

Guidelines for malaria prevention in travellers from the United Kingdom for 2003

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Summary: *This updated guidance from the Advisory Committee on Malaria Prevention for UK Travellers provides the essential information for healthcare workers who advise travellers. The many personal, visit and location-specific factors that need to be taken into account are discussed. Tables include the available antimalarials for prophylaxis and for standby treatment, appropriate choices of regimen by region and country for malarious areas, and the adjustments needed for children and in concomitant disease.*

There is greater emphasis on mefloquine, doxycycline and atovaquone/proguanil as the three options for highly chloroquine-resistant falciparum malarious areas, and changes in emergency standby medication.

Key words:
 adverse drug reaction reporting systems
 antimalarials
 chemoprophylaxis
 drug resistance
 malaria
 travel

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These guidelines are also available in electronic format at www.hpa.org.uk/infections/topics_az/malaria/menu.htm
 Ad hoc updates, when appropriate, will be posted at this site.

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1. Purpose and scope of guidelines

These guidelines on malaria prevention are designed to aid healthcare workers who advise travellers, particularly those who will be overseas for less than a year. The present (to May 2003) revision is the responsibility of the Health Protection Agency Advisory Committee on Malaria Prevention for UK Travellers (ACMP; membership given at the end of the guidelines). The guidelines are in three parts. The first part is a summary that emphasises modifications to the advice given in the recent guidelines, published in 1997¹ and 2001². As oversimplified lists of recommendations by country can be misleading, the second part (sections 3-4) discusses the issues addressed in formulating the guidelines. The second part also addresses the healthcare worker's consultation with prospective travellers. In concept and practice, chemoprophylaxis lies somewhere between vaccinations (for which people expect governments to lay down schedules) and treatment of ill people (which is determined by individual clinical need and choice). The risks of malaria need to be balanced against the risks of the preventive measures, on the basis of the data available. Travellers may ask for an explanation of these risks and doctors and practice nurses need to be well informed and able to present this information to travellers. Doctors, practice nurses and pharmacists are asked to read this section to ensure that due attention is paid to the traveller's history and destination. The third part (sections 5-8) gives specific recommendations for travellers to named destinations and some details of individual drugs. Fuller information on some drugs now less used was given in early versions of the guidelines^{3,4}.

These guidelines reflect a broad range of expert professional opinion. Data are inadequate for unequivocal views to be given on several issues, but all available evidence has been taken into consideration. There is often a range of acceptable options, but to meet the requests of general practitioners the guidelines aim to give one recommended option and state the alternatives, suggesting when and how different regimens can be used to good effect. However, there are now several options for effective prophylaxis of highly chloroquine-resistant falciparum malaria, and the choice between them will depend on details of the journey and individual preferences. The choice should involve adviser and traveller, with the aim of improved compliance. Authorisation to market drugs for use in the UK is the responsibility of the Medicines and Healthcare products Regulatory Agency (MHRA), advised by the Committee on Safety of Medicines, not of the ACMP. The guidelines should therefore be read as a supplement to and not as a substitute for the relevant summaries of product characteristics (SPCs or 'data sheets').

The second part (sections 3-4) of these guidelines may also be of use to prospective travellers who wish to read about the options themselves. All readers are recommended to read part three (sections 5-8) in its entirety to get a balanced picture.

2. Summary recommendations

Four steps remain essential to prevent damage to health due to malaria in UK travellers:

Awareness: know about the risk of malaria.

Bites by mosquitoes: prevent or avoid.

Compliance with appropriate Chemoprophylaxis.

Diagnose breakthrough malaria swiftly and obtain treatment promptly.

Recent guidelines give greater emphasis to the importance of balancing the risk of malaria and the risk of adverse reactions to antimalarials. This depends upon:

- place to be visited,
- duration of the visit,
- degree of exposure,
- level of drug resistance,
- type of traveller.

All these factors affect the risk of malaria. Whereas most adverse reactions to antimalarials occur within the first few doses, the cumulative risk of contracting malaria is roughly proportional to the length of stay in a malarious area. The longer the stay, therefore, the more important it is to use a regimen with a high protective efficacy.

It is more important to take an effective antimalarial regimen regularly than to agonise too much over which one to take. When two choices are finely balanced the wrong course of action is to take neither. In travellers who develop fever or a flu-like illness within three months after possible exposure to malaria the need for prompt medical attention cannot be overemphasised. It is also desirable to keep a sense of proportion between malaria and other health problems related to travel and to remember that malaria is both relatively preventable, and treatable if diagnosed early. At present, between 0.5% and 1% of falciparum cases in the UK die of the disease.

The range of antimalarials for protection against highly chloroquine-resistant malaria is expanding. In addition to the highly effective mefloquine which has a weekly regimen, doxycycline is now licensed for malaria prevention. Atovaquone/proguanil (Malarone), now licensed for prophylaxis, is increasingly being considered, especially for brief visits to highly malarious areas. In the case of mefloquine, increased awareness of distressing adverse neuropsychiatric reactions indicates caution in its use, but it remains of great value where there is intense exposure to malaria that is highly resistant to chloroquine.

It is important to observe contraindications to the use of specific antimalarials, and especially not to give mefloquine to people with a history of epilepsy or psychiatric illness, including depression. Chloroquine is relatively contraindicated in people who have had fits or who have psoriasis. Doxycycline is being used more often for those unable to take these drugs and going to high-risk areas, but it does carry a small risk of photosensitisation.

The preferred chemoprophylaxis for the few areas without chloroquine resistance is chloroquine. Those unable to take chloroquine should take proguanil.

For areas such as South Asia (the Indian subcontinent), with low or moderate levels of transmission of falciparum malaria that is slightly or moderately resistant to chloroquine, the preferred chemoprophylaxis is at present proguanil plus chloroquine.

Chemoprophylaxis is not recommended for places where there is a very low risk of acquiring highly multidrug-resistant malaria as the risk of adverse effects exceeds the risk of contracting the disease, but travellers are urged to maintain a high degree of awareness and seek immediate diagnosis and treatment of any febrile illness.

In areas with a high or very high risk of malaria that is strongly chloroquine resistant the frequency of adverse reactions to chemoprophylaxis has to be balanced against the risk of severe malarial illness and of death from falciparum malaria. The overall prevalence of adverse reactions, and of discontinuing chemoprophylaxis because of them, is comparable between regimens. Recent data indicate a significant frequency of subjective distressing neuropsychiatric adverse effects with mefloquine, but the results of different studies vary considerably. In the absence of recognised contraindications it is impossible to predict which individuals will suffer from these side effects.

On the other hand, mefloquine continues to have a substantially greater protective efficacy in East Africa, for example, than proguanil plus chloroquine. Therefore, for most of Africa, proguanil plus chloroquine is not recommended unless neither mefloquine, nor doxycycline, nor atovaquone/proguanil, can be taken.

Full recommendations by country and person are set out in part three (sections 5-8). Alternative regimens are usually given for travellers unable for any reason to take a recommended regimen.

Sources of advice on malaria prevention for travellers

Box 1 gives sources of advice for doctors and practice nurses who need more detailed advice for specific problems than this paper provides.

3. Issues considered in producing guidelines on chemoprophylaxis for malaria

Balancing risks and benefits: the problems of prophylaxis

Since the publication of the previous guidelines on malaria prevention in 2001, drug resistance of malaria parasites has continued to increase. In the light of increased experience with the newer chemoprophylactic agents, and new data, the ACMP has now further modified previous advice, revised its advice on standby medication and added advice for long-term travellers. This section discusses the issues that affect its deliberations on the guidelines, which aim to serve doctors, practice nurses, and an increasingly sophisticated travelling public.

BOX 1 Sources of advice for specific problems

HPA Malaria Reference Laboratory (MRL) (at London School of Hygiene and Tropical Medicine):	020 7636 3924
National Travel Health Network and Centre (NaTHNaC):	020 7380 9234
Glasgow, SCIEH for Travax users only, 2-4pm:	0141 300 1130
Birmingham Heartlands Hospital (Infectious Disease Unit):	0121 424 0357
Liverpool School of Tropical Medicine:	0151 708 9393
Oxford:	01865 225 214
London, Northwick Park Hospital: Hospital for Tropical Diseases Treatment only (ask for the medical officer on duty, Patrick Manson Unit):	020 8869 2831
Recorded advice for travellers from the HPA Malaria Reference Laboratory is available on 09065 508 908 (calls charged at 100p per minute).	

Malaria remains a major health problem worldwide. Over 2000 cases of malaria are imported into the UK each year. The proportion of imported cases due to *Plasmodium falciparum*, which is potentially fatal, has continued to rise so that over half of the cases are now of this type. An average of nine people each year die of malaria in the UK and this figure has tended to rise. Almost all malaria deaths are preventable.

Resistance to chloroquine continues to spread and to become more complete in those areas where it occurs. The resistance of *P. falciparum* to various other prophylactic drugs is already a major problem in Southeast Asia and is becoming commoner elsewhere. Chloroquine-resistant strains of *P. vivax* are also emerging in Southeast Asia.

