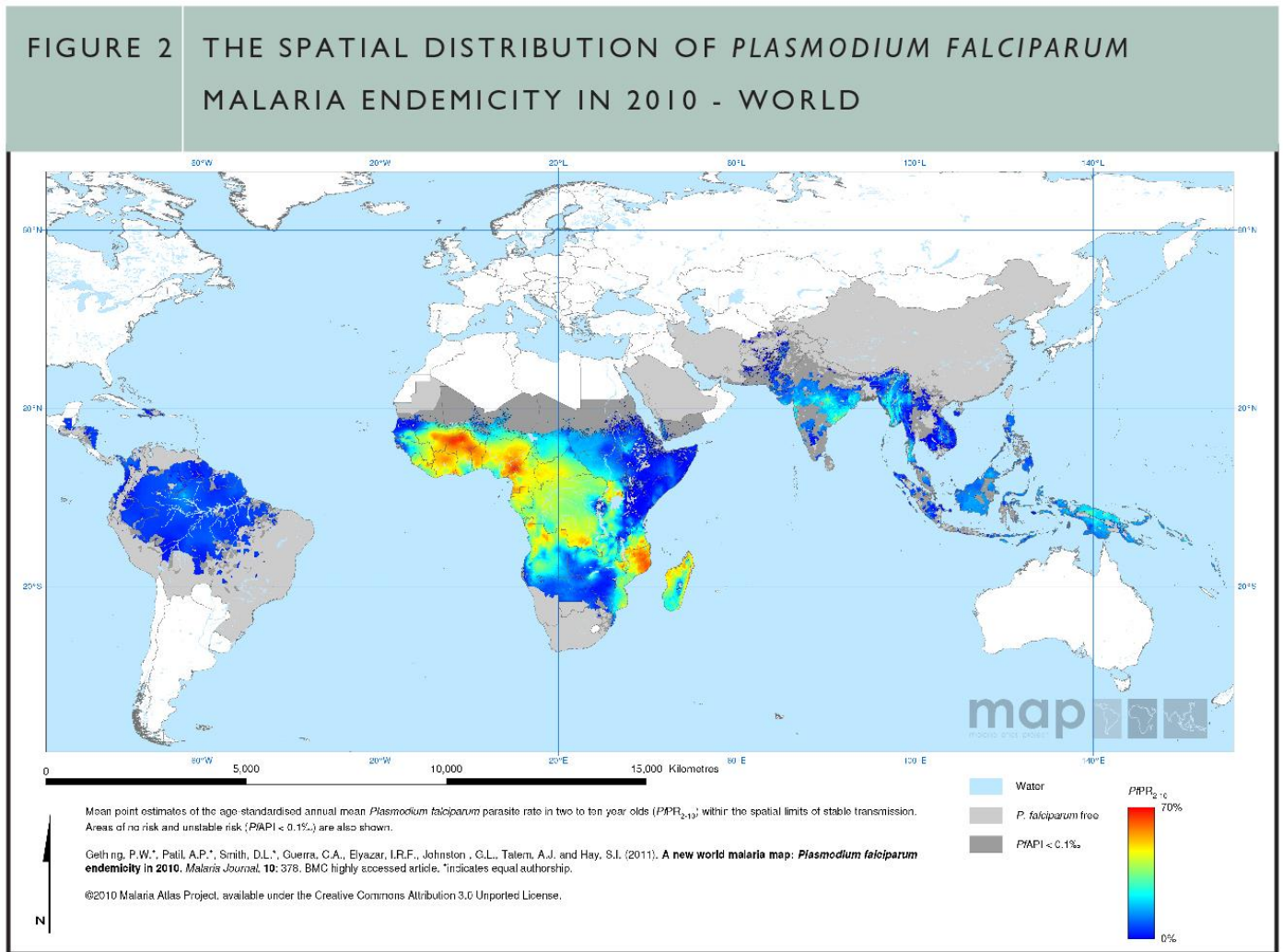
Table 2 Clinical symptoms and signs of malaria (from the ACMP malaria treatment guidelines)

Non-specific symptoms of malaria
Fever/sweats/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 < 0.4ml/kg bodyweight per hour or creatinine >265µmol/l) Acidosis (pH <7.3) Hypoglycaemia (<2.2mmol/l) Pulmonary oedema or acute respiratory distress syndrome (ARDS) Haemoglobin ≤8g/dL Spontaneous bleeding/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 <7.3) Hypoglycaemia Severe anaemia Prostration (inability to sit or stand) Parasitaemia >2% red blood cells parasitised

“Once you get malaria it keeps coming back” – true or false?

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.

Figure 2 The spatial distribution of *Plasmodium falciparum*



2.4 Where is malaria found?

Figure 2 shows the global distribution of falciparum and vivax malaria courtesy of the Malaria Atlas Project (3). It is for illustration and should not be used to advise individual travellers on chemoprophylaxis. Choice of preventive measures should be based on the information stated in Table 7.

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

Practitioners should be aware of the recent 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.

2.5 Level of risk of exposure to malaria and what affects it

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 (4).
- 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 temperature)
- parasite maturation in the mosquito usually cannot take place at altitudes greater than 2000 metres. However, it has been reported at altitudes up to 2500 metres in some countries
- seasonal rainfall increases mosquito breeding and in some areas malaria is highly seasonal

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 (5) but as Africa becomes increasingly urbanised, the risk of contracting malaria in African or other cities of malaria-endemic areas must not be discounted (6)

Type of accommodation:

- an impregnated bed net should be used unless the accommodation is fitted with functioning air-conditioning and windows and doors which are sufficiently well sealed to prevent mosquito entry
- backpackers 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 equipped with mosquito protection measures appropriate to their particular circumstances

Patterns of activity:

- being outdoors between dusk and dawn when *Anopheles* mosquitoes bite increases the risk

Length of stay:

- the longer the stay, the higher the risk of contracting malaria

2.6 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 Chapter 4
- there is currently no recorded drug resistance to *P. ovale* and only one report of drug-resistant *P. malariae* (to chloroquine) (7)
- 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 (8)
- *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 (8)

3. Bite prevention

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

3.1 When do female *Anopheles* mosquitoes bite?

Biting time varies between species, so travellers should assume they are at risk of being bitten 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 eg those which transmit yellow fever, dengue fever and other arboviral infections, bite during the daytime, it would be prudent also to maintain bite precautions during daylight hours.

3.2 Measures to prevent mosquito bites

3.2.1 Repellents

ACMP recommends DEET-based insect repellents as concentrations over 20% give a longer duration of protection than currently available formulations of other agents. If DEET is not tolerated (or is not available), an alternative preparation should be used, but few are as effective as DEET (see below) (9).

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 (10). It is available in a variety of concentrations and in various preparations including sprays and a slow release polymer. A variety of studies has concluded that there is a low risk of adverse effects when DEET is applied according to product directions (10).

As a guide, duration of protection is 1 to 3 hours for 20%, up to 6 hours for 30% and up to 12 hours for 50% DEET. There is no further increase in duration of protection beyond a concentration of 50% (11). Sweat-off time varies with activity. The interval between applications depends on this as well as the DEET formulation and concentration used.

DEET and sunscreen

Several studies have studied the impact of co-application of sunscreen and DEET. DEET (33 %) has been shown to decrease the protection from SPF 15 sunscreen (12) but there is no evidence that sunscreen reduces the efficacy of DEET when used at concentrations above 33 % (13, 14). Frequent (every 2 hours) reapplication of sunscreen over DEET applied at below the recommended 20 % (17 %), was found to reduce the mean repellency rate and also mean protection time (by about one hour) compared with DEET alone (14).

Stanczyk et al (15) recommended advising travellers to: apply repellent first; use a combined repellent and sunscreen product; be aware that repellent may wear off more quickly if reapplying only sunscreen on top.

New ACMP recommendation for 2015: Repellent activity will reduce more quickly than that of a sunscreen if reapplying only sunscreen on top and 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.** 30 to 50 SPF sunscreen should be applied to compensate for DEET-induced reduction in SPF. Sunscreen is not required from dusk to dawn.

DEET is not recommended for infants below the age of 2 months.

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 (16). 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:

- DEET is suitable for all individuals over the age of 2 months (unless allergic)
- 50% has the longest duration of action, and needs fewer applications per day
- there is no current evidence that any group (including pregnant women and small children) is at increased risk from using 50% DEET
- lower concentrations are available:
 - they need more frequent application and may not be as effective as 50%
 - care must be taken to re-apply or use a higher concentration DEET preparation if mosquito biting occurs after their use
 - lower concentrations are not suitable for individuals who may expect prolonged exposure, such as that encountered by backpackers and expedition travellers
 - ACMP considers concentrations below 20% inappropriate in almost any circumstances
- DEET applications can damage some plastic watch straps, watch 'glasses' 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

p-menthane 3,8 diol (lemon eucalyptus)

p-menthane 3,8 diol (PMD) gives about the same amount of protection afforded by 15% DEET (17) but is reported to provide a shorter period of protection than extended duration (microencapsulated) DEET (18).

Icaridin (Picaridin)

Icaridin (KBR3023) (1piperidinecarboxylic acid, 2-(2hydroxyethyl)-,1-methyl-propylester) is reported to have repellent properties comparable to those of DEET (19-21). Icaridin is available in various concentrations (22, 23). If a traveller elects to use icaridin for mosquito bite prevention, ACMP advises use of at least a 20% preparation.

3-ethlyaminopropionate

3-ethlyaminopropionate (IR3535) has a shorter duration of protection than DEET (20, 24) which gives protection times against *Anopheles* 20 to 25% higher than IR3535 at equal concentrations (25).

Oil of citronella

While oil of citronella-based products do have repellent properties, they provide short-lived protection (24) and are not recommended by ACMP. Citronella has been withdrawn in Europe.

3.2.2 Insecticides

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

3.2.3 Nets

If sleeping outdoors or in unscreened accommodation, insecticide-treated mosquito nets should be used. Protective efficacy for travellers has been estimated at 50% (26).

Mosquito bed nets must be free of tears and should be tucked in under the mattress. 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 (c) diversion of mosquitoes from someone under a net to someone in the same room without a net (27). Most of the nets now available are long-lasting impregnated nets. In these products the pyrethroid is incorporated into the material of the net itself or bound to it with a resin (28). They have an expected useful life of at least 3 years. If using standard nets these will need to be re-impregnated every 6 to 12 months (depending on how frequently the net is washed) to remain effective (29). If a traveller purchases a standard impregnated net, the 6 months starts from the date when it starts to be used and washed, as washing and handling are the main factors removing the pyrethroid.

