

Guidelines for malaria prevention in travellers from the United Kingdom for 2001

DJ Bradley and B Bannister on behalf of the Advisory Committee on Malaria Prevention for UK Travellers

These guidelines on malaria prevention are designed to aid health care workers who advise travellers, particularly those who will be overseas for less than a year. The present, and any future, revisions are the responsibility of the Advisory Committee on Malaria Prevention in UK travellers (ACMP; membership given at the end of the Guidelines). This has replaced the consensus meetings which produced earlier versions from 1980 to the 1997 version. The guidelines are in three parts. The first part is a summary that emphasises modifications to the advice given in the last set of guidelines, published in 1997¹. The second part discusses the issues addressed in formulating the guidelines. Oversimplified lists of recommendations by country can be misleading. The second part also addresses the health care worker's consultation with prospective 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 gives specific recommendations for travellers to specific destinations and some details of individual drugs. Fuller information on some drugs now less used was given in earlier versions of the guidelines^{2,3}.

These guidelines reflect experienced 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. Decisions on the terms under which different drugs are licensed for use are the responsibility of the Licensing Authority, advised by the Committee on Safety of Medicines and not of the ACMP. The guidelines should therefore be read as a supplement to and not as a substitute for the relevant data sheets.

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. The second part 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 two in its entirety to get a balanced picture.

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DJ Bradley
PHLS Malaria Reference Laboratory, London School of Hygiene and Tropical Medicine, WC1E 7HT

B Bannister
Chairman of ACMP, UCL Royal Free Hospital, Hampstead

Address for correspondence:

Dr Barbara Bannister
Chairman, ACMP, UCL Royal Free Hospital
London NW3 2QG
tel: 020 7830 2648
fax: 020 7431 8845
e-mail: barbara.bannister@rfh.nthames.nhs.uk

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Part 1: Summary recommendations

Four steps remain essential to prevent suffering 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 one of the appropriate antimalarial regimens 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, doxycycline is now licensed for malaria prevention, and atovaquone/proguanil (Malarone), now licensed for prophylaxis, is increasingly being considered for prophylactic use, especially for brief visits to highly malarious areas. Increased awareness of distressing adverse neuropsychiatric reactions to mefloquine, 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 contra-indicated in people who have had fits. 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 photosensitization.

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 trans-

mission 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 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 greater frequency of subjective distressing neuropsychiatric adverse effects with mefloquine than with proguanil plus chloroquine, 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 now only appropriate if neither mefloquine, nor doxycycline, nor atovaquone/proguanil, can be taken.

Full recommendations by country and person are set out in part three. 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.

BOX1 Sources of advice for specific problems

PHLS Malaria Reference Laboratory (at London School of Hygiene and Tropical Medicine) 020 7636 3924

Other sources of advice:

Birmingham Heartlands Hospital (Inf. Dis. Unit): 0121 424 0357

Glasgow, SCIEH for Travax users only, 2-4pm: 0141 300 1130

Liverpool School of Tropical Medicine: 0151 708 9393

Oxford: 01865 225214

London: PHLS Communicable Disease Surveillance Centre 020 8200 6868

Hospital for Tropical Diseases

for treatment only ask for the medical officer on duty,

Patrick Manson Unit 020 7387 9300

Travel prophylaxis 020 7388 9600

Recorded advice for travellers from the PHLS Malaria Reference Laboratory is available on 09065 508 908 (calls are charged at 100p per minute).

Part 2: 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 1997¹, drug resistance of malaria parasites has continued to increase. In the light of new chemoprophylactic agents, new data and increased experience with some regimens the ACMP now recommends substantial modifications to previous advice. This section discusses the issues that affected its deliberations on these guidelines, which aim to serve doctors, practice nurses, and an increasingly sophisticated travelling public.

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 is tending 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 south east Asia and is becoming commoner elsewhere. Chloroquine resistant strains of *P. vivax* are also emerging in south east 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 effects⁴, 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 balanced⁵. 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 all⁶). 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^{6,7}. 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 compliance⁸.