The aim of malaria prophylaxis is to prevent illness and death in people who travel to areas where malaria is transmitted. It should never be forgotten that reducing mosquito bites has negligible adverse effects⁵, and it significantly reduces (but does not abolish) the risk of contracting malaria. It also protects from a number of other insect-borne infections. Antimalarial drugs used for chemoprophylaxis carry a risk of adverse reactions and so the risks of disease and of prophylaxis have to be balanced⁶. As malaria parasites become resistant to the drugs in use, it is necessary to use new and temporarily more effective drugs, which may have new or more frequent side effects. Inevitably, we have less experience of new drugs, or knowledge of the rate at which resistance to them may emerge and of their long-term adverse effects.

The situation is complicated by two other phenomena. The first is that subjective adverse events

ascribed to medicines are very common, (even to placebo tablets that contain no active drug at all⁷). Secondly, every year hundreds of thousands of people take chemoprophylaxis against malaria for an average of about two months each (before, during, and for four weeks after travel). This may amount to over half a million person-months of prophylaxis each year. Some members of so large a population would develop various illnesses and symptoms during that time even if they were not taking drugs.

Adverse events are likely to be observed, but deciding whether they are truly due to or simply coincident with medication is very difficult, especially for rare events.

The nature of the evidence

The best evidence for efficacy and for adverse effects comes from double-blind randomised controlled trials, in which neither the traveller nor the doctor knows which prophylactic is being taken. This avoids bias and more such trials are needed. Relatively few of those conducted on malaria chemoprophylaxis have compared relevant regimens in appropriate populations^{7,8}. Such trials have proved difficult to organise, have been relatively small, and have often used military populations, consisting mainly of healthy young men. Large trials are needed to measure the frequency of rare adverse events. The results of comparable trials can be pooled and reviewed systematically to help overcome the limitations of small trials, but this still requires several controlled trials to have been done. It is difficult to conceal the nature of the medication if drug regimens require people to take different numbers of tablets. The numbers of tablets themselves are also thought to influence compliance⁹.

The second best sort of study is a retrospective cohort study, which follows a lot of people who take different antimalarials, each of whom completes a standard questionnaire shortly after travel. This is less satisfactory and open to bias as the people on different drugs may be going to or coming from different countries, may already have opinions about possible side effects before taking the drugs, or may have tried one drug but switched to another before travel. Several such studies have been carried out and a few have covered large numbers of travellers^{10,11}. They have tended to be the most influential in formulating guidelines.

The third sort of study is based on case reports and these are the most difficult data to evaluate. They often describe individual tragedies (either due to malaria or ascribed to drugs), but do not relate to a defined population other than the total number of people on the drug. They neither enable different regimens to be compared nor convey any sense of proportion.

There are two large databases that store information about malaria and adverse events. Malaria is a notifiable disease in the UK and the Office for National Statistics reports notifications to the HPA Malaria Reference Laboratory (MRL) at the London

School of Hygiene and Tropical Medicine, which sends questionnaires to doctors, seeking detailed information about each case. This system gives a minimum estimate of verified cases, as reporting is undoubtedly incomplete; also it cannot include cases that are cured or result in death while the traveller is overseas. Suspected adverse reactions to medicines are reported voluntarily by doctors, nurses and pharmacists to the MHRA using the yellow card system. Adverse events are underreported and the data cannot distinguish with certainty between adverse reactions due to the drug and adverse events due to unrelated factors. In interpreting data on adverse events it is important to distinguish between numbers of events and numbers of people affected. One person may suffer several adverse symptoms.

Both over- and under-reporting of adverse reactions occur. Suspected adverse reactions reported voluntarily may be under-reported to a considerable but unknown extent, partly because neither doctors nor those taking the medicine may be aware that a particular symptom could be due to the drug. Conversely, with any drug taken for several months, it is likely that unpleasant events will occur by chance. These are often ascribed to the drug even when the drug may not be responsible. When a particular series of events receives publicity, reports of such events increase.

Adverse reactions to antimalarials are classified by the symptoms caused. The term 'serious' has a specific technical meaning in official databases: an apparent threat to life, requiring or prolonging admission to hospital, or resulting in severe disability or death. Other methods of classifying severity are specific to particular studies.

There is no way of knowing how many travellers take each of the prophylactic regimens each year, as not all antimalarials require a prescription; most are also used for purposes other than malaria prophylaxis, and drugs for malaria prophylaxis have not been prescribable on the NHS since 1995. Although travellers' use of antimalarial regimens was studied in detail twelve years ago¹² and more recently, recommendations have changed since these studies were performed.

Differences in perception of the risk of malaria versus the risks of adverse events

Epidemiologists who study malaria are particularly concerned about preventable deaths from malaria, which are usually associated with failure to take appropriate chemoprophylaxis. Individual patients are concerned if they contract malaria or if they suffer adverse events while on prophylaxis. Their doctors' views are much influenced by their personal experiences. The public are most aware of publicised adverse events associated with the most widely used drugs. The apparently good safety records of some prophylactic medicines may be due to their being rarely used!

Risk assessment

The risk of getting malaria varies greatly between different malarious places. At one extreme are rural, humid parts of West Africa where over 3% of travellers taking chloroquine alone⁹ and 6% or more on no chemoprophylaxis acquire malaria each month. The intensity of transmission will depend on the numbers, feeding and survival habits of the vector mosquitoes, and this in turn is climate dependent (particularly temperature and rainfall) as well as varying with the local mosquito ecology.

In much drier parts of Africa and in some parts of Asia¹² the rate is ten or even 100 times lower. If adverse events never occurred, then travellers to all these areas could take effective chemoprophylaxis. As risks must be balanced, the differences in malaria risk become important. The main determinants of malaria risk are the place(s) to be visited, duration of visit, pattern of activity (especially between dusk and dawn), and mode of travel, for example backpackers will be much more exposed than those who stay in air-conditioned urban hotels, although both may be at significant risk. Because resistance to chloroquine (and other drugs) is spreading, chemoprophylaxis that was effective five years ago may no longer be so.

P. falciparum is the only one of the four species of malaria parasite that poses a substantial risk of life-threatening illness and death. All cases of falciparum malaria have the potential to be severe and even fatal if untreated. These guidelines are therefore concerned mainly with the prevention of falciparum malaria. *P. falciparum* is the predominant parasite in hotter and more tropical areas, particularly Africa. Unfortunately, this is the main species that has become resistant in many countries to chloroquine and, lately, to other drugs. However, disease in those taking chemoprophylaxis may be milder or less rapidly progressive even if the parasites exhibit a degree of drug resistance. *P. falciparum* does not have persistent liver stages and it is rare to encounter first attacks of falciparum malaria more than three months after leaving a malarious area.

The other species (*P. vivax*, *P. ovale*, and *P. malariae*) can also make people very ill. These species are usually susceptible to chloroquine, which kills the blood stages that cause illness but cannot prevent the parasites hiding in the liver. These can emerge sometimes over a year later. However, some Asian strains of *P. vivax* are relatively insusceptible to chloroquine.

The risk of malaria is roughly proportional to the duration of stay in a malarious place. A visit of three months carries a risk around six times greater than a visit that lasts a fortnight, so it is important to maintain chemoprophylaxis throughout a long visit. In contrast, the risk of drug adverse events accumulates swiftly at the start of dosing, then more slowly. Adverse reactions to antimalarials tend to occur most often after the first dose for rapidly excreted drugs and after one of the first few doses for drugs that are excreted more slowly.

Short-acting drugs that are excreted rapidly have to be taken frequently; for example, proguanil is taken daily. Mefloquine is longer lasting and is taken once a week. The concentration of mefloquine builds up after the first few doses and the blood level takes three weeks to halve after the last dose. Travellers should therefore start taking mefloquine two and a half weeks before going abroad. The drug will then have reached a protective level before the traveller arrives in a malarious area. Most adverse reactions will have appeared by then also, and there is therefore time to change to a different drug.

For many other antimalarials it is usual to recommend starting the doses a week before travelling. This is to get the traveller into the habit of remembering to take the medicine regularly. They are to be continued whilst abroad and for four weeks after return. This is to allow developing falciparum malaria parasites to emerge from the liver into the bloodstream and be killed by the antimalarials. However, atovaquone/proguanil is started one or two days before departure and continued for a week after return, since it is believed to act as a causal prophylactic (killing parasites before they reach the blood).

These general principles have been applied in the formulation of these guidelines, which are also designed to allow for shortcomings in our current knowledge of drug effects and parasite and human behaviour.

Update on drugs for chemoprophylaxis^{1,2,3,4}

Proguanil plus chloroquine

The combination of proguanil 200 mg daily, and chloroquine base 300 mg weekly, has been used extensively. It remains a very safe combination but the efficacy of protection it offers has decreased. According to large retrospective surveys it was about 70% effective a decade ago in Africa^{10,11}. It is now much less effective than that in much of Africa south of the Sahara. The overall level of mild, moderate, and also of serious adverse events experienced by travellers taking this combination is similar to that with mefloquine^{8,13,14}, but the types of adverse events differ^{9,13}. The incidence of mouth ulcers is appreciable, due mainly to proguanil¹⁵.

Proguanil plus chloroquine regimens continue to require 16 tablets to be taken each week, in contrast to the single weekly tablet that made mefloquine popular before its side effects attracted media attention. Combined blister packs of proguanil and chloroquine are now available to simplify keeping track of dosing. In France a combined tablet is sold that contains both proguanil and chloroquine (Savarine™), and is taken in a dose of one tablet daily. It contains twice the level of chloroquine usually advocated in the UK and elsewhere and is not licensed for use here, but it exemplifies a welcome step towards simplifying compliance.

