Malaria Prophylaxis

See related separate articles Malaria and Malaria in Pregnancy.

The ABCD of malaria prophylaxis:[1]

- Awareness of the risk of malaria.
- Bites - reducing likelihood of bites from anopheline mosquitoes.
- Chemoprophylaxis.
- Diagnosis and prompt treatment to prevent complications.

No single measure is 100% effective but the combination of measures will significantly lessen the risk.

Clinical Editor's Note

December 2017 - Dr Hayley Willacy draws your attention to the recently updated PHE guidelines on malaria prevention for travellers from the UK.[2] Between 2000 and 2015 the global incidence of malaria decreased by 37% overall, with the majority of cases in 2015 occurring in the WHO Africa and Asia regions. Prompted by these changes, PHE’s Advisory Committee on Malaria Prevention undertook an extensive review of the malaria recommendations for individual countries. Changes to the risk level and/or malaria prevention recommendation have been made for 41 countries. In some areas, including some countries in Asia, parts of the Caribbean, and Central and South America, the malaria risk is now deemed to be below the threshold for which chemoprophylaxis is considered necessary. In response to data which indicate a predominance of imported cases and almost all deaths originating from Africa, the PHE recommends that clinicians engage as much as possible with travellers planning to visit Africa to emphasise that the malaria situation there remains serious and requires rigorous application of preventive measures.

Awareness of risk[1, 3, 4]

Risk assessment should include:

- Geographical destination - the Foreign and Commonwealth Office’s information online is very helpful.[5]
- Travellers to remote locations should seek expert advice.
- The current highest-risk areas are Africa, South and Central America, Asia and the Middle East. About 90% of the one million deaths occurring worldwide are in Africa.
- Health Protection Agency (HPA) figures for 2013 showed that of cases of malaria imported into the UK, 1,192 were due to Plasmodium falciparum, 179 were due to P. vivax, 78 to P. ovale and 39 to P. malariae. There were seven deaths.[6]
- Type of travel: there is higher risk for tourists travelling outside urban areas to countryside or game parks, business travellers to downtown offices, overland backpackers, those undertaking prolonged travel, and expatriates intending to reside in the area.
- High-risk categories - pregnant women, asplenic patients, young children, people with HIV/AIDS.[7]

Avoidance of bites[1, 8]

- Avoidance of bites is important, particularly because chemoprophylaxis is never 100% effective, problems of drug resistance are increasing and there is evidence that the risk of contracting malaria is proportional to number of bites. Bites occur mainly between dusk and dawn, although some species of mosquito which can transmit dengue fever bite during the day also.
- Keep the arms and legs covered after sunset.
- There is good evidence that covering exposed limbs with repellant containing diethyltoluamide (DEET) is effective. When sunscreen is applied, it should be used before DEET. It is suitable for all adults and for children over the age of 2 months. Various strengths are available. 50% is the most effective. There is no evidence of serious toxicity, even in small children and pregnant women. Some patients develop an allergic or irritant response, in which case lower strengths are available. Preparations weaker than 50% will require more frequent application. There is no evidence of effectiveness of strengths of less than 20%.
- Picaridin (KBR3023) (1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methyloxyester) is reported to have repellent properties comparable with those of DEET. If a traveller elects to use picaridin for mosquito bite prevention, a 20% preparation should be used.[1] There is evidence that picardin is an appropriate option for patients who develop contact dermatitis with DEET.[9]
- Permethrine is a useful insecticide to spray on clothing. Pre-treated clothing is available for purchase.
- Patients should be advised to sleep in air-conditioned rooms if possible, or screened accommodation.
- Use of sprays with knockdown insecticide or electrical pyrethroid vapourisers every evening after dusk is recommended.
- Insecticide-treated nets should be used by those sleeping outdoors or in unscreened rooms. The effectiveness is about 50%. Pyrethroid-impregnated nets improve protection and should be re-impregnated every 6-12 months, although resistance is becoming a problem. The search for newer, more effective insecticides is ongoing.
Chemoprophylaxis

- Reinforce that prophylaxis is not absolute, breakthrough infection can occur, and that risk avoidance is still necessary.
- Consider risks versus benefits based on risk assessment. A suitable risk assessment template may be found in the document Guidelines for Malaria Prevention in Travellers from the United Kingdom from Public Health England.\(^1\)
- Start weekly drug regimes one week before entering a malarious area (exceptions: 1-2 days for doxycycline or atovaquone with proguanil (Malarone\(^\text{®}\)), two to three weeks for mefloquine) to become used to side-effects before travelling. Take after meals.\(^10\)
- Continue until four weeks after return, to deal with infection contracted towards the end of the stay (except Malarone\(^\text{®}\) which should be stopped one week after leaving).\(^{10}\)
- Discuss possible side-effects, and recommend seeking advice if there is any concern or medication has to be stopped.
- Warn that antimalarial medication bought abroad or purchased over the internet may be fake, and should be avoided.
- Seek specialist advice if the patient has severe hepatic or renal impairment.
- Where a journey requires two regimes, use the regime for the higher-risk area for the whole journey. Warn settled immigrants or long-term visitors to the UK that they may have lost some of their immunity and that previously uninfected areas may now be malarious.
- Malaria chemoprophylaxis is not prescribable on FP10. Chloroquine and proguanil can be bought over the counter. Mefloquine, doxycycline, and Malarone\(^\text{®}\) require a private prescription.