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^{9,10}. 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 cases are reported to the PHLS Malaria Reference Laboratory (MRL) at the London School of Hygiene and Tropical Medicine, which sends questionnaires to reporting 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 to

the Medicines Control Agency (MCA) 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 events and 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. Issues of causality and of reporting therefore become intertwined. 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 the government stopped general practitioners from prescribing antimalarials on the NHS in 1995. Travellers' use of antimalarial regimens was studied in detail ten years ago¹¹ but recommendations have changed greatly since then.

Epidemiologists who study malaria are concerned most about preventable deaths from malaria, which are usually associated with failure to take appropriate chemoprophylaxis. Individual patients are concerned if they suffer from malaria or from adverse events while on prophylaxis. Their doctors' views are much influenced by their personal experiences. The public are most aware of the 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 alone⁸ and 6% or more on no chemoprophylaxis acquire malaria each month.

In much drier parts of Africa and in some parts of Asia¹¹ 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. 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. *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. All cases of falciparum malaria have the potential to be severe and even fatal if untreated. Disease in those taking chemoprophylaxis may be milder or less rapidly progressive even if the parasites exhibit a degree of drug resistance.

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

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, enabling them to have received three doses, with three subsequent days before departure. 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^{1,2,3}

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. It was about 70% effective according to large retrospective surveys a decade ago in Africa^{9,10}, and is probably now 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^{7,12,13}, but the types of adverse events differ^{8,12}. The incidence of mouth ulcers is appreciable, due mainly to proguanil¹⁴.

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 that contains both proguanil and chloroquine has been licensed for sale under the name Savarine. One tablet is taken daily. This contains twice the level of chloroquine usually advocated in the UK and elsewhere and is not licensed for use here, but it represents a welcome step towards simplifying compliance.

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%^{9,10,15} in Africa, of particular value in East Africa, where the combination of proguanil plus chloroquine has a low protective efficacy. Mefloquine became the preferred chemo-prophylactic for east Africa (1993 guidelines³) and then for most of sub-Saharan Africa (1995²). 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^{16,17}. Recent concern has focused mainly on neuropsychiatric reactions. This term is used to cover one main neurological phenomenon (convulsions) and a wide range of reported neurological symptoms (paraesthesiae, vertigo, dizziness, and headache), and several psychiatric disorders including insomnia, vivid and unpleasant dreams, agitation, anxiety, irritability, depression, feelings of unreality, panic attacks, hallucinations, and frankly psychotic episodes. 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 retrospectively¹⁸, 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^{7,8,19,20}, 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 neuro-psychiatric adverse events are commoner in women taking mefloquine than in men^{8,17}. Age does not affect the pharmacokinetics of the drug. Psychological tests of mood have confirmed the existence of subjective adverse reactions to the drug²¹, but neurological signs other than epilepsy are rare. Although the blood level of mefloquine 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^{22,23}.

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 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 antimalarials²⁴. 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 malaria⁶ 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 south east Asia and an alternative drug to mefloquine for people visiting highly chloroquine resistant areas²⁵. Doxycycline is unsuitable during pregnancy or lactation and for children under 12 years of age. It is now licensed in the UK for antimalarial chemoprophylaxis. In SE Asia it had a similar protective efficacy to that of mefloquine against falciparum malaria⁶. Trial results from Africa are very limited^{25,26}.

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 properly⁶.

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 prolonged²⁷. Exfoliative dermatitis has been reported but is rare. Excessive exposure to sun should be avoided, which limits the drug's value to people on tropical seaside holidays but is less difficult now that effective sunscreens are widely available. Doxycycline may cause diarrhoea but also may protect against some bacterial causes of travellers' diarrhoea. A suggestion that doxycycline offered some protection against the liver cell stages of falciparum malaria was not substantiated by a specific trial²⁸.

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 doxycycline²⁹.

Atovaquone/proguanil (Malarone)

This fixed combination of atovaquone 250mg with proguanil 100mg 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 up to 28 days in a malarious area and gives good protection^{30,31}. Use of atovaquone alone leads to rapid emergence of resistant parasites. The combination of drugs appears to be highly synergistic and delays resistance developing. The mode of action seems to depend on proguanil itself and continues even in the absence of its active metabolite cycloguanil and in parasites resistant to cycloguanil³².