Hydroxychloroquine is comparably effective against chloroquine-sensitive malaria parasites to

chloroquine itself, and so patients under high-dose hydroxychloroquine therapy have been considered protected. It is much less effective than chloroquine against chloroquine-resistant parasites so an alternative drug or switching to chloroquine therapy temporarily may be indicated.

Mefloquine (Lariam)

Mefloquine was licensed as a prophylactic in the UK in 1990. The evidence from a small number of large trials indicates a protective efficacy of over 90% in Africa^{10,11,16}, of particular value in East Africa, where the combination of proguanil plus chloroquine has a low protective efficacy. Mefloquine became the preferred chemoprophylactic for East Africa (1993 guidelines⁴) and then for most of sub-Saharan Africa (1995³). In the UK, partly because of its side effects, recommendations of mefloquine have been more conservative than in the United States and parts of continental Europe, where mefloquine gained favour earlier.

Adverse reactions to mefloquine, as to other antimalarials, have been recognised for many years^{17,18}. Recent concern has focused mainly on neuropsychiatric reactions. This term is used to cover one main neurological phenomenon (convulsions) and several psychiatric disorders including insomnia, vivid and unpleasant dreams, agitation, anxiety, irritability, depression, feelings of unreality, panic attacks, hallucinations, and frankly psychotic episodes. A wide range of reported neurological symptoms (paraesthesia, vertigo, dizziness, and headache), and have received much publicity. With the exception of convulsions and psychoses, these conditions are difficult to assess objectively and rigorous data have proved elusive. Perception of many of these symptoms and conditions by physicians depends on the clinical context and the doctor's awareness. The observed incidence of adverse reactions was rare when case notes were examined retrospectively¹⁹, but it increased when physicians became aware of them and looked for them prospectively. Double-blind randomised controlled trials come closest to yielding useful data^{8,9,20,21}, but have not been big enough to measure rarer but severe events. It is worth remembering that, in all studies, the majority of individuals taking mefloquine had no adverse effects.

Several studies have shown that neuropsychiatric adverse events are commoner in women taking mefloquine than in men^{9,18}. Age does not affect the pharmacokinetics of the drug. Psychological tests of mood have confirmed the existence of subjective adverse reactions to the drug²², but neurological signs other than epilepsy are rare. Although the blood level of any drug is in general terms a determinant of adverse events, people on standard prophylactic doses with and without adverse events have been shown to have similar levels of mefloquine and its metabolites^{23,24}.

Over 75% of adverse reactions to mefloquine are apparent by the third dose. People who are to use

mefloquine would be well advised to start taking it two and a half weeks before departure, thus taking the third dose early enough to make a change if they encounter adverse reactions before leaving the UK and also building up the level of mefloquine.

Those few individuals who contract falciparum malaria after taking mefloquine for a short visit overseas, tend to become ill later on average after returning home than those who have taken other antimalarials²⁵. Cases of vivax malaria may occur much later and the diagnosis should be considered even in cases of fever that arise a year or more after leaving a malarious area.

Doxycycline

Doxycycline, an antibiotic of the tetracycline group, is active against falciparum malaria⁷ but offers limited protection against *P. vivax*. It, or atovaquone/proguanil, are the drugs of first choice for prophylaxis in areas of mefloquine-resistant malaria in Southeast Asia, and alternative drugs to mefloquine for people visiting highly chloroquine-resistant areas²⁶. Doxycycline is unsuitable for use during pregnancy or lactation and for children under 12 years of age. In Southeast Asia it had a similar protective efficacy to that of mefloquine against falciparum malaria⁷. Trial results from Africa are very limited^{26,27}.

Increasing experience of using doxycycline for malaria prophylaxis in UK travellers has revealed few problems. It has been found very useful for people with epilepsy or histories of psychiatric illness visiting areas of chloroquine-resistant malaria in East and West Africa and in Oceania. Data from a recent trial and from users in Australia have supported its use in Oceania, where a high level of protection is achieved if the drug is taken properly⁷.

In one study, three per cent of people taking doxycycline at therapeutic antimalarial dosage developed photosensitivity. Mostly these were mild transient rashes, but occasionally the effects were severe and prolonged²⁸. Exfoliative dermatitis has been reported but is rare. Excessive exposure to sun should be avoided by people on tropical seaside holidays but effective sunscreens are now widely available. Doxycycline may cause diarrhoea but also may protect against some bacterial causes of travellers' diarrhoea. There are rare reports of doxycycline-associated intracranial hypertension²⁹. A suggestion that it might protect against the liver cell stages of falciparum malaria was not substantiated by a specific trial³⁰.

The doctor prescribing doxycycline should warn against exposure to too much sunlight, and about the risk of vaginal thrush, and that the drug is contraindicated in pregnancy. Doxycycline should not be given to anyone with a history of allergy to tetracycline. Oesophagitis (heartburn) may result from taking the capsule on an empty stomach and/or lying down too soon after taking it. Compliance with the daily dose regimen appears to be particularly important with doxycycline³¹.

Atovaquone/proguanil (Malarone)

This fixed combination of atovaquone 250 mg with proguanil 100 mg has been an effective treatment of highly chloroquine-resistant falciparum malaria for some years. It is now also licensed for prophylaxis in the UK, for journeys involving up to 28 days in a malarious area and gives good protection^{32,33}. Use of atovaquone alone leads to rapid emergence of resistant parasites, but the combination of drugs appears to be highly synergistic and delays the development of resistance. The mode of action seems to depend on proguanil itself; it continues even in the absence of its active metabolite cycloguanil and in parasites resistant to cycloguanil³⁴. Drug resistance has been encountered after treatment with atovaquone/proguanil, but prophylactic efficacy appears high. Some apparent breakthroughs have been recorded but it is unclear whether they involve actual resistance to atovaquone/proguanil.

One tablet daily is taken for prophylaxis. The side effect profile appears comparable with that of other antimalarials, but serious adverse effects appear rare³². There is strong experimental evidence of a causal prophylactic effect³⁵, killing the developing liver stages of falciparum malaria, so that it is proposed that atovaquone/proguanil be continued for only one week after leaving a malarious area. The drug is expensive, but the reduced period of prophylaxis means that the overall cost is similar to that of mefloquine for short visits to malarious areas. It is therefore well suited to visits of a few days to, for example, the Amazon Basin, lowland game parks in South Africa and multidrug-resistant areas of Southeast Asia. However, the bulk of the evidence for efficacy in prophylaxis comes from trials in semi-immune populations (usually resident in malarious places)³⁶⁻³⁸. Because it has not been available for long in any country there is limited experience of atovaquone/proguanil prophylaxis compared with use of the longer established antimalarials, but it may well have an important role to play in the future provided resistance does not emerge³⁹. Atovaquone/proguanil is now licensed for prophylactic use both in adults and in children of weight 11 kg upwards. Because it is not feasible to break the tablets, a specific Malarone Paediatric tablet is made, containing one quarter of the dose in the adult tablet. It may be considered, along with doxycycline and mefloquine, in the choice of prophylaxis for visitors to Africa south of the Sahara.

Dapsone/Pyrimethamine (Maloprim)

This fixed combination of 12.5 mg pyrimethamine with 100 mg dapsone has been in use for many years, especially in southern Africa and Oceania, where it appears to provide good protection, although formal trials are scarce. The dose is one tablet weekly but the therapeutic ratio is low, and cases of agranulocytosis have been seen when this dose has been exceeded. Because of this and also to avoid confusion of Maloprim with Malarone (which is taken daily),

dapsone/pyrimethamine is no longer available in the UK, though it is still available (as Deltaprim) in southern Africa. Dapsone/pyrimethamine was of particular value in travellers with epilepsy, especially children, but atovaquone/proguanil can now fill that role.

Comparing older and newer regimens for Africa

The risk of malaria is very great in Africa south of the Sahara. There are rural areas where the inhabitants experience more than one infectious mosquito bite each night.

Tourists who visit Kenya and do not take chemoprophylaxis develop malaria at a rate of 1.2% per month¹¹. The incidence of falciparum malaria in Peace Corps members in West Africa on chloroquine prophylaxis was 3.8% per month between 1990 and 1992¹⁰. The evidence suggested a protective efficacy for chloroquine at that time and place of approximately 50%^{10,16}. The incidence of falciparum malaria without prophylaxis over a two-week period is therefore likely to be about 0.6% in East Africa and 3.8% in West Africa.

For optimal protection it is therefore essential both to take measures to avoid infectious mosquito bites and to take chemoprophylaxis regularly.

The recommended regimens for malaria prophylaxis in Africa have progressively changed, for three reasons. In addition to mefloquine, doxycycline and atovaquone/proguanil are both now licensed for prophylactic use. The efficacy of proguanil plus chloroquine for prophylaxis has decreased to the point that it gives little protection in many areas of Africa frequently visited by UK travellers. The choices between these regimens are discussed here and summarised in the section on Africa (see table 7) in the detailed regional advice section of the guidelines. Three regimens are recommended: mefloquine or doxycycline or atovaquone/proguanil. Proguanil plus chloroquine is a markedly less satisfactory option in most parts of Africa⁴⁰ and is no longer recommended for highly endemic areas. In terms of protective efficacy, mefloquine, doxycycline and atovaquone/proguanil are considered comparable at around 90%, but the best-quality evidence is available for mefloquine. In Asian trials⁷, mefloquine and doxycycline were comparably effective and there is no known reason why this should not be similar in Africa. Atovaquone/proguanil has been shown to provide good protection in semi-immune Africans³⁶⁻³⁸ but because it has been more recently introduced for prophylaxis there is less experience of its use than for the other two medicines. The protective efficacy of proguanil plus chloroquine was 70% a decade ago on the East African coast and is now probably much lower. Cases of severe malaria and even death are being seen in travellers to West Africa who have regularly taken proguanil plus chloroquine. In some inland parts of north central Africa there are still extensive areas where proguanil plus chloroquine protects well; but these are not among the areas frequently visited by UK travellers.