3.2.4 Clothing

Within the limits of practicality, cover up with loose-fitting clothing, long sleeves, long trousers and socks if out of doors after sunset, 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, eg permethrin (29) or purchased pre-treated to reduce biting through the clothing. As an alternative, cotton clothing (eg socks) can be sprayed with DEET. It is useful as a clothing repellent but its duration on clothing is shortened due to its volatility (30).

3.2.5 Room protection

Air conditioning reduces the likelihood of mosquito bites as a result of substantial reduction in night time temperature. Ceiling fans 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.

During the night, where electricity is available, use a proprietary heated liquid reservoir device containing insecticide or an electrically heated device to vapourise a “mat” (tablet) containing a synthetic pyrethroid in the room. A new mat is needed each night. Burning of a mosquito coil containing insecticide is an alternative which can repel and kill mosquitoes (31) but is not recommended for use indoors.

3.2.6 Fallacies

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.

Vitamin B1

There is no evidence that vitamin B1 taken orally repels mosquitoes (32, 33).

Vitamin B12

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

Garlic

There is no evidence that garlic taken orally repels mosquitoes (34).

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

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

4. 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 (35), 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 web site.

4.1 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 Figure 1). 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 (36), so ACMP recommends that they are continued for 7 days after leaving a malarious area (see Table 3 of drug regimens in Chapter 4).

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 and thus needs to be taken for several weeks to prevent infection (37).

Therefore, suppressive prophylactic drugs should be continued for 4 weeks after leaving a malarious area (see drug regimens in Table 3, Chapter 4).

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 (38).

Primaquine is occasionally used for terminal prophylaxis (also known as presumptive anti-relapse therapy) to eradicate hypnozoites of *P. vivax* and *P. ovale*. However, the routine use of primaquine for 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 Chapter 9).

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

4.2 The drugs

The British National Formulary (BNF) contains full listings of drug actions, dosages, side effects, interactions and contraindications summarised here and should be consulted as required when recommending malaria chemoprophylaxis. ACMP guidance on individual drugs is not as detailed as that provided for prescribers in manufacturers' information sheets.

Chapter 6 of these guidelines also provides details of contraindications for different medical conditions such as pregnancy and renal impairment.

NOTE: All adverse events of medication, including attacks of malaria, should be reported. 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 Medicines and Healthcare products Regulatory Agency (MHRA) website.

www.mhra.gov.uk

These drugs are not listed in order of preference.

4.2.1 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 & the Dominican Republic). Prophylaxis with chloroquine as a single agent is therefore rarely appropriate (see Table 7). It remains effective against most *P. vivax*, all *P. ovale*, *P. knowlesi*, and virtually all *P. malariae*.

Side-effects

The main side effects are gastrointestinal disturbances and headache. Convulsions are recorded. Chloroquine may cause itching in persons of African descent.

Interactions

Drugs: Amiodarone (increased risk of ventricular arrhythmias); ciclosporin (increased risk of toxicity); digoxin (possibly increases plasma concentration of digoxin); mefloquine (increased risk of convulsions); moxifloxacin (increased risk of ventricular arrhythmias; avoid concomitant use).

Vaccines: Chloroquine may suppress the antibody response to pre-exposure intradermal human diploid cell rabies vaccine (39). This interaction is not seen when rabies vaccine is given intramuscularly (the currently recommended mode of vaccination in the UK).

Contraindications

Chloroquine prophylaxis may exacerbate psoriasis and myasthenia gravis. It is contraindicated 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.

Cautions

Chloroquine is highly toxic in overdosage, so should be stored out of the reach of children. In long term use, eye examinations every 6-12 months should be considered after 6 years' prophylactic usage, though the risk of retinopathy developing on prophylactic dosage is considered to be very low (40). See also long-term traveller section in Chapter 7.

Methods of administration

Tablets contain 155 mg chloroquine base; syrup contains chloroquine base 50 mg/5 ml (see paediatric dosages in Tables 4 and 5). Adult dose 310 mg (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.

4.2.1.1 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.

4.2.2 Proguanil

Mode of action

Proguanil is converted to an active metabolite cycloguanil which inhibits the enzyme dihydrofolate reductase and interferes with the synthesis of folic acid. It acts as a suppressive and also as a causal prophylactic (41). Proguanil itself has a second mode of action, mediated by the parent drug rather than its metabolite, which produces synergy with atovaquone (see atovaquone plus proguanil).

Efficacy

There are very few regions in the world where the local *P. falciparum* strains are fully sensitive to proguanil, so prophylaxis with proguanil as a single agent is rarely appropriate.

Side-effects

The principal side effects of proguanil are mild gastric intolerance and diarrhoea. Mouth ulcers and stomatitis occur occasionally, particularly when combined with chloroquine.

Interactions

Drugs: May enhance the anticoagulant effect of warfarin. Absorption reduced by oral magnesium salts. Antifolate effect is increased when given with pyrimethamine.

Vaccines: None reported

Contraindications

Allergy to proguanil

Cautions

Renal impairment. Pregnancy (folic acid 5mg daily required for at least the first trimester).

Methods of administration

100mg tablets only. Adult dose 200 mg daily, starting one week before entering a malarious area, continuing throughout the time in the area and for 4 weeks after leaving the area.

4.2.3 Chloroquine plus proguanil

For side effects, interactions, contraindications and methods of administration, please see individual agents.

ACMP does not recommend the use of chloroquine plus proguanil for travellers to sub-Saharan Africa. If no alternative is felt to be appropriate, the matter should be discussed with an expert centre (see Chapter 9).

4.2.4 Mefloquine

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 (42, 43). At the present time, significant resistance of *P. falciparum* to mefloquine is a problem only in some areas of south-East Asia (44), but is reported sporadically from the Amazon basin.

Side-effects

ACMP is not aware of any new data on side-effects since the 2014 update, but attention has focused on neuropsychiatric problems and vestibular disorders with mefloquine prophylaxis. 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 (45) but there is no evidence that mefloquine use increases the risk of first-time diagnosis of depression though it may increase the risk of psychosis and anxiety reactions (42, 46) and no association between mefloquine prescriptions and hospitalisation (47). 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. Overall, mefloquine remains an important prophylactic agent which is tolerated by the majority of travellers who take it (42, 48).

Interactions

Drugs: Mefloquine antagonises the anticonvulsant effect of antiepileptics and interacts with a number of cardiac drugs. Mefloquine is metabolised in the liver by CYP3A4. Caution if administered with drugs inhibiting this enzyme (eg itraconazole) (42). Ritonavir levels are reduced by mefloquine due to decreased absorption, but the clinical significance of this interaction is unknown.

Contraindications

See also the manufacturer's SPC.

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

Mefloquine prophylaxis is contraindicated in those currently receiving halofantrine or those with:

- hypersensitivity to quinine or quinidine
- 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
- a history of Blackwater fever
- severe impairment of liver function

Use of a checklist should ensure that proper screening is undertaken prior to mefloquine administration and these contraindications are followed (49).

Cautions

Pregnancy (see Chapter 6, special groups); breast-feeding (see Chapter 6, special groups); cardiac conduction disorders. Not recommended in infants under 5kg.

The SPC suggests that periodic checks on liver function and eye assessments should be taken 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 or not to advise mefloquine chemoprophylaxis should be made on an individual basis after a detailed risk assessment.

Can mefloquine be taken by those who plan to undertake underwater diving?

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.

Methods of administration

Oral. 250mg tablets. Weekly dosage, starting 2-3 weeks before entering a malarious area to assess tolerability, continuing throughout the time in the area and for 4 weeks after leaving the malarious area.

4.2.5 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 (50).

Side-effects

Doxycycline hydrochloride preparations have a low pH and may produce oesophagitis, especially if taken on an empty stomach and/or just before lying down. Doxycycline may cause photosensitivity which is mostly mild and transient (51).

Doxycycline is a broad spectrum antibiotic and may predispose to vaginal candidiasis (52).

Interactions

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 (eg 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 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.

Contraindications

Allergy to tetracyclines. Children under 12 years of age.

Pregnancy: 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, see www.toxbase.org (53). The course of doxycycline, including the 4 weeks after travel, must be completed before 15 weeks' gestation.

Breast feeding: The British National Formulary states that tetracyclines should not be given to women who are breast feeding (54).

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 (52).

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. Myasthenia gravis. Systemic lupus erythematosus.

Methods of administration

Capsules (50 or 100mg) or dispersible 100mg tablets only (consult summary of product characteristics pertaining to individual products). Dose 100mg daily, starting 1 to 2 days before entering a malarious area, continuing whilst there and for 4 weeks after leaving.

Precautions in use

The prescriber should warn against excessive sun exposure (and advise on the correct use of a broad spectrum sunscreen), the risk of vaginal candidiasis and the risk of oesophagitis if taken on an empty stomach and/or lying down too soon after taking it. Doxycycline should be swallowed whole with plenty of fluid during meals while sitting or standing and the traveller should not lie down within an hour of taking it.

4.2.6 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 (55). 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 (56). 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 (57-65). 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 (64, 66). However, like chloroquine-proguanil, mefloquine and doxycycline, it will not protect against hypnozoite-induced episodes of *P. vivax* (or *P. ovale*) malaria.

Side-effects

The most frequent side-effects are headache and gastrointestinal upsets.

Interactions

For proguanil see proguanil section (above).

Drugs: Plasma concentration of atovaquone is reduced by rifabutin and rifampicin (possible therapeutic failure of atovaquone, avoid concomitant use), tetracycline (clinical significance of this is not known) and metoclopramide.

Antiretrovirals: Atovaquone possibly reduces plasma concentration of indinavir. Atovaquone possibly inhibits metabolism of zidovudine (increased plasma

concentration). Avoid concomitant use of atovaquone with ritonavir-boosted protease inhibitors and most non-nucleoside reverse transcriptase inhibitors. If use unavoidable seek expert advice.

Vaccines: None reported.

Contraindications

Pregnancy: The BNF states “Manufacturer advises avoid unless essential.” 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. 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 (67).

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.

Cautions

Renal impairment (avoid for malaria prophylaxis if eGFR less than 30 mL/minute/1.73 m²) diarrhoea or vomiting (reduced absorption of atovaquone).

Methods of administration

Tablets containing proguanil 100 mg and atovaquone 250 mg. Paediatric tablets containing proguanil 25 mg and atovaquone 62.5 mg. Adult dose one tablet daily starting 1 to 2 days before entering a malaria endemic area, continuing throughout the time there and for 1 week after leaving. Paediatric dosage given in Table 6.