The side effect profile appears comparable with that of other antimalarials, but serious adverse effects appear rare³⁰. One tablet is taken daily for

prophylaxis. There is strong experimental evidence of a causal prophylactic effect³³, 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 very 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 or the Kruger National Park in South Africa. However, the bulk of the evidence for efficacy in prophylaxis comes from trials in semi-immune populations (usually resident in malarious places)^{34,35,36}. 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 emerge³⁷. It may be considered, along with doxycycline and mefloquine as a prophylactic for visitors to Africa south of the Sahara.

Dapsone/Pyrimethamine (Maloprim)

This fixed combination of 12.5mg pyrimethamine with 100mg 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. The drug has been largely superseded for large-scale use but is of value in travellers with epilepsy, particularly children, going to areas with falciparum malaria where there is low or moderate resistance to chloroquine. It is particularly important not to confuse the weekly drug 'Maloprim' with Malarone which is taken daily.

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 on average 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 month¹⁰. The incidence of falciparum malaria in Peace Corps members in West Africa on chloroquine prophylaxis was 3.8% per month between 1990 and 1992⁹. The evidence suggests a protective efficacy for chloroquine at that time and place of approximately 50%^{9,15}. 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 are currently changing, for three reasons. Doxycycline is now

licensed for prophylactic use. The efficacy of proguanil plus chloroquine for prophylaxis is decreasing significantly in many areas of Africa frequently visited by UK travellers so as to give little protection in several areas. A new combination medicine, atovaquone /proguanil (Malarone), has undergone trials for prophylactic use and is now licensed for up to a months use in malarious areas. The choices between these regimens are discussed here and summarized 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 Africa³⁸.

In terms of protective efficacy, mefloquine, doxycycline and atovaquone/proguanil are considered comparable at around 90%, but there is more evidence to substantiate that for mefloquine. In Asian trials⁶, 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 Africans^{34,35,36} but because it is only just being introduced for prophylaxis there is less experience of its use than for the other two recommended 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 the adverse events most commonly encountered during their use. The most extensive data concern mefloquine^{29,40} 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 photosensitization 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, and with rather less severe problems than encountered with the other regimens. 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 (unless in the form of Savarine).

Cost also varies greatly, with proguanil plus chloroquine the least expensive, doxycycline next, mefloquine more costly, and atovaquone/proguanil still more expensive. 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 7.

Emergency standby treatment^{1,2,3}

This should be recommended only for travellers 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, but field trials in travellers have given variable results⁴¹. 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.

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 chemo-prophylaxis appropriate to the risk and destination(s). Health care 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, breast feeding.
- 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, 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 to 1969), when risk there was low, or they may believe that they have some persistent immunity. Such immunity fades rapidly, but compliance with prophylaxis in some of these groups is 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 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. Burning mosquito coils or vapourizing mosquito deterrents, and sleeping under a mosquito net impregnated with a synthetic pyrethroid insecticide are also effective. Access to medical attention may be difficult or delayed, and there is a need for standby treatment if medical attention will be over 24 hours away, as well as for chemoprophylaxis that works well in the context of local patterns of drug resistance.

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 and 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, so business travellers 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.

Part 3: 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. Do not, however, exceed the manufacturer's recommendations, 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. 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

TABLE 1 Prophylactic regimens against malaria in adults

Regimen	Dose for chemoprophylaxis	Usual amount per tablet (mg)
<i>Areas of chloroquine resistant P. falciparum:</i>		
Mefloquine*	1 Tablet weekly	250 (228 in US)
Proguanil plus chloroquine	2 Tablets daily plus 2 tablets weekly	100 150 (base)
Pyrimethamine-dapsone (Maloprim) [†] plus chloroquine	1 Tablet weekly [§] plus	12.5 (pyrimethamine) plus 100 (dapsone)
	2 tablets weekly	150 (base)
Doxycycline [‡]	1 Tablet daily	100
Atovaquone-proguanil (Malarone) ^{**}	1 Tablet daily	250 (atovaquone) plus 100 (proguanil)
<i>Areas without drug resistance:</i>		
Chloroquine	2 Tablets weekly	150 (base)
Proguanil	2 Tablets daily	100

All antimalarials to be avoided in severe hepatic and renal 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.

[†] Best avoided in the first trimester of pregnancy. (Maloprim is only available for travellers who have epilepsy and cannot take alternatives).

[‡] Contraindicated during pregnancy and lactation and for children less than 12 years.

[§] Never exceed one tablet of pyrimethamine/dapsone (Maloprim) weekly.