Chloroquine

- Chloroquine is used for the prophylaxis of malaria in areas of the world where the risk of chloroquine-resistant falciparum malaria is still low. It is also used with proguanil when chloroquine-resistant falciparum malaria is present. However, this combination may not be ideal. Advice on individual countries is available from the British National Formulary (BNF).\(^{11}\)
- It is taken at a dose of 310 mg (two tablets) weekly for adults. It is also available as a syrup (equivalent to chloroquine base 50 mg/5 ml).
- It remains effective against most \textit{P. vivax}, all \textit{P. ovale} and virtually all \textit{P. malariae}. It will, however, not prevent dormant liver stages of vivax and ovale malaria which can present up to a year after travel.

Chloroquine plus proguanil

- Proguanil is rarely given as a single agent, due to resistance; however, combined with chloroquine it may be used in areas with moderate chloroquine resistance. The combination provides less protection than mefloquine. It is no longer recommended for travel to sub-Saharan Africa.\(^{11}\)
- Folate supplements are recommended during pregnancy.
- The dose for adults is chloroquine 310 mg (two tablets) weekly and proguanil 200 mg (two tablets) daily.
- Common adverse reactions are nausea, diarrhoea, dyspepsia and itching.
- Chloroquine is available as syrup for young children. Proguanil tablets need to be crushed and can be administered in milk, jam or honey.

Mefloquine

- This is used for areas where there is a high incidence of chloroquine-resistant falciparum malaria (eg, sub-Saharan Africa).
- The usual adult dose is 250 mg weekly.
- It can be recommended for journeys of up to one year.
- It exhibits 90% efficacy in Africa but resistance is high in other areas (eg, there is significant resistance of \textit{P. falciparum} to mefloquine in some areas of Southeast Asia, and it is reported sporadically in the Amazon basin).\(^{11}\)
- Major adverse events (convulsions, coma and psychotic disturbances) are rare - 1 in every 10,000 users; however, they have been given high media profile.\(^{12}\) There is no evidence that mefloquine use increases the risk of first-time diagnosis of depression and no association between mefloquine prescriptions and hospitalisation.\(^{13}\)
- Lesser side-effects are similar to chloroquine and proguanil.
- Avoid in patients with a history of epilepsy or psychiatric disorder.
- It should not be used routinely in pregnancy but, if there is an unavoidable visit to an area where there is a high risk of chloroquine-resistant falciparum malaria, use cautiously during the second and third trimester. Data suggest it is safe in the first trimester.
- It is not for routine use in lactation, as it is secreted in breast milk.
- The Civil Aviation Authority has banned the use of mefloquine for its pilots, although there is no evidence that it affects function.\(^{1}\)

Malarone\(^\text{®}\)

- This is a combination of proguanil and atovaquone.
- Its effectiveness against falciparum malaria is in excess of 90%.
- It is licensed in the UK for adults for stays in endemic areas for up to one year (the previous 28-day restriction has been lifted).\(^{14}\)
- It can be used as an alternative to mefloquine or doxycycline for adults travelling to chloroquine-resistant areas, especially Africa and Southeast Asia.
- It is taken as a single daily dose and only needs to be continued for seven days after travel.
- Adverse effects are few - mainly gastrointestinal and headaches.

Doxycycline
This has comparable efficacy to mefloquine. It may be recommended as first-line for travel to Africa where high levels of protection are desirable but mefloquine is unsuitable. The main side-effects are diarrhoea, photosensitive dermatitis and vaginal thrush. It is not recommended for children aged under 12, pregnancy or lactation. It should be used with caution in patients with hepatic impairment, myasthenia gravis and systemic lupus erythematosus. There is no evidence on the long-term use of doxycycline but long-term use of other tetracyclines for other indications has been favourable.\[1\]

Prescribing for children\[1, 10\]
- Prophylactic doses are based on guidelines from UK malaria experts and may differ from advice in the product literature.
- Weight is a better guide than age.
- Encouraging results have been reported in a study using intermittent sulfadoxine-pyrimethamine in Gabon.\[15\] A Cochrane review reported that in areas with seasonal malaria transmission, giving antimalarial drugs to pre-school children (age <6 years) as intermittent preventative therapy during the malaria transmission season caused a significant reduction in episodes of clinical malaria, including severe malaria. This occurred even in areas where insecticide-treated net usage was high.\[16\]
- If in doubt, telephone prophylaxis advice centres (see ‘Helplines for further information and advice’, listed under ‘Prophylaxis advice centres’, below).