4.3 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 3 Prophylactic regimens against malaria in adults

Regimen	Dose for chemoprophylaxis	Usual amount for tablet (mg)
Areas of chloroquine-resistant <i>P. falciparum</i>		
Mefloquine	One tablet weekly	250
Doxycycline	One tablet/capsule daily	100
Atovaquone-proguanil combination preparation	One tablet daily	250 (atovaquone) plus 100 (proguanil)
Areas of little chloroquine resistance; poorly effective where extensive resistance		
Chloroquine PLUS proguanil	Two tablets weekly PLUS Two tablets daily	155 (base) 100
Areas without drug resistance		
Chloroquine OR Proguanil (if chloroquine not suitable; see text)	Two tablets weekly Two tablets daily	155 (base) 100

Table 4 Doses of prophylactic antimalarials for children

Weight in kilograms	Drug and tablet size			
	Chloroquine 155mg	Proguanil 100mg	Mefloquine 250mg	Doxycycline 100mg
Under 6.0	0.125 dose ¼ tablet	0.125 dose ¼ tablet	See footnote ²	Not recommended
6.0 to 9.9	0.25 dose ½ tablet	0.25 dose ½ tablet	0.25 dose ¼ tablet	Not recommended
10.0 to 15.9	0.375 dose ¾ tablet	0.375 dose ¾ tablet	0.25 dose ³ ¼ tablet	Not recommended
16.0 to 24.9	0.5 dose One tablet	0.5 dose One tablet	0.5 dose ½ tablet	Not recommended
25.0 to 44.9	0.75 dose 1-1/2 tablets	0.75 dose 1-1/2 tablets	0.75 dose ¾ tablet	Adult dose from age 12 years One tablet ⁴
45 and over	Adult dose Two tablets	Adult dose Two tablets	Adult dose One tablet	Adult dose One tablet

NB. 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.

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 Table 6
- As at July 2015, chloroquine syrup is not available in the UK

² The SPC for mefloquine indicates that it can be used for those weighing more than 5 kgs.

Therefore, mefloquine (0.25 dose, ¼ tablet) may be advised for children weighing 5 to 9.9 kg.

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

⁴ The adult dose is necessary when doxycycline is only available in capsule form and 3/4 is not feasible.

Table 5 Table of doses by spoon or syringe⁵ 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
4.5–7.9	1.0 (5.0 ml)	0.16
8.0–10.9	1.5 (2.5 ml plus 5 ml)	0.24
11.0–14.9	2.0 (2 x 5 ml)	0.32
15.0–16.5	2.5 (2.5 ml plus 2 x 5 ml)	0.40

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

Table 6 Table of paediatric dose 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 or 1 adult

See section 7.1 for advice on how to administer antimalarials to children.

⁵ Chemists may dispense dosing syringes for child doses.

4.4 Country recommendations

ACMP recommendations by country are summarised in Table 7

Key to Table 7:

A/P: atovaquone-proguanil combination preparation

BA only: bite avoidance plus awareness of risk

C: chloroquine

C+P: chloroquine plus proguanil

D: doxycycline

M: mefloquine.

Notes

1. Bite avoidance is advised even in malaria-free areas of the countries listed in this table as a preventive measure against other insect vector-borne diseases
2. Some countries not listed in this table may experience occasional instances of malaria transmission. Please check the [NaTHNaC](#) or [TRAVAX](#) websites regularly for clinical updates
3. 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 Chapter 3 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.
4. 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. Whilst the local malaria situation is the same for all travellers to a given location, long-term VFR visitors run a higher risk. Furthermore, once infected, the risk of developing severe or complicated malaria is higher in certain groups, eg the elderly, those with complex co-morbidity and especially pregnant women.

Table 7 Country recommendations

Country name	ACMP recommendations 2015
Afghanistan	There is a risk of malaria below 2000m from May to November (C+P). There is a low risk of malaria in this part of the country during the rest of the year (BA only).
Algeria	There is a very low risk of malaria in a small, remote focus in the Illizi Department of Algeria (BA only). There is no risk in the rest of Algeria.
Andaman and Nicobar Islands (India)	There is a risk of malaria in the Andaman and Nicobar Islands (BA only).
Angola	There is a high risk of malaria in Angola (A/P,D, M).
Argentina	There is a low risk of malaria in low altitude areas of Salta provinces bordering Bolivia and in Chaco, Corrientes and Misiones provinces close to the border with Paraguay and Brazil (C only). There is no risk of malaria in Iguazu Falls and the rest of Argentina (BA only).
Armenia	There is no risk of malaria in Armenia (BA only)
Azerbaijan	There is low to no risk of malaria in Azerbaijan (BA only)
Bangladesh (see Figure 3)	There is a high risk of malaria in the Chittagong Hill Tract districts of Bangladesh (A/P,D, M). There is low to no risk in the rest of Bangladesh (including Chittagong city) (BA only).
Belize	There is a low risk of malaria in rural Belize (C only). There is no risk of malaria in Belize district including Belize City and islands frequented by tourists. (BA only)
Benin	There is a high risk of malaria in Benin (A/P,D, M).
Bhutan	There is a risk of malaria in the southern belt districts of Bhutan along the border with India: Chukha, Geyleg-phug, Samchi, Samdrup Jonkhar and Shemgang (C+P). There is low to no risk in the rest of Bhutan (BA only).
Bolivia	There is a high risk of malaria in the Amazon basin of Bolivia (A/P,D, M). There is a risk of malaria in other rural areas below 2500m (C only). There is no risk above 2500m (BA only).
Botswana	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 low to no risk in the southern half of the country (BA only).
Brazil (see Figure 4)	There is a risk of malaria in the Amazon basin of Brazil, including in the city of Manaus (A/P,D, M). There is a very low risk of malaria in the rest of Brazil (BA only). There is no risk of malaria in Iguaçu Falls (BA only).
Brunei Darussalam	There is very low risk of malaria in Brunei Darussalam (BA only).
Burkina Faso	There is a high risk of malaria in Burkina Faso (A/P, D, M).
Burundi	There is a high risk of malaria in Burundi (A/P, D, M).
Cambodia	There is a high risk of malaria in Cambodia. Chloroquine and mefloquine resistance is widespread in the western provinces of Cambodia bordering Thailand (A/P, D). Chloroquine resistance is present in the rest of Cambodia (A/P, D, M). 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 (BA only).
Cameroon	There is a high risk of malaria in Cameroon (A/P, D, M).
Cape Verde	There is a very low risk of malaria on the Island of Santiago (Sao Tiago) and Boa Vista (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	There is a high risk of malaria in Yunnan and Hainan provinces in China (A/P, D, M). There is a very low risk of malaria in southern and some central provinces, including Anhui, Ghuizhou, Henan, Hubei, Jiangsu below 1500m (BA only). The rest of China, including the main tourist areas and cruises on the Yangtze river, are also very low risk (BA only).
China (Hong Kong)	There is no risk of malaria in Hong Kong.
Colombia	There is a high risk of malaria in most rural areas of Colombia below 1600m (A/P, D, M). There is low to no risk in areas above 1600m and in Cartagena (BA only).
Comoros	There is a high risk of malaria in the Comoros (A/P, D, M).
Congo	There is a high risk of malaria in the Congo (A/P, D, M).
Costa Rica	There is a risk of malaria in Limon Province (C 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	There is a high risk of malaria in the Cote d'Ivoire (A/P, D, M).
Democratic Republic of the Congo	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 risk of malaria in all areas of the Dominican Republic (C only), except in the cities of Santiago and Santo Domingo (BA only).
East Timor (Timor-Leste)	There is a high risk of malaria in East Timor (A/P, D, M).
Ecuador	There is a risk of malaria in areas below 1500m, including the coastal provinces and Amazon basin (A/P, D, M). 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	There is a low risk of malaria in rural areas of Santa Ana, Ahuachapán and La Unión provinces in western El Salvador (BA only). There is low to no risk in the rest El Salvador (BA only)
Equatorial Guinea	There is a high risk of malaria in Equatorial Guinea (A/P, D, M).
Eritrea	There is a high risk of malaria in Eritrea below 2200m (A/P, D, M). There is no risk of malaria in Asmara or in areas above 2200m.
Ethiopia	There is a high risk of malaria in Ethiopia below 2000m (A/P, D, M). There is no risk of malaria in Addis Ababa or in areas above 2000m.
French Guiana	There is a high risk of malaria in French Guiana, particularly in the border areas (A/P, D, M). There is no risk of malaria in the city of Cayenne or Devil's Island (Ile du Diable). (BA only)
Gabon	There is a high risk of malaria in Gabon (A/P, D, M).
Gambia	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	There is a high risk of malaria in Ghana (A/P, D, M).

Guatemala	There is a low risk of malaria in Guatemala below 1500m (C only). There is no risk in Guatemala City, Antigua and Lake Atitlan and areas above 1500m.
Guinea	There is a high risk of malaria in Guinea (A/P, D, M).
Guinea-Bissau	There is a high risk of malaria in Guinea-Bissau (A/P, D, M).
Guyana	There is a high 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).
Haiti	There is a risk of malaria in Haiti (C only).
Honduras	There is a risk of malaria below 1000 m and in Roatán and other Bay Islands (C only). There is no risk of malaria in San Pedro Sula and Tegucigalpa and areas above 1000m.
India (see Figure 5)	There is a risk of malaria sufficiently high to justify chemoprophylaxis 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) ACMP no longer considers the risk of contracting malaria sufficiently high to justify the use of chemoprophylaxis (BA only). There is no risk of malaria in the Lakshadweep islands.
Indonesia	There is a high risk in Lombok and Irian Jaya (Papua) (A/P, D, M). Risk in the rest of Indonesia (C+P). There is very low risk in Bali, and the cities on the islands of Java and Sumatra (BA only). There is no risk in the city of Jakarta.
Indonesia (Borneo)	There is a high risk of malaria in Indonesian Borneo (A/P, D, M).
Iran	There is a 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 (C+P). There is low to no risk in the rest of Iran. (BA only)
Iraq	There is a very low risk of malaria in the rural northern area of Iraq below 1500m, from May to November (BA only). There is no risk in the rest of Iraq.