The four regimens differ in their commonly reported adverse events. The most extensive data concern mefloquine^{41,42} and proguanil plus chloroquine, as discussed above. Both of these have been extensively used in Africa. Doxycycline has been used for many years for other indications, particularly for the prevention of acne, and its main adverse effects are of two sorts: gastrointestinal discomfort is common (very rarely accompanied by *Clostridium difficile* diarrhoea) and photosensitisation may occur. The latter may affect about 3% of travellers on prophylactic medication with doxycycline and is possibly more frequent and certainly more of a disadvantage in those planning to sunbathe or have a seaside holiday. Atovaquone/proguanil appears so far to have a relatively mild adverse event profile, with nausea as the most common symptom, sometimes mouth ulcers, and with rather less severe problems than encountered with the other regimens. It has no adverse psychomotor effects on aircrew. While proguanil plus chloroquine rarely causes severe adverse reactions some find the common gastrointestinal discomfort unpleasant. Experience shows that travellers vary in their preferred antimalarial, judged on the adverse effects profile and convenience of dosage.

The regimens differ greatly in the number of tablets or capsules to be taken, from one weekly for mefloquine, through one daily for both atovaquone/proguanil and doxycycline, to a total of 16 tablets per week, partly taken daily, for proguanil plus chloroquine.

Cost also varies greatly, with proguanil plus chloroquine the least expensive, doxycycline next, mefloquine more costly, and atovaquone/proguanil more costly on a per-tablet basis. The relative cost of atovaquone/proguanil prophylaxis is reduced by the currently shorter period of continuing the medicine after leaving the malarious area for one week as compared with four weeks for all other regimens. The cost differentials become much greater for prolonged travel, so that atovaquone/proguanil, which has advantages as a prophylactic for short visits to malarious areas, becomes very expensive for long-term stays. Comparative data on these drugs are given in table 6.

Emergency standby treatment^{1,2,3,4}

This should be recommended for travellers taking prophylaxis but going to remote places and unlikely to be within 24 hours reach of a doctor. Standby treatment is intended for use by travellers who believe that they may have malaria. They need to be sufficiently well informed to make sensible judgments on when to take medications. Studies from outside the UK have shown that standby treatment is often used wrongly. The increasing availability of commercially purchased diagnostic tests for falciparum malaria can improve the diagnostic capabilities of travellers. Several tests are relatively reliable and sensitive (though some early symptomatic infections may be missed), but field trials in travellers have given variable results⁴³. Until tests become available which can be reliably used by sick

travellers, caution is best exercised in providing them to those who are not themselves health professionals.

Recommended standby regimens are currently changing. The rapid increase of resistance to sulfadoxine/pyrimethamine, especially in East Africa, makes this unreliable as an emergency regimen. Both co-artemether and atovaquone/proguanil now appear effective, relatively easy to take in a curative regimen and have limited adverse effects. The curative regimen of quinine alone is sufficiently toxic that the course is often not completed, and it is now only recommended for pregnant women for whom there are no satisfactory alternatives.

Long-term travellers

(The needs of these travellers are discussed more fully in 'Malaria prophylaxis for long-term travellers' on page 200⁴⁴.)

These guidelines discussed here apply primarily to short-term visitors from the UK to malarious areas. An important minority of travellers stays overseas for more than six months, and are exposed to a steadily increasing cumulative malaria risk. Those abroad for many months have a high chance of acquiring malaria.

The chief practical problem encountered by such 'expatriates' is that several antimalarials are licensed with an upper limit on duration of use. This has usually been due to lack of data rather than by any evidence of new toxicity problems from long-term use of these antimalarials.

Travellers deal with this time limit in several ways: by switching from one chemoprophylactic to another as the limit is reached; by using chloroquine plus proguanil on the grounds of its long-term safety, even though it gives poor protection in much of Africa now; by abandoning prophylaxis and seeking treatment for malaria attacks; or by continuing with an efficacious chemoprophylactic beyond its licensed limit of use. For highly malarious areas with drug-resistant falciparum parasites, the last is probably preferable since there is no evidence of new types of adverse events from long-term use for any of the first line drugs used for preventing chloroquine-resistant malaria. This statement, however, is made on the basis of the absence of reported new events in countries where there is no time limit for use, rather than upon definite evidence of safety.

Most adverse events from the use of antimalarials tend to occur shortly after the first few doses, and the incidence of later-onset events is very low. On the available evidence the ACMP considers that (in the absence of problems in the short term), mefloquine can continue to be used for up to three years, though if side effects do develop later, the medication should be discontinued. There is no evidence against longer-term use of doxycycline (which is already licensed for up to two years for managing acne). There is as yet no evidence to limit the duration of atovaquone/proguanil, whose components have a short half-life and which is licensed for indefinite use in the USA, though experience of this combination is limited.

More generally, long-term visitors to malarious areas should be meticulous in avoiding mosquito bites and should also have the malaria risk of their places of work and residence assessed carefully by a travel medicine specialist allowing an individual approach to minimising risk.

4. Advising travellers

A consultation on malaria with an intending traveller should ascertain the degree of risk, emphasise the need for protection against mosquito bites, advise the need for seeking immediate medical attention in the event of a febrile illness within three months (or even a year) of leaving the malarious area, and recommend chemoprophylaxis appropriate to the risk and destination(s). Healthcare workers should avoid giving unnecessary medication and be aware of contraindications.

The level and duration of risk depends upon destination, duration, activities to be undertaken, and style of travel. The choice of drug will depend on previous history, pregnancy, relevant family history, and concomitant illness or medication.

In deciding on the preferable chemoprophylactic regimen for a particular traveller, the following variables need to be assessed:

- Countries and localities to be visited and their malaria risk. This may vary during the year; and according to whether the destination is rural or urban.
- Type of accommodation to be used.
- Duration of intended stay in malarious areas.
- Intended activities (beach/jungle explorations/safaris, etc), particularly between dusk and dawn, when the risk of being bitten is present.
- Style of travel (business/backpacking/package tour/visiting relations etc).
- Age, sex, pregnancy and intended conception, breastfeeding.
- Weight of young children, a better guide than age to the dose of antimalarials.
- Previous travel and experience with antimalarials.
- Previous reactions to an antimalarial drug.
- Current illnesses (renal and hepatic function, cardiac conduction, myasthenia gravis, psoriasis).
- Current medication (anticoagulants, anticonvulsants, cimetidine, cyclosporin, cardiac glycosides, cytotoxic drugs, antibacterials, probenecid).
- Relevant previous illnesses or medication (fits, psychiatric disorders, drug reactions, psoriasis).
- Personal or family history of epilepsy in first degree relatives.
- History of psychiatric disorder, depression or anxiety requiring treatment.

Travel activities and risk

Travellers undertaking different types of travel and activities in the same country may be exposed to a wide range of risks, depending on the degree of exposure to anopheline mosquito bites between dusk

and dawn. The risk of acquiring malaria is always substantial for tourists in tropical Africa.

Visiting friends and relations

Malaria attack rates are particularly high among those who travel to malarious areas to visit friends and relations. Many such travellers are immigrants who settled in the UK long ago. They may have left Asia during the eradication era (1955-69), when risk there was low, or they may believe that they have some persistent immunity. Such immunity fades rapidly. Compliance with prevention measures in some of these groups is therefore poorer than in other travellers. These travellers are often accompanied by their children, who may be at greater risk than adults of severe illness if they contract malaria. It is therefore particularly important to emphasise both mosquito avoidance and compliance with chemoprophylaxis. Risk is very high in West Africa and many of the comments for backpackers apply to these visitors.

Backpacking

Backpacking, working in rural areas, and going on safari bring travellers close to the breeding and resting habitats of anopheline mosquitoes, against which they are unprotected by screens and air-conditioning. It is therefore particularly important to reduce mosquito biting by the use of repellents such as diethyltoluamide (DEET) on exposed skin from dusk. Other effective measures are: burning mosquito coils; vaporising mosquito deterrents; and sleeping under a mosquito net impregnated with a synthetic pyrethroid insecticide. Access to medical attention may be difficult or delayed, and, as well as chemoprophylaxis that works well in the context of local patterns of drug resistance, standby emergency medication should be considered if medical attention will be over 24 hours away.

Business travel

Most business travellers will stay at night in screened or air-conditioned hotels in cities. A knockdown insecticide (for example, containing synthetic pyrethroids) should be sprayed in the hotel room each evening to kill any mosquitoes that entered during the day. Risk exists in most African cities (excluding central Nairobi, cities at high altitude such as Addis Ababa and cities in southern Africa) because the vector can flourish in suburban areas. Urban transmission occurs in Indian cities due to an urban-dwelling vector (*Anopheles stephensi*). The main risk to business travellers is a short unexpected trip to visit a game park, to take an evening meal, or to stay in the country. Surveys show that business travellers have a substantially higher incidence of malaria than tourists, and often lower stated compliance with prophylaxis. Business travellers therefore need to take greater care than is usual at present. Malarone (atovaquone/proguanil) is now available and will be useful to cover short visits to risk areas.