Standby therapy\[1\]
- If chemoprophylaxis is contra-indicated or of limited effectiveness and it is necessary to travel to high-risk areas where access to medical expertise within 24 hours of the onset of fever is unlikely, medication may be prescribed to self-treat an episode of malaria.
- The patient must be carefully counselled regarding presenting symptoms, indications and safe use of drugs.
- Treatment should be started if the patient is unable to seek medical help as soon as fever occurs. An antipyretic such as paracetamol should be taken to reduce fever, as this also reduces the risk of vomiting antimalarial drugs. Once the fever is under control, standby therapy should be commenced. Other preventative measures should be continued.
- The standard treatment course should be completed and antimalarial chemoprophylaxis commenced one 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.
- A second full treatment dose of the antimalarial medication should be taken if vomiting occurs within 30 minutes of taking it (half dose if vomiting occurs after 30-60 minutes).
- The drug used for emergency standby treatment should differ from that used for chemoprophylaxis, both to minimise drug toxicity and due to concerns over drug resistance.
- Warn the patient concerning the adverse reactions of quinine - for example, tinnitus, headache, flushed skin, nausea.
- Patients should be advised not to buy antimalarial drugs over the internet, as the sale of counterfeit products has been reported.

<table>
<thead>
<tr>
<th>Situation for use</th>
<th>Standby treatment regimen</th>
<th>Usual amount per tablet</th>
<th>Adult dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine or multidrug-resistant falciparum malaria.</td>
<td>Artemether plus lumefantrine combination preparation.</td>
<td>20 mg artemether plus 120 mg lumefantrine.</td>
<td>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.</td>
</tr>
<tr>
<td>Chloroquine or multidrug-resistant falciparum malaria.</td>
<td>Atovaquone plus proguanil combination preparation.</td>
<td>250 mg atovaquone plus 100 mg proguanil.</td>
<td>4 tablets as a single dose on each of three consecutive days.</td>
</tr>
<tr>
<td>Chloroquine or multidrug-resistant falciparum malaria.</td>
<td>Quinine plus doxycycline.</td>
<td>300 mg quinine 100 mg doxycycline.</td>
<td>Quinine 2 tablets 3 times a day for 3 days, accompanied by 1 tablet of doxycycline twice daily for 7 days.</td>
</tr>
<tr>
<td>Recommended where no chloroquine resistance present. NB: now applies to very few geographical areas.</td>
<td>Chloroquine.</td>
<td>155 mg chloroquine base.</td>
<td>4 tablets on days 1 and 2, 2 tablets on day 3.</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Quinine plus clindamycin.</td>
<td>300 mg quinine. 150 mg clindamycin.</td>
<td>Quinine 2 tablets 3 times a day for 5-7 days. Clindamycin 3 tablets (450 mg) 3 times a day for 5 days.</td>
</tr>
</tbody>
</table>

Chloroquine doses are given as the base. Pregnant travellers should avoid malarious areas. If that is not possible, quinine plus clindamycin (or chloroquine alone in the very few non-resistant areas) is the only regimen to be used in pregnancy.
Chemoprophylaxis for long-term travellers\textsuperscript{[1,10]}

Seek specialist advice, especially if there are clinical reasons to extend use beyond evidence-based limits. Long-term travellers are defined as those travelling through or visiting malaria-endemic countries for over six months. As for short-term prophylaxis, a risk assessment should be done which includes risk of malaria, adverse events profile, compliance and efficacy.

- Chloroquine and proguanil can be used for up to five years but their effectiveness is reduced in some areas, due to resistance. Check for retinopathy if chloroquine is used for more than six months).
- Licensing restrictions can be mitigated by switching from one regime to another. Occasionally, strategies such as reliance on standby treatment or ignoring licensing restrictions have been employed.
- Mefloquine is licensed for up to one year (although it has been used for up to three years without problems).
- Doxycycline can be used for up to two years.
- Malarone\textsuperscript{®} can be used for up to one year.