Kenya	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 2500m (BA only).
Kyrgyzstan	There is a very low risk of malaria in the southwest of Kyrgyzstan, in areas bordering Tajikistan and Uzbekistan, from June to October (BA only). There is no risk in the rest of Kyrgyzstan.
Lao People's Democratic Republic (Laos)	There is a high risk of malaria along the Laos-Myanmar border in the provinces of Bokeo and Louang Namtha and along the Laos-Thailand border in the province of Champasak and Saravan (A/P, D). There is a high risk of malaria in the rest of Laos (A/P, D, M). There is low to no risk in the city of Vientiane (BA only).
Liberia	There is a high risk of malaria in Liberia (A/P, D, M).
Libya	There is no risk of malaria in Libya (BA only)
Madagascar	There is a high risk of malaria in Madagascar (A/P, D, M).
Malawi	There is a high risk of malaria in Malawi (A/P, D, M).
Malaysia	There is a risk of malaria in the inland, forested areas of peninsular Malaysia (A/P, D, M). There is a very low risk in the rest of peninsular Malaysia, including the Cameron Highlands and the city of Kuala Lumpur (BA only).
Malaysia (Borneo)	There is a high risk of malaria in inland areas of Sabah and in the inland, forested areas of Sarawak (A/P, D, M). 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	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 risk of malaria in Mayotte (A/P, D, M).

Mexico	There is a low risk of malaria in the states of Oaxaca and Chiapas in southern Mexico (C only). There is a very low risk of malaria in the states of Chihuahua, Durango, Nayarit, Quintana Roo and Sinaloa and the rest of Mexico (BA only).
Mozambique	There is a high risk of malaria in Mozambique (A/P, D, M).
Myanmar	There is a high risk of malaria in Myanmar (A/P,D). There is no risk in the cities of Mandalay and Yangon (BA only).
Namibia	There is a high risk of malaria from November to June in the northern third of Namibia (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 Caprivi Strip, Kavango and Kunene river regions the risk is throughout the year (A/P, D, M). There is low to no risk of malaria in the rest of Namibia (BA only).
Nepal	There is a risk of malaria in areas of Nepal below 1500m, particularly in the Terai district (C+P). There is no risk of malaria in the city of Kathmandu and on typical Himalayan treks (BA only).
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 (C only).
Niger	There is a high risk of malaria in Niger (A/P, D, M).
Nigeria	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	There is a risk of malaria in areas of Pakistan below 2000m (C+P). There is low to no risk above 2000m (BA only).
Panama	There is a risk of malaria east of the Canal Zone in Panama (C+P). There is a low risk of malaria west of the Canal Zone (C only). There is no risk of malaria in Panama City or the Canal Zone itself (BA only).
Papua New Guinea	There is a high risk of malaria in Papua New Guinea below 1800m (A/P, D, M). There is low to no risk above 1800m (BA only).

Paraguay	There is a low risk of malaria in the departments of Alto Paraná and Caaguazú (C only). There is a very low risk of malaria in all other areas of Paraguay (BA only).
Peru	There is a high risk of malaria in the Amazon basin of Peru along the border with Brazil, particularly in Loreto province (A/P, D, M). . There is a risk of malaria in the other rural areas of Peru below 2000m including that part of the Amazon Basin which borders Bolivia (C only). There is no risk in the city of Lima and the coastal region south of Chiclayo (BA only)
Philippines	There is a risk of malaria in rural areas of the Philippines below 600m and on the islands of Luzon, Mindanao, Mindoro, and Palawan (C+P). There is no risk in cities or on the islands of Boracay, Bohol, Catanduanes, Cebu and Leyte (BA only).
Rwanda	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	There is a risk of malaria in the south western provinces of Saudi Arabia, along the border with Yemen including Asir province below 2000m (C+P). There is no risk in the cities of Jeddah, Makkah (Mecca), Medina, Riyadh, and Ta'if, or in Asir province above 2000m (BA only).
Senegal	There is a high risk of malaria in Senegal (A/P, D, M).
Sierra Leone	There is a high risk of malaria in Sierra Leone (A/P, D, M).
Singapore	There is no risk of malaria in Singapore.
Solomon Islands	There is a high risk of malaria in the Solomon Islands (A/P, D, M).
Somalia	There is a high risk of malaria in Somalia (A/P, D, M).
South Africa (see Figure 6)	There is a moderate risk of malaria in South Africa from September to May only in the low altitude areas of Mpumalanga and Limpopo which border Mozambique and Zimbabwe; this includes the Kruger National Park (A/P, D, M). There is a low risk of malaria in northeast KwaZulu-Natal (BA only). The areas bordering these are low risk (BA only).

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 a low risk of malaria in the area north of Vavuniya in Sri Lanka (BA only). There is very low to no risk in the rest of Sri Lanka (BA only). There is no risk of malaria in Colombo and Kandy.
Sudan	There is a high risk of malaria in the central and southern parts of Sudan and a risk of malaria in the rest of the country (A/P, D, M). There is a very low risk in Khartoum (BA only).
Suriname	There is a high risk of malaria in Suriname (A/P, D, M). There is a very low risk of malaria in coastal districts (BA only). There is no risk in the city of Paramaribo (BA only).
Swaziland	There is a high risk of malaria in the northern and eastern regions bordering Mozambique and South Africa, including all of 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).
Syria	There is a very low risk of malaria in small, remote foci of El Hasaka (BA only).
Tajikistan	There is a risk of malaria in Tajikistan from June to October, in areas below 2000m (C+P). There is a low risk of malaria in this part of the country during the rest of the year (BA only). There is no risk of malaria above 2000m.
Tanzania	There is a high risk of malaria in all areas below 1800m (A/P, D, M). There is no risk of malaria above 1800m. There is a risk of malaria in Zanzibar (A/P, D, M).

Thailand	<p>There is a high risk of malaria in the rural, forested borders of Thailand with Cambodia, Laos and Myanmar (CQ and M resistance) (A/P, D).</p> <p>There is a very low risk of malaria in the remaining areas of Thailand including Kanchanaburi (Kwai Bridge) (BA only).</p> <p>There is no risk of malaria in the cities of Bangkok, Chiang Mai, Chiang Rai, Koh Phangan, Koh Samui, and Pattaya (BA only).</p>
Togo	There is a high risk of malaria in Togo (A/P, D, M).
Turkey	<p>There is a low risk of malaria in Turkey along the border plain with Syria, around Adana and to the east of Adana from May to October (C only). There is a very low risk of malaria in this part of the country during the rest of the year (BA only).</p> <p>The rest of Turkey, including most tourist areas, is very low risk (BA only).</p>
Uganda	There is a high risk of malaria in Uganda (A/P, D, M).
Uzbekistan	There is a very low risk of malaria in the extreme southeast of Uzbekistan (BA only).
Vanuatu	There is a risk of malaria in the whole of Vanuatu (A/P, D, M).
Venezuela	There is a high risk of malaria in all areas of Venezuela south of and including the Orinoco River and Angel Falls (A/P, D, M). There is a risk of malaria in rural areas of Apure, Monagas, Sucre and Zulia states (C+P). There is no risk in the city of Caracas or on Margarita Island (BA only)
Vietnam	<p>There is a risk of malaria in the southern part of the country in the provinces of Tay Ninh, Lam Dong, Dac Lac, Gia Lai, and Kon Tum (A/P, D). There is also a risk of malaria in all other rural areas of Vietnam (A/P, D).</p> <p>There is a very low risk in the Mekong River delta (BA only) until the border area with Cambodia. There is no risk in large cities, including Hanoi and Ho Chi Minh (Saigon), the Red River delta, coastal areas north of Nha Trang and Phu Quoc Island (BA only).</p>
Western Sahara	There is no risk of malaria in this country (BA only)

Yemen	There is a risk of malaria in Yemen below 2000m (C+P). There is very low risk of malaria on Socrota Island (BA only). There is no risk of malaria above 2000m including Sana'a city (BA only).
Zambia	There is a high risk of malaria in Zambia (A/P, D, M).
Zimbabwe	There is a high risk of malaria in Zimbabwe below 1200m 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).

4.5 Popular destinations

Figure 3 Map of Bangladesh showing the areas with appropriate malaria prevention measures recommended

FIGURE 4 BANGLADESH SHOWING THE AREA WHERE CHEMOPROPHYLAXIS RECOMMENDED

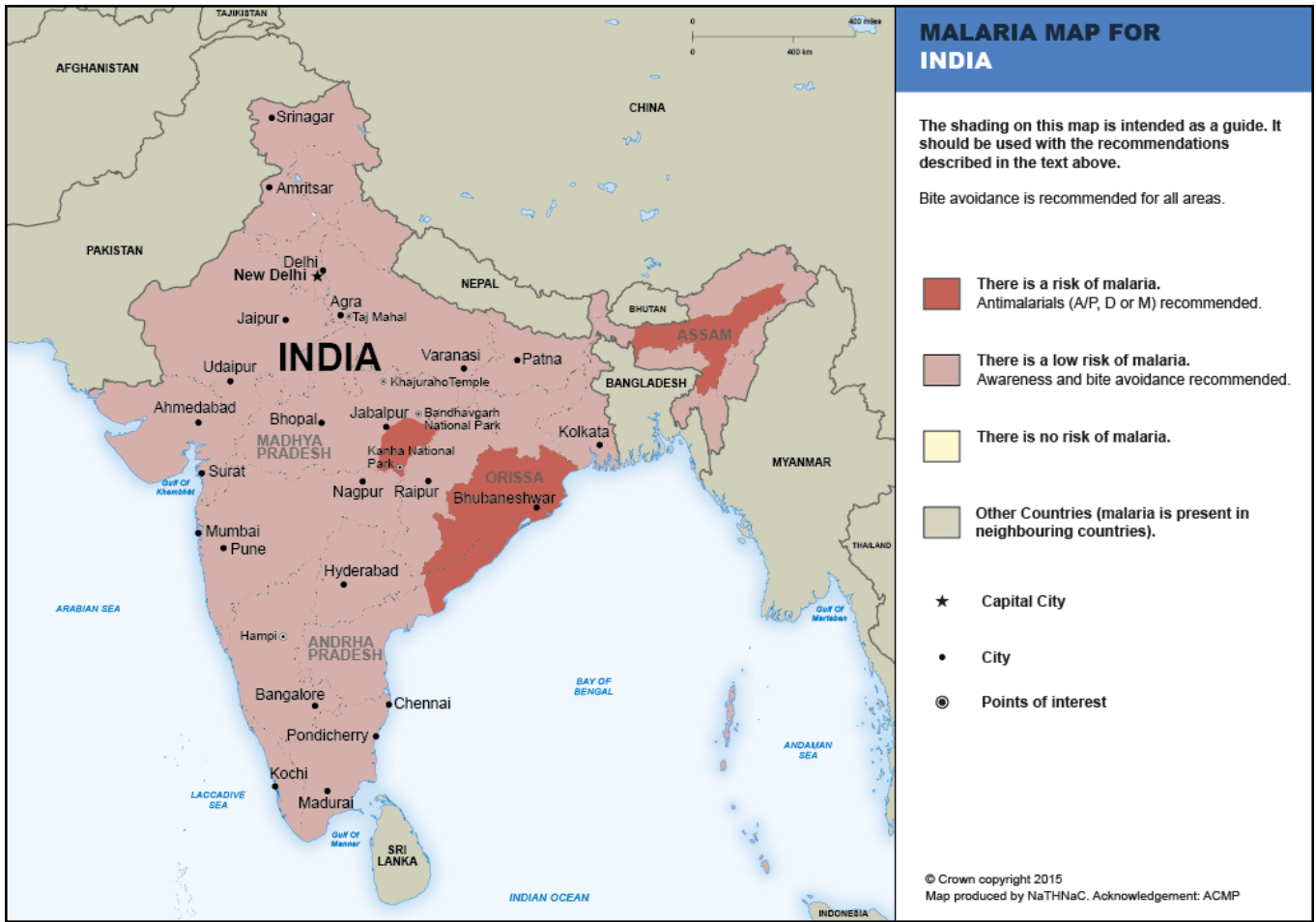


Figure 4 Map of Brazil showing the states with appropriate malaria prevention measures recommended