Those who travel on business to remote or rural areas are in the same risk category as backpackers.

5. Detailed recommendations

The principles of prevention are the same throughout the world: awareness of risk; avoiding mosquito bites; taking appropriate chemoprophylaxis; and seeking immediate medical attention in the event of fever during and up to a year after travel to a malarious area.

Awareness of risk

All travellers to malarious areas *must* be aware of the risk of malaria in the areas they visit, take action to reduce the risk, and seek medical advice urgently if they get a fever or flu-like symptoms.

Bites by mosquitoes: prevent or avoid

Sleep in rooms that are properly screened, with close fitting gauze over windows and doors, no holes in the gauze, and no unscreened entry points. Spray the room with a knockdown insecticide before evening to kill any mosquitoes that may have entered the room during the day.

When sleeping outdoors or in an unscreened room, use mosquito nets around the bed at night, checking that there are no holes in the net. The net should be impregnated with pyrethroids, such as permethrin 0.2 g/m² of material, every six months and the net should be long enough to fall to the floor all round the bed or be tucked under the mattress.

Synthetic pyrethroids should be vaporised overnight, using an electrically heated mat. Alternatively, mosquito coils (slow burning mixture of repellent and insecticide) may be burned. Electronic buzzers are sometimes marketed as repellents; they do not work.

Long-sleeved clothing, long trousers, and socks should be worn out of doors after sunset. Light colours are less attractive to mosquitoes. Insect repellents containing over 30% DEET will repel mosquitoes effectively and should be applied to exposed skin. Avoid exceeding the manufacturer's recommendations for 50% DEET, particularly on small children. Impregnating cotton garments with 30 ml of DEET in 250 ml of water makes them repellent. Refined lemon eucalyptus oil on skin also repels mosquitoes.

Compliance with appropriate Chemoprophylaxis

The usual regimens for chemoprophylaxis for adults and children are given in tables 1 and 2. As the child weights at which the dose of atovaquone/proguanil changes differ from those for other antimalarials, they are given in table 2a. Four paediatric tablets of atovaquone/proguanil are equal in drug content to one adult tablet.

Appropriate drugs are listed by region and country below. Several general principles apply:

Take appropriate drugs. If the drug or drugs first recommended cause adverse effects or there are reasons for not taking them, use one of the other

TABLE 1 Prophylactic regimens against malaria in adults

Regimen	Dose for chemoprophylaxis	Usual amount per tablet (mg)
Areas of chloroquine-resistant <i>P. falciparum</i>:		
Mefloquine*	1 tablet weekly	250 (228 in United States)
Doxycycline**	1 tablet/capsule daily	100 mg
Atovaquone-proguanil (Malarone)†	1 tablet daily	250 (atovaquone) plus 100 (proguanil)
Areas of little chloroquine resistance: poorly effective where marked resistance		
Proguanil <i>plus</i> Chloroquine	2 tablets daily <i>plus</i> 2 tablets weekly	100 mg 150 (base)
Areas without drug resistance:		
Chloroquine	2 tablets weekly	150 (base)
Proguanil	2 tablets daily	100 mg

All antimalarials are to be avoided in severe hepatic impairment. Chloroquine doses are given as the base. Folate supplements should be given to those taking proguanil or Maloprim when pregnant.

* Avoid during pregnancy, during lactation and avoid pregnancy for three months after stopping it. Do not prescribe mefloquine if there is a history of epilepsy, depression or severe psychiatric disorder. Appropriate for up to one-year abroad. Caution in cardiac conduction disorders.

** Contraindicated during pregnancy and lactation and for children less than 12 years.

† Licensed for up to 28 days in malarious area. Do not give in pregnancy. Begin 1-2 days before departure. Continue for one week after return.

appropriate drugs listed. If all are unsuitable, consult the Malaria Reference Laboratory (see box on page 182) or seek expert advice at a specialist Travel Clinic.

Compliance is essential; most deaths occur in those who take drugs irregularly or not at all.

Start medication a week before going abroad (1-2 days for atovaquone/proguanil). When using mefloquine, start two and a half weeks before travelling so that if adverse events occur there will be time to switch to an alternative before travelling.

Continue medication while in the malarious area and for four weeks after leaving it (atovaquone/proguanil should be continued for a week after leaving). Taking the chemoprophylaxis *regularly* throughout is at least as important as choosing the right drug. A drug that is not taken offers no protection and to take antimalarials irregularly is a dangerous gamble.

Take antimalarials after meals, with water, to minimise minor side effects. Doxycycline should not be taken lying down, nor immediately before lying down, as it may then cause heartburn and great pain.

Oral typhoid and oral cholera vaccines, and intradermal rabies vaccination should, if used, be given before starting antimalarial prophylaxis⁴⁵.

TABLE 2 Doses of prophylactic antimalarials for children*

Weight in kg	Drug and tablet size				
	Chloroquine 150 mg base	Proguanil 100 mg	Mefloquine 250 mg	Doxycycline 100 mg	Age
Under 6.0	0.125 dose ¼ tablet	0.125 dose ¼ tablet	Not recommended	Not recommended	Term to 12 weeks
6.0 to 9.9	0.25 dose ½ tablet	0.25 dose ½ tablet	0.25 dose ¼ tablet	Not recommended	3 months to 11 months
10.0 to 15.9	0.375 dose ¾ tablet	0.375 dose ¾ tablet	0.25 dose** ¼ tablet	Not recommended	1 year to 3 years 11 months
16.0 to 24.9	0.5 dose 1 tablet	0.5 dose 1 tablet	0.5 dose ½ tablet	Not recommended	4 years to 7 years 11 months
25.0 to 44.9	0.75 dose 1½ tablets	0.75 dose 1½ tablets	0.75 dose ¾ tablet	Adult dose from age 12 years 1 tablet†	8 years to 12 years 11 months
45kg and over	Adult dose 2 tablets	Adult dose 2 tablets	Adult dose 1 tablet	Adult dose 1 tablet	13 years and over

* For children under 11kg in areas of chloroquine resistance the appropriate drug is mefloquine or chloroquine plus proguanil. Chloroquine is available as a syrup but the proguanil has to be powdered on to jam or food. Antimosquito bite measures are especially important. Doxycycline is unsuitable for children under 12 years.

When both are available, weight is a better guide than age for children over 6 months.

Caution: In other countries tablet size may vary.

N.B. Atovaquone/proguanil (Malarone) paediatric dosage is given in table 2a.

** For this medicine at this age/weight, 0.375 dose would be preferable, but cannot be safely provided by breaking the adult tablet.

† The adult dose is necessary when doxycycline is only available in capsule form and ¾ is not feasible.

Diagnose breakthrough malaria swiftly and obtain treatment promptly

Standby emergency medication

Travellers who will be unable to obtain medical advice within 24 hours of becoming ill may be provided with a standby course of antimalarials for self-medication (as may those who have access to advice but will be in places where suitable drugs are unavailable). Indications include travel to remote malarious areas, or remote areas anywhere after being in a malarious area in the preceding three months; multiple short visits to, or residence in low-risk areas with highly drug-resistant malaria, or having to use sub-optimal chemoprophylaxis in a high-risk area. Standby medication is an unlicensed use for all current regimens, and studies have shown that less than 17% of users had subsequently confirmed malaria.

Criteria for providing standby drugs should be quite restrictive, and travellers should be given clear written instructions and criteria for their use, such as a temperature of 38°C or more over a week after arriving in a malarious place, with medical help unavailable that day. All those who start standby treatment should subsequently seek medical advice as soon as possible. Standby drugs should not be provided for trips of less than a week, because the interval between getting an infective bite and becoming ill with malaria is at least seven days. In general, a drug used for emergency self-medication should be a different drug from that used for chemoprophylaxis by that person.

Table 4 shows the recommended standby regimens. Chloroquine is suitable as a standby drug in areas without chloroquine resistance, for individuals who will be taking either no prophylaxis, or prophylaxis with proguanil. Atovaquone/proguanil, or co-artemether, is recommended in areas with chloroquine resistance. There is a risk of neuropsychiatric side effects with a therapeutic dose of mefloquine, but the hazards of untreated malaria are greater.

Resistance to sulfadoxine/pyrimethamine is widespread in Africa so this combination is no longer recommended. Halofantrine is unsuitable as a standby drug because of the risk of fatal cardiac arrhythmias due to QT interval prolongation, especially when used following mefloquine.

In areas where there is a low risk of becoming infected but where the malaria is highly resistant to

TABLE 2a Paediatric dosage of atovaquone/proguanil

Weight in kg	Proportion of adult dose	Number of paediatric tablets
Under 11.0	Do not use	Not recommended
11.0 to 20.9	0.25	1 paediatric
21.0 to 30.9	0.50	2 paediatric
31.0 to 40.0	0.75	3 paediatric
Over 40.0	1.00	4 paediatric or 1 adult

TABLE 3 Table of doses by spoon measures for chloroquine syrup

Weight in kg	Number of 5 ml measures (there is often a half size measure at the other end)	Proportion of adult dose	Age
Under 4.5	0.5 (2.5 ml)	0.083	Under 6 weeks
4.5 to 7.9	1.0 (5.0 ml)	0.167	6 weeks to 5 months
8.0 to 10.9	1.5 (2.5 ml plus 5 ml)	0.250	6 months to 12 months
11.0 to 14.9	2.0 (2 x 5 ml)	0.333	13 months to 2 years 11 month
15.0 to 16.5	2.5 (2.5 ml plus 2 x 5 ml)	0.417	3 years to 3 years 11 months

N.B. These dose-steps are not the same for chloroquine tablets, which differ from the syrup in chloroquine content.

chloroquine and other drugs, and no chemoprophylactic drug is being taken, either co-artemether or atovaquone/proguanil is the most suitable standby treatment.