### Long-term chemoprophylaxis for adults\textsuperscript{[1]}

<table>
<thead>
<tr>
<th>Malaria chemoprophylaxis</th>
<th>Advisory Committee on Malaria Prevention (ACMP) advice on long-term use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>Consider 6- to 12-monthly ophthalmic examination, commencing at 6 years of cumulative prophylactic usage.</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>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 is possible if justified by the risk of exposure to malaria.</td>
</tr>
<tr>
<td>Proguanil</td>
<td>Considered safe for long-term use*.</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>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 is possible if justified by the risk of exposure to malaria.</td>
</tr>
<tr>
<td>Atovaquone/ Proguanil</td>
<td>No evidence of harm in long-term use. Can be used confidently for travel of up to one year. Longer-term use is possible if justified by the risk of exposure to malaria.</td>
</tr>
</tbody>
</table>

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

### Diagnosis and prompt treatment

Advise patients regarding symptoms of malaria, to report any illness within three months of return, to make their doctor aware of history of malaria exposure and to monitor for symptoms of malaria for up to one year after travel.

### Special situations\textsuperscript{[1]}

**Epilepsy**

- Chloroquine and mefloquine are unsuitable.
- In areas without chloroquine resistance, prescribe proguanil 200 mg daily.
- In areas with chloroquine resistance, consider doxycycline or Malarone\textsuperscript{®}.
- In theory, doxycycline can reduce the plasma concentration of anticonvulsants but there is no evidence that this happens in practice and an increase in dosage of anticonvulsants is not recommended.

**Asplenia and severe splenic dysfunction**

These patients are at high risk of severe malaria. If travel is unavoidable, take rigorous precautions and use drugs that give good protection.

**Renal impairment**

- Avoid or reduce the dosage of proguanil, as it is excreted by the kidneys.
- Avoid Malarone\textsuperscript{®} in patients with low creatinine clearance (less than 30 ml/minute).
- Chloroquine only needs dosage reduction in severe renal impairment.
- Mefloquine and doxycycline can be used in normal dosage.

**Liver impairment**
• Severe impairment - specialist advice should be sought. Doxycycline can be used, according to experts in the field (and despite BNF warnings about tetracycline use in liver disease in general) because the mechanism of excretion minimises the metabolic risk. Malarone® can be used and the manufacturers do not recommend any particular precautions or dosage adjustment.

• Moderate impairment - doxycycline, proguanil, or Malarone® may be used.
- Mild impairment - chloroquine, proguanil, chloroquine plus proguanil, Malarone® or doxycycline may be used.
Pregnancy

- Evidence suggests pregnant women are twice as likely as non-pregnant women to be bitten by anopheline mosquitoes, the malaria is more severe and the disease can cause miscarriage.
- Avoid travel to malarious areas if possible.
- If unavoidable, preventative measures (remaining indoors between dusk and dawn, use of DEET) are recommended.
- Chloroquine and proguanil are safe during all trimesters and can be given in usual doses in areas where *P. falciparum* strains are sensitive.
- If proguanil is used, prescribe folic acid 5 mg daily.
- Mefloquine is suitable for the second and third trimesters; in the first trimester lack of safety data concerning miscarriages suggests that caution should be exerted before prescribing.
- Doxycycline should be avoided. However, under special circumstances, if required before 15 weeks of gestation, it should not be withheld if other options are unsuitable. The course should be completed before 15 weeks of gestation (including the four-week post-travel period).
- Malarone® in general should not be used due to lack of safety data. However, if a risk-benefit analysis suggests it is an appropriate option, it may be given in the second and third trimesters.
- Consult prophylaxis advice centres for travel to resistant areas.

Lactation

- Mefloquine is suitable for lactating mothers.
- Doxycycline is contra-indicated.
- There is lack of safety data concerning Malarone® but this may be considered if there is no suitable alternative.
- Prophylaxis is required in breast-fed infants, as the amounts of antimalarial present in milk are too variable to give reliable protection.

Prophylaxis advice centres

<table>
<thead>
<tr>
<th>Helplines for further information and advice</th>
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</thead>
<tbody>
<tr>
<td>Public Health England (PHE)</td>
</tr>
<tr>
<td>Prophylaxis Advice Fax Service</td>
</tr>
<tr>
<td>(complete the template available from the PHE website <a href="http://www.hpa.org.uk/webw/HPAweb&amp;HPAwebStandard/Page/1200660023262">www.hpa.org.uk/webw/HPAweb&amp;HPAwebStandard/Page/1200660023262</a>)</td>
</tr>
<tr>
<td>National Travel Health Network and Centre</td>
</tr>
<tr>
<td>(<a href="http://www.nathnac.org">www.nathnac.org</a>)</td>
</tr>
</tbody>
</table>

Further reading & references

- Malaria: Country Profiles; Department of International Development, 2011
- Foreign travel advice by country; GOV.UK
- Imported malaria cases and deaths, United Kingdom: 1994-2013; Malaria Reference Laboratory, Public Health England (archived content)
- Malaria; World Health Organization, 2014 (updated 2016)
- British National Formulary
- Malaria; National Travel Health Network and Centre (NaTHNaC)
- Rusted Summary of Product Characteristics for Malarone®; National Travel Health Network and Centre (NaTHNaC), 2012

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