FIGURE 5 MAP OF BRAZIL SHOWING THE STATES WHERE CHEMOPROPHYLAXIS IS REQUIRED

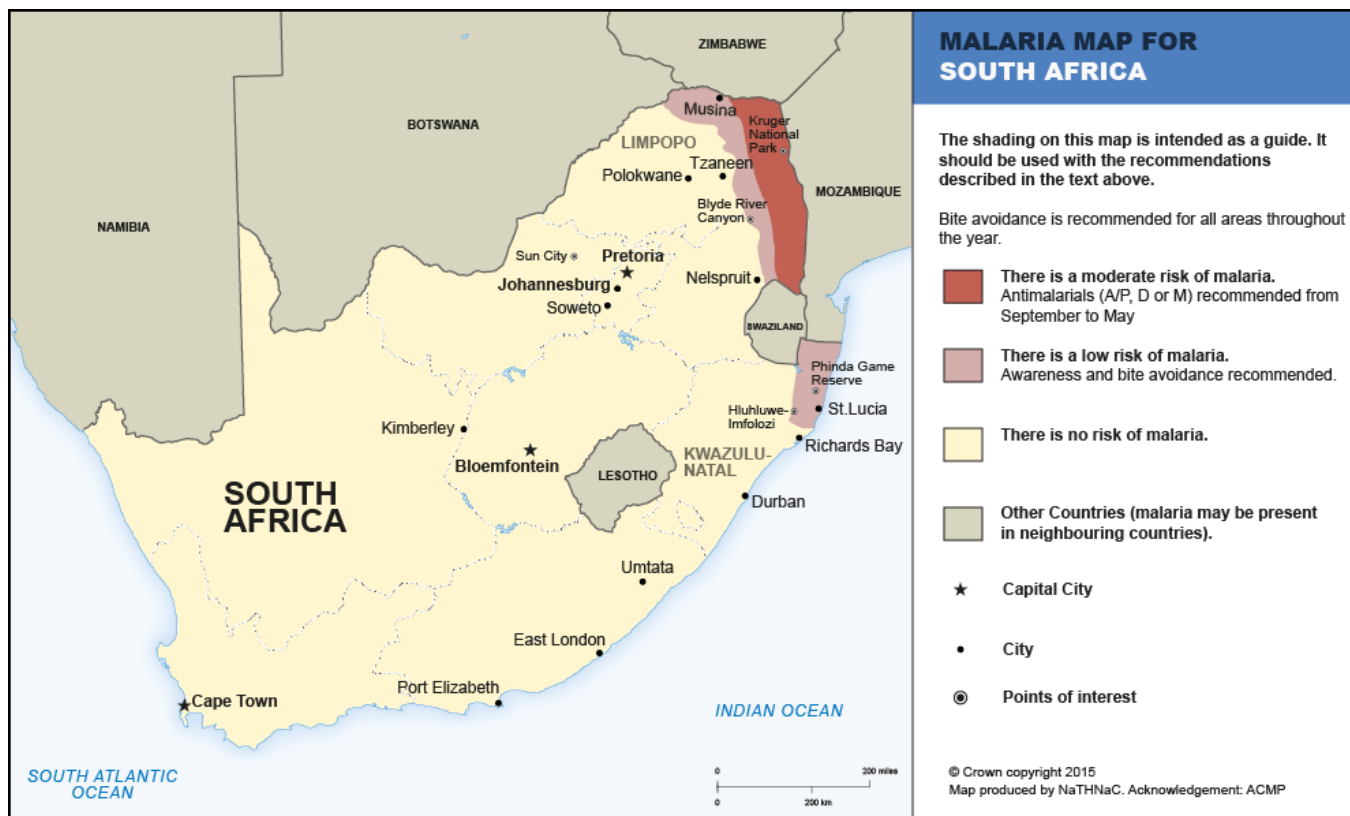


Figure 5 Map of India showing the states with appropriate malaria prevention measures recommended



The new India and South Africa maps were provided by NaTHNaC; note that the format is slightly different to the maps for Bangladesh and Brazil so check the key on the maps carefully for correct interpretation of risk areas. In future updates of the guidelines, all maps will be in the same format.

Figure 6 Map of South Africa showing the areas with appropriate malaria prevention measures recommended



4.6 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, so written instructions for its use are required (68).

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 1 week after taking the first treatment dose, except in the case of mefloquine prophylaxis, which should be resumed at least twelve hours after the last treatment dose if quinine was used for standby treatment. 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 30–60 minutes) (69).

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 (69).

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 (69). ACMP recommended regimens for emergency standby treatment are given in Table 8.

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 (70).

Antimalarials purchased in the tropics may be fake (35) 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 8 Emergency standby treatment for adults

Situation for use	Standby treatment regimen	Usual amount per tablet	Adult dose
Chloroquine or multi-drug resistant falciparum malaria	Artemether plus lumefantrine combination preparation	20 mg artemether plus 120 mg 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	Atovaquone plus proguanil combination preparation	250 mg atovaquone plus 100 mg proguanil	4 tablets as a single dose on each of three consecutive days
Chloroquine or multi-drug resistant falciparum malaria	Quinine plus doxycycline	300 mg quinine 100 mg doxycycline	Quinine 2 tablets 3 times a day for 3 days, accompanied by 1 tablet of doxycycline twice daily for 7 days
Pregnancy ⁶	Quinine plus clindamycin	300 mg quinine 150 mg clindamycin	Quinine 2 tablets 3 times a day for 5-7 days Clindamycin 3 tablets (450 mg) 3 times a day for 5 days

Please see [Appendix 3](#) for Emergency standby medication traveller information leaflet which can be copied and pasted for use.

⁶ Pregnant travellers should avoid malarious areas. If that is not possible, quinine plus clindamycin is the only regimen to be used in pregnancy.

5. 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 three 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*.

5.1 Blood tests and how to request them in the UK

An EDTA-anticoagulated venous blood sample should be taken.

The 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 PHE Malaria Reference Laboratory (MRL) for confirmation, see:

<https://www.gov.uk/guidance/mrl-reference-diagnostic-and-advisory-services>.

Laboratories in Scotland should refer to the Scottish Parasite Diagnostic Laboratory, see: <http://www.nhsggc.org.uk/about-us/professional-support-sites/scottish-microbiology-reference-laboratories/scottish-parasite-diagnostic-reference-laboratory/>

5.2 Rapid Diagnostic Tests (RDTs)

ACMP does not recommend travellers use Rapid Diagnostic Tests (RDTs) for self-diagnosis.

RDTs, sometimes known as “dipsticks”, 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 (71) however there is evidence of travellers being unable to use them correctly and thus failing to detect parasites (72).

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 (73). Therefore, care must be taken to transport and store them correctly and thus prevent deterioration in their performance in the field.

The WHO has an extensive product testing programme for RDTs. Prospective purchasers should consult the WHO web site for information to inform their decision.

5.3 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 every 12 to 24 hours 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 the main parasite biomass may be sequestered in the placenta such that peripheral blood films are negative despite the patient having malaria (see Chapter 9 for expert advice listing).

5.4 Resources for treatment advice

The treatment of malaria is outside the scope of this document and is addressed in the ACMP malaria treatment guidelines available at:

<http://www.britishinfection.org/files/3514/1617/4227/malariatreatmentBIS07.pdf>

Expert advice on malaria treatment may be obtained from:

- Hospital for Tropical Diseases: <http://www.thehtd.org/>
- Liverpool School of Tropical Medicine: <http://www.liv.ac.uk/lstm/>
- your local infectious diseases unit

5.5 Notification

Malaria is a statutorily notifiable disease in England and Wales and the clinician caring for the patient must complete a notification form (74). 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.

The Malaria Reference Laboratory (MRL) reporting form (<https://www.gov.uk/government/publications/malaria-report-form>) should also be completed and sent to the MRL separately or along with referred specimens.

6. Special groups (medical conditions)

6.1 Smoking cessation

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

6.2 Pregnancy

Pregnant women are advised to avoid travel to malarious areas.

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

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

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 have to be outdoors at night they should adhere rigorously to bite precautions (see Chapter 3).

DEET should be used in a concentration of not more than 50%. DEET has a good safety record in children and pregnancy (24) but ingestion should be avoided. Nursing mothers should wash repellents off their hands and breast skin prior to handling infants. See Chapter 3 for further details on DEET.

Chloroquine and proguanil

Safe in all trimesters of pregnancy. Their major disadvantage is the relatively poor protection they give in many geographical areas due to the presence of drug-resistant *P. falciparum*. Pregnant women taking proguanil should receive supplementation with 5 mg folic acid daily for at least the first trimester.

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 (75). There is no strong association between mefloquine in treatment doses (76, 77) and stillbirths or miscarriages in the second and third trimesters.

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 (78).

The decision whether or not 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 Chapter 4) 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 Chapter 9).

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.

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 SPC). ACMP advises against the use of atovaquone/proguanil for antimalarial chemoprophylaxis in pregnancy. However, if there are no other appropriate options, its use may be considered in the second and third trimesters after careful risk assessment

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.

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

6.3 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 (54). 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 (52). 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.

Nursing 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 Tables 4, 5 and 6 for paediatric doses.

6.4 Anticoagulants

6.4.1 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, although there is a caution in the SPC for chloroquine.

Proguanil

An isolated report of an enhanced effect of warfarin when taken together with proguanil (79).

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 (54).

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 (see above under proguanil).