Pregnant women should avoid situations in which standby treatment may be needed; the only appropriate drug in pregnancy is quinine for seven days. Quinine in malaria therapeutic doses is safe and will not threaten the pregnancy or promote premature labour, whereas an attack of malaria can do both.

Malaria prophylaxis in people with other clinical conditions or pregnancy

Other illnesses, or the drugs required for their treatment, can affect advice on appropriate antimalarial precautions. Many situations need specialist advice, but epilepsy and renal or hepatic failure are common problems.

Epilepsy

Both mefloquine and chloroquine are unsuitable. Proguanil alone (200 mg daily) is recommended for malarious areas without chloroquine resistance. For areas with a high risk of chloroquine-resistant malaria, such as sub-Saharan Africa, doxycycline or

atovaquone/proguanil can be used; they are also effective against mefloquine-resistant malaria in the Far East. Phenytoin, carbamazepine, and barbiturates reduce the half-life of doxycycline, so in theory its dose should be increased for patients taking these drugs. However, there is currently no direct evidence that this is necessary. Dapsone/pyrimethamine is also suitable for children with epilepsy: it is no longer available in the UK but is found as Deltaprim in some parts of Africa.

Renal failure

Proguanil is excreted by the kidney and the prophylactic dose is liable to be affected in renal failure. Two approaches are possible: either reduce the dose of proguanil (table 5) or use an alternative drug. Table 5 relates dosage to serum creatinine levels and grades of renal impairment, derived from appendix three of the British National Formulary⁴⁶. Atovaquone/proguanil contains proguanil and is contraindicated in severe renal failure. In areas with a high risk of chloroquine-resistant malaria, mefloquine or doxycycline may be used since they are metabolised and excreted through the liver. The dose of mefloquine is unchanged for patients on dialysis⁴⁷. Some

TABLE 4 Emergency standby treatment for adults

Situation for use	Standby treatment regimen	Usual amount per tablet	Adult dose
Multidrug-resistant falciparum malaria	Atovaquone-proguanil (<i>Malarone</i>)	250 mg plus 100 mg	4 tablets as a single dose on each of three consecutive days
Multidrug-resistant falciparum malaria	Co-artemether (<i>Riamet</i>)	20 mg artemether plus 120 mg lumefantrine	6 doses of 4 tablets over a period of 60 hours
Multidrug-resistant falciparum malaria	Quinine plus doxycycline	200 mg quinine and 100 mg doxycycline	Quinine 2 tablets 3 times a day for 3 days, accompanied by 1 tablet of doxycycline twice daily for 7 days
Recommended where no chloroquine resistance present	Chloroquine (<i>Nivaquine/Avlocor</i>)	150 mg chloroquine base (<i>Nivaquine</i>) or 155 mg chloroquine base (<i>Avlocor</i>)	4 tablets on days 1 and 2, 2 tablets on day 3
Pregnancy	Quinine	300 mg quinine	Quinine 2 tablets 3 times a day for 5-7 days

All antimalarials to be avoided in severe hepatic and renal impairment. Chloroquine doses are given as the base. Quinine alone (or chloroquine in non-resistant areas) is the only regimen to be used in pregnancy.

TABLE 5 Doses of proguanil in adults with renal failure

Renal impairment grade	Serum creatinine $\mu\text{mol/litre}$	Creatinine clearance ml/min/1.73m^2	Prophylactic dose of proguanil
(None)	<150	60	200 mg daily (standard dose)
Mild	150-300	20-59	100 mg daily
Moderate	300-700	10-19	50 mg every second day
Severe	>700	<10	50 mg once weekly

chloroquine is excreted in urine but most is metabolised in the liver.

Hepatic dysfunction

Nearly all antimalarial drugs are excreted or metabolised by the liver and severe liver impairment may result in their persistence and accumulation. No data are available that relate dose to degree of impairment. Particular care is needed with mefloquine and doxycycline in hepatic failure as both are excreted exclusively through the liver. In practice proguanil and chloroquine are the main chemoprophylactic agents used in mild hepatic impairment. Proguanil or atovaquone/proguanil tend to be preferred in moderate impairment. More data are urgently needed on patients with cirrhosis or chronic hepatitis. All antimalarial drugs except, possibly, atovaquone/proguanil are contraindicated in people with severe liver failure.

Post-splenectomy

Travellers without spleens are at particular risk of severe malaria and need to take meticulous precautions against contracting the disease, including rigorous use of antimosquito measures, strict compliance with appropriate chemoprophylaxis, and avoidance of unnecessary visits to malarious areas.

Pregnancy

Pregnant women are at particular risk of severe malaria and should avoid visiting endemic areas if possible. Their advisers must balance the risks and benefits of chemoprophylaxis carefully for those who must travel. Chloroquine and proguanil have a long history of safe use during pregnancy. Dapsone/pyrimethamine, if obtainable, can also be used cautiously after the first trimester if a visit to an area of transmission is unavoidable. There is evidence that mefloquine treatment during pregnancy may be associated with an increased frequency of stillbirths, so this drug should only be used during pregnancy if the need for it is great. Regimens which include pyrimethamine or proguanil should be supplemented with 5 mg of folic acid daily in those who are pregnant or seeking to become pregnant. None of these gives

complete protection in areas where malarial parasites are resistant to multiple drugs. Women capable of childbearing should take contraceptive precautions while taking mefloquine and for three months after the last dose. Having taken mefloquine inadvertently during pregnancy is usually not viewed as an indication to terminate a pregnancy.

Doxycycline and atovaquone/proguanil are contraindicated during pregnancy and neither should be used while breastfeeding. Further details are in 'Malaria prophylaxis for long-term travellers' on pages 200-8⁴⁴.

6. Recommendations by area

Tables 6 to 12 present preferred chemoprophylaxis recommendations for each country, and an alternative where possible for those who are unable or unwilling to follow a recommended regimen. Sometimes there are several regimens of comparable overall benefit, and the choice between them will depend on the particular circumstances of the traveller. Such a choice will particularly occur in areas of Africa with highly chloroquine-resistant falciparum malaria and involve the first three prophylactic medicines in table 6. Measures to avoid mosquito bites are always applicable. If transmission occurs in particular seasons or localities the months or places associated with risk are indicated, but space does not permit a detailed description of localised risks of transmission in each country. Those visiting parts of a country where transmission is patchy and who will deviate from the tourist routes should visit a travel clinic or ask their doctor or nurse to consult a source of detailed information, such as the Malaria Reference Laboratory, giving their precise itinerary.

North Africa and the Middle East (table 7)

The risk of malaria is very small in the areas most visited by tourists. For many areas the best advice is to avoid mosquito bites and remember the remote possibility of malaria in the event of fever within a year of returning to the UK. This applies to all North Africa (except for the El Faiyum area of Egypt southwest of Cairo) and to Turkish tourist areas as far east as Antalya. Eastwards along the coast from Antalya to the Syrian border and inland in southeast Turkey, and in parts of Syria and Iraq, as well as parts of the former USSR (see table 7), chloroquine prophylaxis is recommended against vivax malaria. Falciparum malaria, often resistant to chloroquine, occurs in remote parts of Oman (Muscat itself is malaria-free), parts of Saudi Arabia, Yemen, Iran, and Afghanistan.

Africa south of the Sahara (table 8)

Everyone visiting malarious parts of sub-Saharan Africa should take adequate chemoprophylaxis and protection against biting mosquitoes; both should be used regularly throughout the visit. The chemoprophylactic cover needs to be maintained for a month after leaving the malarious area (or one week

TABLE 6 Features of antimalarials used in the prevention of chloroquine-resistant falciparum malaria

	Recommended regimen			Alternative regimen
	Mefloquine	Doxycycline	Malarone	Proguanil plus chloroquine
Efficacy against chloroquine-resistant <i>P. falciparum</i>	Very good (c. 90%)	Very good Less evidence	Very good Less evidence	Limited protection
Efficacy against <i>P. vivax</i> and other malaria species	More limited Relapses can occur	More limited Relapses can occur	More limited Little information Relapses can occur	Good Relapses can occur
Most notable adverse effects	Neuropsychiatric	Gastrointestinal, photosensitisation	Relatively low	Gastrointestinal
Half-life of blood level	3 weeks	18-22 hours	A 2-3 days; P 17 hours	C 30-60 days; P 17 hours
Frequency of administration	250 mg/week	100 mg daily	1 tablet daily	2 tablets daily plus 2 tablets weekly
Duration of medication after leaving malarious area	4 weeks	4 weeks	1 week	4 weeks
Main contraindications	Epilepsy, psychiatric disorders, early pregnancy	Childhood, pregnancy	Pregnancy	Present epilepsy
Adult for 3 days in a malarious area				
Cost	2.0 CU*	3.2 CU	3.6 CU	1.0 CU
Number of tablets	7	38	12	88 (76 + 12)
Adult for 2 weeks in a malarious area				
Cost	2.6 CU	4.1 CU	7.0 CU	1.3 CU
Number of tablets	9	49	23	112 (98 + 14)
Adult for 8 weeks in a malarious area				
Cost	4.4 CU	7.6 CU	Not licensed for more than 28 days use	2.4 CU
Number of tablets	15	91		212 (182 + 26)

* CU (cost units) are units of approximate relative cost, based on entries in the Monthly Index of Medical Specialities (April 2000). There is little change if British National Formulary (BNF) prices for 2003 are used.

for atovaquone/proguanil). The risk of falciparum malaria is very high, except in the extreme south of Africa, and much of the malaria is resistant to chloroquine. Most cases of imported falciparum malaria and almost all fatal cases in UK travellers have contracted the infection in Africa. Breakthrough malaria may occur on all regimens. It is essential to regard all fevers and flu-like illnesses occurring up to a year (and especially in the first three months) after leaving Africa as possible malaria and investigate them urgently.