Advice for travellers needing malaria chemoprophylaxis who are taking warfarin

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

A baseline INR should be checked prior to starting chemoprophylaxis, and re-checked after 1 week of taking chemoprophylaxis to determine whether or not 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 (80). Self-monitoring of the INR may be suitable for some travellers, but must be under the supervision of an anticoagulant clinic (81). 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 (81). 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

6.4.2 New oral anticoagulants (NOAC)

Dabigatran etexilate, rivaroxaban and apixaban are the most commonly available NOAC. They do not interact with food, do not require laboratory monitoring and have a lower potential for drug interactions than the coumarins (see below) (82).

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

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 NOAC plasma concentrations which might lead to an increased bleeding tendency (82).

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

Neither atovaquone nor proguanil inhibits p-glycoprotein (82).

If doubt exists after following this guideline, take expert advice from an anticoagulant clinic.

6.5 Epilepsy

NB. 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: unsuitable.
- mefloquine: 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.

6.6 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-) (83).

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 (54) and G6PD levels are not usually checked before using chloroquine in treatment doses.

Atovaquone-proguanil, doxycycline, mefloquine or proguanil

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 (38). 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.

6.7 Sickle cell disease and thalassaemia (84)

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.

6.8 Immunocompromised travellers

6.8.1 Risks for transplant patients

A review on the prevention of infection in adult travellers after organ transplantation (85) recommended that ciclosporin levels should be monitored if chloroquine is co-administered.

6.8.2 Risks for those with HIV/AIDS

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 are limited. Doxycycline is the simplest chemoprophylaxis against malaria for most people on antiretrovirals. However, information in this area is accumulating rapidly and the travel health adviser should check the manufacturer's SPC and the BNF on an individual agent basis and discuss the options for chemoprophylaxis with the traveller's own HIV physician who should make the decision on choice of agent.

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

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 (86) although this varies by area (87).

A study of imported malaria in France reported that severe malaria in HIV-1 infected patients was associated with decreased CD4 cell count (88).

Co-infected pregnant women are at risk from higher parasite density, anaemia and malarial infection of the placenta.

Children born to women with HIV and malaria infection have low birth weight and are more likely to die during infancy. Malaria during pregnancy increases the risk of mother-to-child transmission of HIV-1 (89).

6.9 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 (52). 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 (SPC).
- **moderate impairment:** doxycycline, proguanil, or atovaquone-proguanil combination preparation, or mefloquine may be used
- **mild impairment:** chloroquine, or proguanil, or chloroquine plus proguanil, 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 [http://www.liverpoolmedics.co.uk/clinicalcalculator/childpugh.php?valid=\[ss11\]](http://www.liverpoolmedics.co.uk/clinicalcalculator/childpugh.php?valid=[ss11]) or

<http://www.hepatitis.va.gov/provider/tools/child-pugh-calculator.asp>

6.10 Renal impairment

Chloroquine is partially excreted via the kidneys while proguanil is wholly excreted via the kidneys.

Chloroquine

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

Proguanil

Should be avoided or the dose reduced as shown in Table 9. Not to be used in patients receiving renal dialysis

Atovaquone/proguanil

Not recommended for patients with an eGFR of less than 30mL/minute (54). 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 (54).

Table 9 Doses of proguanil in adults with renal failure

ESTIMATED GFR (eGFR) ML/MIN/1.73M ²	PROPHYLACTIC DOSAGE OF PROGUANIL
≥60	200mg daily (standard dose)
20-59	100mg daily
10-19	50mg every second day
<10	50mg once weekly

6.11 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 chemoprophylaxis. 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 (eg greater than 50% with *P. falciparum*).

6.12 Acute porphyrias

Doxycycline is unsafe in porphyria (54) so should not be used for antimalarial chemoprophylaxis in patients with acute porphyria.

7. Special categories

7.1 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 Tables 4-6 in Chapter 4:

Chloroquine

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

Proguanil

Difficult to use for children since proguanil is only available in adult formulations and, dependent on the weight of the child, the adult-dose tablets must be broken and powdered into food.

Chloroquine plus proguanil

See individual agents above.

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 should be swallowed whole and must not be crushed.

Atovaquone-proguanil combination preparation

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

- weight 5 to 8 kg: half a paediatric tablet daily
- weight >8 to 10 kg: three quarters of a paediatric tablet daily

The paediatric tablets are a quarter of the strength of adult tablets and can be crushed if necessary for ease of administration.

Whilst it is preferable to avoid breaking and crushing tablets, the appropriate dose of proguanil or mefloquine or atovaquone-proguanil combination preparation may be broken if dosing requires it and the drugs crushed if necessary and mixed with jam, honey, pasteurised yoghurt or similar food to aid administration to young children. Tablet-cutters can be purchased from some pharmacies or travel shops. If further advice is required a dispensing 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 **visiting friends and relatives** (90).

7.2 Elderly travellers

The elderly are at particular risk of dying from malaria once acquired (69). 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.

7.3 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 four weeks on, four weeks off, might be taking chemoprophylaxis for most or all of 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 area(s) 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.

7.4 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.

As examples, cruises in the Caribbean may include several days travelling along the Amazon in Brazil, or Orinoco River in Venezuela. 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 require malaria chemoprophylaxis.

7.5 Oil rigs

Many staff are employed in the oil industry, predominantly based around West Africa. Employees commonly travel to these areas every 4-6 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 and therefore antimalarial chemoprophylaxis should be taken for the whole of this first trip, by when the situation will be known.

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.

7.6 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, eg in a safari lodge, they should also take chemoprophylaxis.

7.7 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, in order 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).

7.8 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.

Retail pharmacy outlets can supply over-the-counter antimalarials (chloroquine and/or proguanil) and antimosquito products, but mefloquine, doxycycline and atovaquone-proguanil combination preparation are currently prescription only medicines (POMs). Some pharmacists are now prescribers and thus able to prescribe the prescription only antimalarials.

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 or proguanil or chloroquine plus proguanil one week before, and mefloquine 2-3 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.

7.9 Visiting friends and relatives

[Adapted from the HPA Migrant Health Report 2006 (91) updated 2011 (92). See also the PHE Migrant Health Guide at <http://www.hpa.org.uk/MigrantHealthGuide/> (93)]

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 of any kind to malaria, and that their children are particularly vulnerable.

Effective chemoprophylaxis taken correctly should reduce 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. Health advisers for this group, including primary care practitioners working in areas with large numbers of migrants, can have a major role to play.

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 even doctors, can underestimate the severity of malaria in this group.

7.10 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 section 7.1.1 on long term visitors to the UK returning to live in malarious parts of the world

Those who are making short visits home (eg 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 actually occur in term time whilst they are in the UK. Therefore, it is essential that school/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 / 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 (eg if they are lost or side effects occur) information on the replacement medication should be supplied to the nurse when the child returns to the UK. This is important especially if the child becomes unwell after return and requires treatment with other medication

7.11 The long-term traveller

7.11.1 Risk assessment

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

One major problem for the long-term traveller is the variable access to and quality of medical care available overseas (94). 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, ie 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 uncertainty 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 section 7.9 on VFR in this chapter).

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 two years and many cases can be attributed to poor compliance with prophylaxis (95).

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.

7.11.2 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 three-month visit carries a risk around six times greater than a visit of two 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 Figure 7). 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

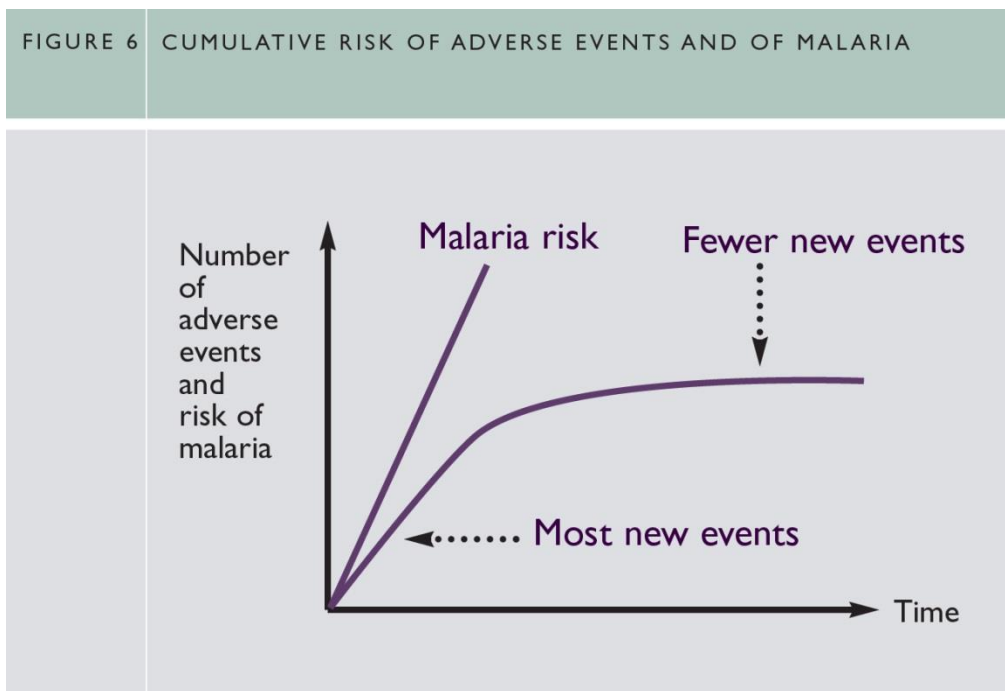
Compliance has been shown to decrease with the duration of travel (96), except where military-style discipline tends to support compliance. There is also evidence of weekly regimens having increased adherence over daily regimens (96). Long term adherence decreases for both daily and weekly prophylactic regimens (52).

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/daily tablets
- reduced confidence if intercurrent fever misdiagnosed as malaria
- perception from anecdotal evidence that chemoprophylaxis is unnecessary (97)

In addition, long-term travellers may overlook personal protective measures against mosquitoes (98).

Figure 7 Cumulative risk of adverse events and malaria



Efficacy of regimens

It is important to stress that no chemoprophylactic regimen is 100% effective and that anti-mosquito 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.

Licensing restrictions

The specific problem relating to prophylaxis advice for long-term travellers is that long-term use of some of the currently advised malaria drugs falls outside the terms of their current Marketing Authorisation (Licence). There have been a number of approaches in response to this time limit:

- 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 physician-guided 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 compliance. 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 Table 10.

7.11.3 Specific considerations for women

See section on pregnancy and breastfeeding in Chapter 6, which includes advice on chemoprophylaxis prior to conception.

7.11.4 Specific considerations for infants and older children

Refer to section 7.1 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.

Proguanil

Safe for use by infants and young children (99).

Mefloquine

Well tolerated (100). Long-term use of mefloquine is reported to be safe, well tolerated and not associated with an increase in adverse effects (101-103)

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 (104).

Atovaquone-proguanil combination preparation

Both agents highly effective and safe (61).

7.12 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.

7.12.1 Preventive measures appropriate to an endemic setting (105)

Bednets

Bed nets and other personal barrier protective measures (eg 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 World Health Organization/national country guidance on the appropriate measures in endemic settings which include IPT, insecticide-treated bednets and case-management of illness with therapy.

7.12.2 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 four to six 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 to diagnose and manage malaria.

Table 10 Long term chemoprophylaxis for adults

MALARIA CHEMOPROPHYLAXIS	ACMP ADVICE ON LONG-TERM USE
Chloroquine	Considered safe for long-term use ⁷ . Consider ophthalmic examination 6 to 12 monthly, commencing at 6 years' cumulative prophylactic usage.
Proguanil	Considered safe for long-term use ⁷ .
Mefloquine	No evidence of harm in long-term use if tolerated in the short term. Suggest can be used safely for up to three years in the absence of side effects. Longer term use possible if justified by the risk of exposure to malaria. The SPC 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 two 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 11 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
Proguanil	14 to 21 hours

⁷ Considered safe for long-term use but considerable concern regarding level of protective efficacy of the combination of chloroquine plus proguanil in certain geographical areas where the regimen used to be useful.

8. Frequently asked questions

8.1 What malaria prevention should be advised for travellers going on cruises?

A. 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.

As examples, cruises in the Caribbean may include several days travelling along the Amazon in Brazil, or Orinoco River in Venezuela. 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 require malaria chemoprophylaxis. Risks in specific destinations can be determined by referring to the country table in Chapter 4. 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 Chapter 3).

8.2 What alternative antimalarial drugs can be used for areas where chloroquine and proguanil are advised if they are unsuitable for a particular traveller?

A. If a traveller is unable to take the combination of chloroquine plus proguanil, the alternative is a choice between one of three prescription drugs available: mefloquine, doxycycline or atovaquone / proguanil.

The choice of alternative depends on the reason why chloroquine and proguanil are not suitable (eg those unable to take chloroquine due to epilepsy should not take mefloquine; if a traveller does not tolerate proguanil, then they should avoid atovaquone/ proguanil as this also contains proguanil). For advice on malaria prevention in pregnant women there is a specific FAQ below.

8.3 Which antimalarial can I give to a traveller with a history of psoriasis?

A. Proguanil, 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.

8.4 Which antimalarial can I give a traveller who is taking anticoagulants?

A. 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, although there is a caution in the SPC for chloroquine
- **proguanil**: an isolated report of an enhanced effect of warfarin when taken together with proguanil (79)
- **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 (54)
- **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 (see above under proguanil)

Advice for travellers needing malaria chemoprophylaxis who are taking warfarin:

- travellers should inform their anticoagulant clinic and start taking their malaria tablets 2-3 weeks prior to their departure
- a baseline INR should be checked prior to starting chemoprophylaxis, and re-checked after 1 week of taking chemoprophylaxis to determine whether or not 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 (80). Self-monitoring of the INR may be suitable for some travellers, but must be under the supervision of an anticoagulant clinic, see Ringwald et al (81). 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 (81). 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.

New oral anticoagulants (NOAC)

Dabigatran etexilate, rivaroxaban and apixaban are the most commonly available NOAC. They do not interact with food, do not require laboratory monitoring and have a lower potential for drug interactions than the coumarins (see below) (82).

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

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 NOAC plasma concentrations which might lead to an increased bleeding tendency (82).

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

Neither atovaquone nor proguanil inhibits p-glycoprotein (82).

If doubt exists after following this guideline, take expert advice from an anticoagulant clinic.

8.5 How long can a traveller take different antimalarial drugs?

A. Guidelines for the long term traveller are summarised in Chapter 7. Further detail is available in reference (75).

The main issues influencing the choice of malaria chemoprophylaxis on a long-term basis are the same as for short-term, ie 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, two thresholds for the risk of retinopathy have been suggested:

- a total cumulative dose of 100g of chloroquine base
- a daily dose of 250mg base (4mg / kg) (106)

The first threshold would require an adult to take chloroquine continuously, weekly, for a period of six years. The second threshold is far in excess of the prophylactic dosage. It has been concluded that the risk of retinopathy from prophylactic dosage alone is negligible (40). Further reassurance can be gained from the fact that retinopathy has only rarely been reported in patients taking weekly prophylactic dosages (106, 107).

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

Proguanil

There is no time limit specified for the use of proguanil. Therefore, it can be taken continuously for several years.

Mefloquine

There are few data on the use of mefloquine for periods exceeding two years, although there is no evidence of cumulative toxicity, and mefloquine taken for over 1 year is well tolerated. The SPC 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 three 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 two 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.

There is a report of atovaquone/proguanil use for periods from 9 to 34 weeks, in which there was no excess of adverse effects and no appearance of unexpected adverse effects (108). 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.

8.6 Which antimalarial drugs are suitable for women during pregnancy?

A. Malaria during pregnancy is a serious illness for both the mother and the foetus. 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 foetal 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 (SPC).

The UK National Teratology Information Service (<http://www.uktis.org/>) 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 (SPC).

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. 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.

Both chloroquine and proguanil have been taken safely during pregnancy for many years although this combination offers insufficient protection in areas with chloroquine-resistant *P. falciparum*. Folic acid 5 mg po daily should be taken for at least the first trimester if proguanil is used in those who are pregnant or and also by those taking proguanil who are seeking to become pregnant.

8.7 Which antimalarial drugs can be taken by women breastfeeding?

A. Chloroquine plus proguanil can be used during breastfeeding, although this combination provides suboptimal protection for the mother in areas of chloroquine-resistant *P. falciparum* malaria.

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 (52).

8.8 Which antimalarial drugs can be given to babies and young children?

A. Both chloroquine and proguanil can be given from birth. Chloroquine is available as syrup but proguanil will need to be crushed and given with jam or food.

Mefloquine can be given to infants weighing 5 kg or more (see Summary of Product Characteristics). Atovaquone / proguanil can be given to infants weighing 5 kg 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 4-6 in Chapter 4, and in the British National Formulary (BNF). The dose for children will be dependent on the weight / age of the infant or child. Weight is a better guide than age.

Mosquito bite avoidance is extremely important for this age group.

8.9 What is the easiest way to calculate the correct dose of chloroquine for babies and young children?

A. 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 Tables 4 and 5, Chapter 4). 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 50 mg chloroquine base / 5 mls syrup. The amount of chloroquine base contained within the tablets is 155mg.

The ACMP guidelines and BNF 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 (ie either tablet or syrup). Eg 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 Chapter 4 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 Tables 4-6 in Chapter 4.

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

8.10 Many travellers I see are travelling through areas where different antimalarials are recommended as they progress through their journey. How do we advise these travellers?

A. Travellers planning extensive journeys across continents will often travel into areas which have different malaria chemoprophylaxis recommendations. In these situations it is important that the traveller is protected in all areas of risk and the choice of medication needs to reflect the overall risk.

It may be possible to move from one regimen to another, although for shorter trips this may not be practical. For example, a traveller spending 2 weeks in an area where chloroquine plus proguanil may be recommended and then going for 6 weeks to an area where doxycycline or atovaquone/proguanil may be recommended would be advised to take either doxycycline or atovaquone/proguanil for the whole of the visit rather than change from chloroquine and proguanil to one of the other agents.

8.11 Which antimalarial drugs can I advise for a traveller who has epilepsy?

A. 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 antimalarials 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.

8.12 What do I advise for the traveller with Glucose 6-phosphate dehydrogenase deficiency?

A. 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

(83). 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 (54) 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, mefloquine or proguanil 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 (38). 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.

8.13 What do I advise people working on oil rigs?

A. There is a large number of staff employed in the oil industry predominantly based around West Africa. Employees commonly travel to these areas every 4-6 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.

8.14 What do I advise for the traveller on a stopover?

A. 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, in order 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).

8.15 Can doxycycline affect oral contraception?

A. Doxycycline is a non-enzyme-inducing antibiotic. The Faculty of Sexual and Reproductive Healthcare (<http://www.fsrh.org/>) 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.

8.16 What advice can I give to travellers who discontinue chemoprophylaxis on or after return to the UK due to drug side-effects?

A. 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, proguanil, 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

8.17 What alternative antimalarial drugs can be used for Central America (and Dominican Republic/Haiti) if chloroquine is unsuitable for a traveller?

A. Chloroquine is the recommended chemoprophylaxis for many Central American countries and the island of Hispaniola. If a traveller is unable to take chloroquine, the alternative is a choice between one of three prescription drugs available: mefloquine, doxycycline, or atovaquone-proguanil. The particular drug selected will depend on the reason why chloroquine is not suitable (eg those unable to take chloroquine due to epilepsy should not take mefloquine).

Due to increasing drug resistance, proguanil alone is no longer recommended as an alternative antimalarial for these areas.

9. Information resources

9.1 Expert centres

9.1.1 Prophylaxis advice

Malaria Reference Laboratory (MRL)

<http://www.malaria-reference.co.uk>

Fax enquiry line for healthcare professionals: 020 7637 0248. Please fax a completed risk assessment form which can be downloaded from the MRL web site.

National Travel Health Network and Centre (NaTHNaC)

<http://travelhealthpro.org.uk/>

Advice line for healthcare professionals: 0845 602 6712

TRAVAX (Health Protection Scotland)

<http://www.travax.nhs.uk/>

Advice line for healthcare professionals: 0141 300 1130

9.1.2 Diagnostic advice

Malaria Reference Laboratory (MRL)

<http://www.malaria-reference.co.uk>

Diagnostic advice for health care professionals 020 7927 2427

The Hospital for Tropical Diseases (HTD)

<http://www.thehtd.org/>

The Liverpool School of Tropical Medicine (LSTM)

<http://www.liv.ac.uk/lstm/>

9.1.3 Treatment advice

The treatment of malaria is outside the scope of this document and is addressed in the ACMP malaria treatment guidelines available at:

<http://www.britishinfection.org/files/3514/1617/4227/malariatreatmentBIS07.pdf>

Expert advice on malaria treatment may be obtained from:

Hospital for Tropical Diseases (HTD)

<http://www.thehtd.org/>

Requests for emergency admission or very urgent clinic attendance should be made to the

Duty Doctor, who is contacted via switchboard.

Telephone: 0845 155 5000 and ask for the duty doctor for tropical medicine.