Mefloquine, doxycycline and atovaquone/proguanil give good protection in areas of Africa south of the Sahara where there is much chloroquine resistance. Mefloquine gives very good protection, for which there is much evidence, but there has been concern about neuropsychiatric adverse effects in a small proportion of users. Doxycycline, on the basis of trials outside Africa, is considered to give comparable protection to mefloquine. It may not be

used in children below the age of 12 years or in pregnancy. Recently a fixed combination of atovaquone and proguanil (Malarone) has been licensed for malaria prophylaxis. Experience so far suggests that adverse events are relatively minor, but long courses are very expensive. On the basis of a limited number of tests, it appears to prevent falciparum malaria from getting established in the liver as well as red blood cells. Therefore it can be taken for 1-2 days before entering a malarious area, whilst there, and for one week after leaving a malarious area, rather than the four weeks needed for other drugs, which are active only against the bloodstream forms. Mefloquine, doxycycline and atovaquone/proguanil have similar overall effectiveness for malaria prevention in Africa, but have differing balances between efficacy, adverse events, and convenience. Their contraindications for particular groups of people also differ. They are summarised in table 6.

TABLE 7 Malaria in North Africa, the Middle East and Central Asia

Risk	Country	Preferable regimen*	Alternative regimen
Risk very low	Algeria (tiny remote focus) Egypt (tourist areas are malaria-free) Georgia (some SE villages, July-October) Kyrgyzstan (some southern and western areas) Libya Morocco (few rural areas only) Turkey (most tourist areas) Uzbekistan (sporadic cases in extreme SE only)	Avoid mosquito bites	
Risk low	Armenia (June-October) Azerbaijan (southern border area, June-September) Egypt (El Faiyum only, June-October) Iraq (rural north, also Basrah, May-November) Syria (north border, May-October) Turkey (plain around Adana, Side, Southeast Anatolia, March-November) Turkmenistan (June-October in SE only)	Chloroquine	Proguanil
Risk present, chloroquine resistance present	Afghanistan (below 2,000m, May-November) Iran Oman (remote rural areas only) Saudi Arabia (except northern, eastern and central provinces, Asir plateau, and western border cities where there is very little risk; no risk in Mecca) Tajikistan (June-October especially south border area) Yemen (no risk in Sana'a city)	Chloroquine plus proguanil	

* See table 1 for details of regimen.

The forest zone of West Africa (table 8) has high rates of transmission of falciparum malaria throughout the year, including in areas visited by travellers from the UK. The incidence of infective bites often exceeds 100 per person per year and the incidence of malaria in unprotected travellers is up to 3.8% per fortnight. Under such circumstances it is foolhardy to travel without taking chemoprophylaxis. Chloroquine-resistant parasites have become widespread in recent years but their distribution is still patchy. The recommended prophylaxis is mefloquine or doxycycline or atovaquone/proguanil. Proguanil plus chloroquine is an unsatisfactory alternative: it gives substantially less protection.

Moving north towards the Sahara, transmission becomes seasonal but remains intense, with most infections being contracted during or soon after the rainy season. Inland, chloroquine resistance is patchy but widespread. Closer to the Sahara the high transmission season becomes still shorter. In particular, most cases in the Gambia (which receives many British visitors) are contracted from June to December. Mefloquine or doxycycline or atovaquone/proguanil are the drugs of choice for the Gambia as chloroquine resistance is increasing, as for much of Africa. Needless fatalities have occurred in visitors to the Gambia, mainly in those who took no prophylaxis, or who ignored fevers whilst on prophylactic medicines. Cases of malaria which occur in those on chemoprophylaxis need immediate medical attention. The cumulative risk of malaria in people who make long visits to sub-Saharan Africa justifies use of mefloquine or doxycycline, as the vast

majority of travellers encounter no significant adverse effects. Atovaquone/proguanil is proving valuable for those on single or multiple short visits.

South Asia (table 9)

Visitors to all parts of the Indian subcontinent, except for the high mountains, are at risk of malaria, both in rural areas and some cities. *P. vivax* predominates, but falciparum malaria is also present and often resistant to chloroquine; mixed infections occur. Immigrants to the UK and their families are at special risk when visiting friends and relations in Asia as many left during the malaria eradication campaigns and may not realise that malaria has re-emerged in most areas. Measures against mosquito bites protect against malaria and other mosquito-borne diseases, and the appropriate chemoprophylaxis is proguanil plus chloroquine. However, in the Chittagong Hill Tract Districts of Bangladesh, mefloquine or doxycycline or atovaquone/proguanil is required.

Southeast Asia (table 10)

The extent of malaria transmission varies greatly, with low risk in many areas, but falciparum malaria resistant to multiple drugs predominates and transmission is intense in some hilly forested areas along international borders. The risk is low in much of Thailand; tourists to Bangkok and Chiangmai and to the main coastal holiday resorts of Pattaya, Phuket, and KoSamui do not need to take antimalarials. They should remain aware of the low risk of malaria, however, and should take any attack of fever very seriously⁴⁸. The risk in Ko Chang in Thailand is substantial and chemoprophylaxis is recommended.

TABLE 8 Malaria in sub-Saharan Africa

Risk	Country	Preferable regimen*	Alternative regimen	
Risk very high, or locally very high; chloroquine resistance very widespread	Angola	Mefloquine OR Doxycycline OR Malarone	Proguanil plus chloroquine (limited protection)	
	Gambia			
	Principe			
	Benin			Rwanda
	Ghana			São Tomé
	Burkina Faso			Guinea
	Guinea			Senegal
	Burundi			Guinea-Bissau
	Senegal			Sierra Leone
	Cameroon			Ivory Coast
	Sierra Leone			Somalia
	Central Africal Republic			Kenya
	Somalia			Liberia
	Chad			Sudan
	Comoros			Madagascar
Swaziland	Congo			
Malawi	Tanzania			
Djibouti	Mali			
Togo	Equatorial Guinea			
Mozambique	Uganda			
Eritrea	Niger			
Zaire	Gabon			
Nigeria	Zambia			
Ethiopia (below 2,200m; no risk in Addis Ababa)				
South Africa (north east, low altitude areas of Mpumalanga and Northern Provinces, Northeast KwaZulu-Natal as far south as Tugela River)				
Areas of Zimbabwe in the Zambezi valley				
Risks in parts of country. Some chloroquine resistance	Botswana (only in the northern half of the country, November-June)	Chloroquine plus proguanil	Mefloquine OR Doxycycline OR Malarone	
	Mauritania (year round in the south; in north July-November)			
	Namibia (northern third only, November-June; all year long Kavango and Kunene Rivers)			
	Zimbabwe (areas below 1,200m, November-June; all year in the Zambezi valley where Mefloquine or Doxycycline or Malarone is preferable. Risk negligible in Harare or Bulawayo)			
Low risk	Cape Verde (remember low risk if fever develops)	Avoid insect bites		
	Mauritius (except a few rural areas where Chloroquine prophylaxis is appropriate)			

* See table 1 for details of regimen.

On the borders with Cambodia and with Myanmar (Burma) malaria is resistant to many drugs, including mefloquine, and those who work or spend substantial periods there should use doxycycline (or possibly atovaquone/proguanil) as a prophylactic.

Overland travellers backpacking in northern Thailand who go near the Myanmar border for a night or two face a low but significant risk of malaria. Such travellers should either take doxycycline or atovaquone/

proguanil, (with the slight risk of adverse reaction) or take all possible precautions to avoid being bitten. If they take no chemoprophylaxis they must be aware of the need to seek immediate medical attention for any fever. The non-drug approach is more appropriate for those who will spend only a short time near the border.

In peninsular Malaysia and Sarawak the malaria risk is low except for jungle areas where proguanil plus chloroquine is appropriate. In Sabah, where the

TABLE 9 Malaria in South Asia

Risk	Country	Preferable regimen*	Alternative regimen
Risk variable. Chloroquine resistance usually moderate	Bangladesh (except Chittagong Hill Tracts; no risk in Dhaka City)	Chloroquine plus proguanil	Will vary locally
	Bhutan (southern districts only)		
	India (no risk in parts of mountain states of north)		
	Nepal (below 1,500m, especially Terai districts; no risk in Kathmandu)		
	Pakistan (below 2,000m)		
Sri Lanka (no risk in and just south of Colombo)			
Risk high. Chloroquine resistance high	Bangladesh (only in Chittagong Hill Tract Districts)	Mefloquine OR Doxycycline OR Malarone	Chloroquine plus proguanil

* See table 1 for details of regimen.