Liverpool School of Tropical Medicine (LSTM)

<http://www.liv.ac.uk/lstm/>

Advice line for Healthcare professionals 0151 705 3100 Mon to Fri 9 am to 5pm. Via Royal Liverpool Hospital switchboard at all other times 0161 706 2000

Your local infectious diseases unit

9.2 Useful websites

British National Formulary (BNF)

<http://www.bnf.org>

British Infection Association (BIA)

<http://www.britishinfection.org/>

Department of Health

<https://www.gov.uk/government/organisations/department-of-health>

Electronic Medicines Compendium (for Summaries of Product Characteristics)

<http://www.medicines.org.uk/emc/>

Liverpool School of Tropical Medicine (LSTM)

<http://www.liv.ac.uk/lstm/>

London School of Hygiene and Tropical Medicine (LSHTM)

<http://www.lshtm.ac.uk/>

Malaria Reference Laboratory (MRL)

<http://www.malaria-reference.co.uk>

Medicines and Healthcare products Regulatory Agency (MHRA)

<http://www.mhra.gov.uk>

National Travel Health Network and Centre (NaTHNaC)

<http://travelhealthpro.org.uk/>

Public Health England (PHE)

<https://www.gov.uk/government/organisations/public-health-england>

Royal Society of Tropical Medicine and Hygiene (RSTM&H)

<http://www.rstmh.org/>

TRAVAX (Health Protection Scotland)

<http://www.travax.nhs.uk/>

World Health Organization (WHO) International Travel and Health

<http://www.who.int/ith/en/>

9.3 Information leaflets

Public Health England. Malaria: information for people travelling overseas.

<https://www.gov.uk/government/publications/malaria-information-for-people-travelling-overseas>

Public Health England. Travelling overseas to visit friends and relatives?

<https://www.gov.uk/government/publications/travelling-overseas-to-visit-friends-and-relatives-health-advice>

Appendices

Appendix 1a: ACMP - Terms of reference 2015

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 Public Health England (PHE).

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 PHE Malaria Reference Laboratory, London (MRL), the Medicines & 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/non-medical professionals who have expertise in:

- antimalarial drug resistance
- the use of antimalarial drugs
- malaria prevention/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 three 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 electronically circulated 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/knowledge when necessary.
- a PHE scientific secretariat will coordinate and provide scientific secretariat support to the ACMP.

Confidentiality/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 PHE scientific secretariat who will inform the committee.

Funding

ACMP is supported by Public Health England

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
David Lalloo	Chair, lead author for Treatment Guidelines Tropical medicine expert. Liverpool School of Tropical Medicine (LSTM)
Peter Chiodini	Deputy Chair, lead author for Prevention Guidelines Clinical parasitology expert, reference diagnosis. PHE Malaria Reference Laboratory (MRL)
Chris Whitty	Tropical medicine expert, epidemiologist. PHE MRL
Vanessa Field	Travel medicine expert. National Travel Health Network and Centre (NaTHNaC)
Dipti Patel	Travel medicine expert. NaTHNaC
Hilary Kirkbride	Expert epidemiologist. Travel and Migrant Health, PHE
Kitty Smith	Travel medicine expert. Health Protection Scotland (HPS)
Ron Behrens	Travel medicine expert. Hospital for Tropical Diseases
Fiona Genasi	Travel medicine expert. HPS
George Kassianos	Expert general practitioner. Royal College of General Practitioners
David Bell	Infectious diseases expert. NHS Greater Glasgow and Clyde
Heenabeen Patel	Pharmacy expert. British National Formulary
Andrew Green	Expert microbiologist, Defence Medical Services
Larry Goodyear	Pharmacy expert
Mair Powell	Clinical pharmacology expert. Medicines and Healthcare products Regulatory Agency
Olaseni Subair	Expert obstetrician. Royal College of Obstetricians and Gynaecologists
Delane Shingadia	Paediatric infectious diseases Expert. Institute of Child Health
Hilary Ranson	Expert entomologist. LSTM
Observers	
Marie Blaze	Expert advisor on malaria prevention. MRL
Valerie Smith	Expert advisor on malaria prevention. MRL

Appendix 1c: ACMP - Conflict of interest statements

ACMP MEMBER	PERSONAL INTERESTS (Relevant within the past 4 years)		NON-PERSONAL INTERESTS (Relevant within the past 4 years)	
	Name of organisation	Nature of Interest	Name of organisation	Nature of interest
Dr Ron Behrens	<ol style="list-style-type: none"> 1) Sigma Tau 2) Norgine Pharmaceuticals 3) Shoreland 4) ExxonMobil 	<ol style="list-style-type: none"> 1) Advisory Board Fee 2) Advisory Board Fee 3) Consultancy 4) Consultancy 	<ol style="list-style-type: none"> 1) Intercell USA. 2) Norgine Pharmaceutical 3) Sigma Tau 	<ol style="list-style-type: none"> 1) Research Funding 2) Educational Grant 3) Research Funding
Dr George Kassianos	<ol style="list-style-type: none"> 1) GSK 2) SPMSD (UK) 3) Novartis 4) Johnson & Johnson 5) SP & SPMSD Lyon France 6) British Global & Travel Health Association 7) Royal College of General Practitioners 8) Sigma tau 	<ol style="list-style-type: none"> 1) None in last 2 years. Before that: received fees for lectures that I determined the content 2) None in last 1 year. Before: Advisory Board and lectures 3) None in last 1 year. Before: Advisory Board and lectures 4) None in last 2 years: Lectures 5) Lectures in Europe, South Africa Advisory Board over a year ago but none during last 18 months 6) President 7) Clinical Lead on Immunisations 8) Advisory Board Fee 	None	None
Dr David Bell	<ol style="list-style-type: none"> 1) Gilead Pharmaceuticals 2) Roche Pharmaceuticals 3) Janssen Pharmaceuticals 4) Merck Pharmaceuticals 5) Abbvie Pharmaceuticals 6) ViiV Pharmaceuticals 	I have received honorarium from these pharmaceutical companies for attendance at advisory boards and for speaker fees relating to blood borne virus infections	None	None
Professor Larry Goodyer	Nomad Travel Store and Clinics	Medical Director of a National network of Travel Clinics	Sigma Tau Advisory Board (till 2013)	Antimalarial manufacturer

Professor Peter Chiodini	1) Parasitology Services Limited 2) Institute of Tropical Medicine, Antwerp	1) Director, private practice 2) Scientific Advisory Council	1) Travel Health Training Limited 2) Foundation for Innovative New Diagnostics 3) Intellectual Ventures, Global Good 4) PATH Seattle	1) Spouse, Jane Chiodini is Director 2) Research funding 3) Research funding and consultancy 4) Research funding
Ms Heenaben Patel	None	None	None	None
Group Captain Andrew Green	None	None	None	None
Dr Mair Powell	None	None	None	None
Dr Olaseni Subair	None	None	None	None
Dr Delane Shingadia	None	None	None	None
Professor Hilary Ranson	None	None	None	None
Dr Dipti Patel	None	None	None	None
Dr Nick Beeching	None	None	None	None
Mrs Marie Blaze	None	None	None	None
Mrs Valerie Smith	None	None	None	None
Professor David Laloo	None	None	None	None
Professor Chris Whitty	None	None	None	None
Dr Hilary Kirkbride	None	None	None	None
Dr Chris Redman	None	None	None	None
Ms Fiona Genasi	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:

- World Health Organization Global Malaria Programme
- World Malaria Report

- estimates of the *P. falciparum* parasite rate and entomological inoculation rate published by the Oxford University Malaria Atlas project <http://www.map.ox.ac.uk/>
- the number of cases and deaths in-country from published and unpublished sources
- Centers for Disease Control information for Central and South America, a region where the CDC has local knowledge
- local, expert contacts of the LSHTM Malaria Centre as necessary.

Returned traveller data

- the PHE Malaria Reference Laboratory, London (MRL) database captures 56% of cases (66% for *P. falciparum*) (109)
- numbers of cases are also converted to attack rates where good denominator data are available
- details of the data requested on all imported malarias can be seen in the MRL case report form at <https://www.gov.uk/government/publications/malaria-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 (eg pregnant travellers) is sought
- deaths are all subject to a detailed confidential audit
- MRL data on molecular markers of resistance to anti-malarial agents are 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:

- bite prevention products using data from the published literature and the WHO Pesticide Evaluation Scheme (WHOPES)
- chemoprophylaxis and Standby Emergency Medication, using data from:
 - Medicines & 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. When malaria data are 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

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. **NB.** 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 from the General Medical Council on remote prescribing is available at www.gmc-uk.org

Traveller details

Name of traveller	
Age	
Sex	
Date/s of travel	

Underlying condition

Condition		Yes/No
Pregnancy	Actual number of weeks:	
	Planned while on trip	
Sickle cell	Disease	
	Carrier	
Thalassaemia	Disease	
	Carrier	
Epilepsy	Patient	
	First degree relative ⁸	
History of depression requiring treatment		
Severe mental health disorder	Patient	
	First degree relative ⁸	
Asplenic		
Liver disease		
Renal failure (state eGFR)		
Diabetes mellitus		
Cardiovascular	Ischaemic heart disease	
	Arrhythmias	
	Other	
Immunocompromised		
Psoriasis		

⁸ 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.

Allergies

Give details of allergies to drugs or other below

Medication

Current medication	Yes/No	Comments
Antiarrhythmics		
Anticonvulsants		
Anticoagulants		
Antiretrovirals		
Corticosteroids		
Bupropion (Zyban®)		
Other		

Previous antimalarial chemoprophylactic agent taken	Describe any problems

Area to be visited

See country table and maps in Chapter 4.

Destination	Length of stay	Risk of malaria	Urban/rural/both	Prophylaxis advised from country table ⁹

⁹ If the recommended regimens differ between the countries to be visited, see note on multi-trips in Chapter 7.

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

Purpose of visit/accommodation	Tick if applies
Visiting friends and relatives	
Safari	
Backpacking	
Business/work	
Study > six months	
Study < six months	
House	
Hotel	
Hostel	
Tent	
Oil rig	
Cruise ship	
Urban	
Rural	
Other (please give details below)	

Record of advice given to traveller

1. Bite prevention: please tick measures advised

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

2. Chemoprophylaxis

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

Antimalarial	Tick regimen advised	Dose	Duration
Chloroquine			
Proguanil			
Chloroquine/Proguanil			
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 suspicious symptoms (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/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/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 a febrile illness 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, please 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 30–60 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 prophylactic drug(s) 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 twelve hours after completing the course of quinine before you restart mefloquine

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