TABLE 10 Malaria chemoprophylaxis in Southeast Asia

Risk	Country	Preferable regimen*	Alternative regimen
Risk very low, remember malaria possible if fever	Bali (part of Indonesia) China (main tourist areas) Hong Kong Malaysia (except Sabah, see below, where mefloquine etc; and deep forests where chloroquine plus proguanil) North Korea (a few southern areas have limited risk) South Korea (limited risk in extreme Northwest) Sarawak (part of Malaysia) Thailand, Bangkok and main tourist centres	Avoid mosquito bites	
Risk substantial, drug resistance common	Cambodia (except no risk in Phnom Penh [see below]) China (only in Yunnan and Hainan; chloroquine in other remote areas of China) East Timor (= Timor-Leste) Irian Jaya, Lombok (parts of Indonesia) Laos (except no risk in Vientiane) Myanmar (formerly Burma [see below for Shan State]) Sabah (part of Malaysia) Vietnam (except no risk in cities, Red River delta area, coastal plain north of Nha Trang)	Mefloquine OR Doxycycline OR Malarone	
Risk variable, some chloroquine resistance	Indonesia (other than Bali and cities where low risk, and Irian jaya and Lombok where mefloquine recommended) Philippines (rural below 600m; no risk in cities, nor Cebu, Bohol and Catanduanes) Deep forest of peninsular Malaysia and Sarawak	Chloroquine plus proguanil	
Risk great, chloroquine resistance prevalent	Cambodia, western provinces Thailand, near borders with Cambodia and Myanmar; Ko Chang Myanmar, eastern part of Shan State	Doxycycline OR Malarone	

* See table 1 for details of regimens.
No risk in Brunei, nor in Singapore.

rate of transmission is high, mefloquine or doxycycline or atovaquone/proguanil is recommended, as also for East Timor (Timor-Leste) and for Lombok and Irian Jaya in Indonesia. Recommended prophylaxis for the rest of Indonesia is proguanil plus chloroquine. The risk in Bali is relatively low and specific chemoprophylaxis is not recommended, but awareness of the risk is needed, with immediate medical attention to any fevers.

There is little or no risk in many parts of China, where chemoprophylaxis is not needed. Those going to remote areas, off the usual tourist routes, should seek special advice or take chloroquine. Falciparum malaria is to be found only in South Yunnan and in Hainan Province, where mefloquine or doxycycline or atovaquone/proguanil is appropriate. Kunming, Dali, and Lijiang are free from malaria. Recent outbreaks of vivax malaria have occurred in other areas of China.

Chloroquine-resistant *P. vivax* is becoming prevalent in parts of Southeast Asia. In Southeast Asia malaria tends to be absent from major cities and resorts and the risk is relatively patchy elsewhere. A detailed knowledge of the traveller's itinerary is needed to give appropriate advice. Singapore is malaria free.

Oceania (table 11)

In Papua New Guinea, the Solomon Islands, and Vanuatu transmission of relatively chloroquine-resistant falciparum malaria is intense. There are some reports of chloroquine-resistant vivax malaria. Doxycycline or mefloquine or atovaquone/proguanil are now the recommended drugs, with dapsone/pyrimethamine (if available) plus chloroquine as an alternative for those unable to take any of them. As is usual with vivax malaria, there is a risk of later attacks for a year or more after travel in spite of prophylaxis.

TABLE 11 Malaria chemoprophylaxis in Oceania

Risk	Country	Preferable regimen*	Alternative regimen
Risk high, chloroquine resistance high	Papua New Guinea, below 1,800m Solomon Islands Vanuatu	Doxycycline OR Mefloquine OR Malarone	Maloprim plus chloroquine

See table 1 for details of regimens.

TABLE 12 Malaria in Latin America and Caribbean

Risk	Country	Preferable regimen*	Alternative regimen
Risk high, marked chloroquine resistance	Brazil ('legal Amazon') area, Amazon basin, Mato Grosso, and Maranhão only; (very low risk and no chemoprophylaxis elsewhere) Colombia (most areas below 800m) Ecuador (Esmeraldas Province; see below for elsewhere) French Guiana (especially border areas) Guyana (all interior regions) Suriname (except Paramaribo and coast) Amazon basin areas of Bolivia, Venezuela and Peru	Mefloquine OR Doxycycline OR Malarone	Chloroquine plus proguanil
Risk variable or high, chloroquine resistant present	Bolivia (rural areas below 2,500m) Ecuador (areas below 1,500m) (no malaria in Galapagos Islands nor in Guayaquil) Panama, east of canal Peru (rural areas below 1,500m) Venezuela (rural areas other than coast, Caracas free of malaria)	Chloroquine plus proguanil	Mefloquine OR Doxycycline OR Malarone
Risk variable to low, no chloroquine resistance	Argentina (rural areas along northern borders only) Belize (rural except Belize district) Costa Rica (rural below 500m) Dominican Republic El Salvador (only Santa Ana province in west) Guatemala (below 1,500m) Haiti Honduras Mexico (in some rural areas less often stayed in by tourists) Nicaragua Panama (west of canal) Paraguay (some rural areas)	Chloroquine	Proguanil

* See table 1 for details of regimens.
No malaria risk in Uruguay or Chile.

Latin America and Caribbean (table 12)

A high risk of highly chloroquine-resistant malaria exists in the basin of the river Amazon⁴⁹, chiefly the area of Brazil comprising the 'legal Amazon' (the Amazon region, Mato Grosso, and Maranhão), but also affecting adjacent parts of Colombia, Peru, Bolivia, and Venezuela. Mefloquine or doxycycline (or atovaquone/proguanil for short visits) are the most suitable antimalarials for the whole Amazon basin, also for all malarious areas of Colombia. Other South American countries have patchy transmission mainly of *P. vivax* but also of some chloroquine-resistant falciparum malaria. The malaria risk in most of Brazil outside the Amazon region is low enough for chemoprophylaxis not to be recommended. Central America, where vivax malaria also predominates, is free of chloroquine resistance. Malaria is not a risk in most of the Caribbean islands, but malaria (mainly falciparum) is transmitted on the island that includes Haiti and the Dominican Republic. It remains sensitive to chloroquine. The risk is substantial in Haiti and, although much lower in the Dominican Republic, the chloroquine regimen should be followed by travellers to both parts of the island. Chile and Uruguay are free of malaria.

7. Surveillance

In the face of changing patterns of drug resistance of malaria parasites, these guidelines can only be kept optimal and up to date if reliable and comprehensive data are collected on cases of malaria imported into the UK, and related to populations at risk. Adverse

events in those taking antimalarials also need to be recorded. In drawing up the guidelines the ACMP strongly recommended setting up and maintaining a surveillance system with the participation of travel clinics in order to obtain data on the numbers of travellers in various categories and adverse event rates, as well as the reported information about malaria available through the MRL.

Doctors are required by statute to notify the proper officer of their local authority of cases of malaria. The forms used for this purpose provide insufficient information for epidemiological purposes. All cases of imported malaria should be reported to MRL by the doctor diagnosing the case on a blue form obtainable from MRL (telephone 020 7636 3924). Routine reporting needs to be more complete, and consultants in communicable disease control (CsCDC) and public health may be able to help in this by copying reports to MRL and by sending MRL blue forms to notifying doctors.

All adverse events believed to be related to use of antimalarial regimens should be reported to the MHRA on a standard yellow card, or using the electronic yellow card system. Doctors, nurses, midwives and pharmacists are all entitled to make reports. Both atovaquone/proguanil and co-artemether are currently 'black triangle' labelled, to emphasise the need for further information on adverse events from these recently introduced drugs.

Interpretation of data from yellow cards is difficult without knowing how many people take each regimen. Addition of two questions: 'What

antimalarial regimen did you take? Did you take your tablets regularly?' to the International Passenger Survey (a government-run regular questionnaire survey at airports) has provided invaluable information for 1999 and needs to be implemented regularly.

More randomised controlled trials are needed, together with studies on compliance behaviour, for the future development of sound policies. The frequency of adverse effects for the main regimens needs to be determined in a double-blind controlled trial, of sufficiently large size, in travellers whose symptoms are recorded adequately. The relative protective efficacies of mefloquine, doxycycline and atovaquone/proguanil, and of proguanil plus chloroquine, also need to be reassessed in controlled trials in West Africa. More data are needed on the frequency of disabling adverse events associated with doxycycline and on any long-term problems of atovaquone/proguanil use. The protective efficacy of atovaquone/proguanil, discontinued a week after returning from a malarious area, needs careful monitoring.

8. Future prospects

While the chemoprophylactic options against chloroquine-resistant falciparum malaria have long been far from ideal, the situation is improving, with the recent licensing of doxycycline and atovaquone/proguanil for this purpose. The various regimens still tend to suffer from at least one of the following limitations: inadequate protection, unpleasant adverse reactions, high cost, inadequate trials or experience, need for prolonged continuation of the medicines after leaving the malarious area, and frequent dosing. There is hope of further progress, with more drugs under trial for prophylaxis either alone or in combination. Malaria vaccines remain another hope for the more distant future, but for the present we are dependent on reducing the risk of being bitten by mosquitoes and on available medicines for chemoprophylaxis.

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