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

TABLE 2 Doses of prophylactic antimalarials for children¹

Drug and tablet size	Chloroquine 150mg base	Proguanil 100 mg	Mefloquine 250mg	Doxycycline 100mg	Maloprim [one size] ^{**}	Age
Weight in kg						
Under 6.0	0.125 dose ¼ tablet	0.125 dose ¼ tablet	NR	NR	NR	Term to 12 weeks
6.0 to 9.9	0.25 dose ½ tablet	0.25 dose ½ tablet	0.25 dose ¼ tablet	NR	0.25 dose 1/4 tablet [†]	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	NR	0.25 dose* 1/4 tablet [†]	1 year to 3 yrs 11 months
16.0 to 24.9	0.5 dose 1 tablet	0.5 dose 1 tablet	0.5 dose ½ tablet	NR	0.5 dose ½ tablet	4 years to 7 yrs 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 12yrs 1 tablet ^{**}	0.75 dose ¾ tablet	8 years to 12 yrs 11 months
45 kg & over	Adult dose 2 tablets	Adult dose 2 tablets	Adult dose 1 tablet	Adult dose 1 tablet	Adult dose 1 tablet	13 years and over

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

Caution: In other countries tablet size may vary

NR: Not Recommended

* For these two medicines 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.

*** Do not confuse this drug with Malarone! (Atovaquone/proguanil)

[†] For children aged under 2 years 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 specially important. Doxycycline is unsuitable for children under 12 years.

[‡] Not feasible to prepare unless a paediatric formulation is available.

NB Atovaquone/proguanil (Malarone) is not licensed in the UK for prophylaxis in children.

TABLE 3 Doses by spoon measures for chloroquine syrup

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

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

reasons for not taking them, use one of the other appropriate drugs listed. If all are unsuitable, consult the Malaria Reference Laboratory (see box on page 85).

- Compliance is essential; most deaths occur in those who take drugs irregularly or not at all.
- Start medication at least a week before going abroad (1-2 days for atovaquone/proguanil). When using mefloquine it is advisable to 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. Also, higher blood levels will be achieved.
- Continue medication while in the malarious area and for four weeks after leaving it. Atovaquone/proguanil, if used, needs to 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 cause heartburn.
- Oral typhoid and oral cholera vaccines, and intradermal rabies vaccination should, if used, be given before starting antimalarial prophylaxis⁴².

Standby treatment

Travellers who will be unable to get medical advice within 24 hours of becoming ill may be provided with a standby course of antimalarials for self treatment (as may those who have access to advice but are in places where suitable drugs are unavailable). Criteria for providing standby drugs should be quite restrictive, and travellers should be given clear written instructions for their use. All those who start standby treatment should subsequently seek medical advice as soon as possible. Standby drugs are not needed for trips of less than a week, because the interval between getting an infective bite and becoming ill with malaria is at least that long.

Table 4 shows the recommended standby regimens. Chloroquine is suitable as a standby drug in areas without chloroquine resistance if no prophylaxis, or prophylaxis with proguanil alone, is being taken. People taking chloroquine alone as prophylaxis should use pyrimethamine with sulfadoxine (Fansidar). Atovaquone/proguanil, or co-artemether, or mefloquine, or quinine (followed by another drug) are appropriate in areas with chloroquine resistance. Resistance to pyrimethamine with sulfadoxine is becoming widespread in Africa. Halofantrine is unsuitable

TABLE 4 Emergency standby treatment for adults who will take longer than 24 hours to access medical facilities

Standby treatment regimen	Usual amount per tablet	Dose
Pyrimethamine-sulfadoxine (Fansidar)	25mg plus 500 mg	3 Tablets in one dose
Mefloquine (Lariam)	250mg	15mg/kg, not exceeding 4 tablets in split dose, six hours apart
Quinine plus Fansidar	300mg quinine and as above for Fansidar	Quinine 2 tablets 3 times a day for 3 days followed by 3 tablets of Fansidar once
Quinine plus doxycycline	300mg quinine and 100mg doxycycline	Quinine 2 tablets 3 times a day for 3 days accompanied by 1 tablet of doxycycline twice daily for 7 days
Atovaquone-proguanil (Malarone)	250mg plus 100mg	4 Tablets as a single dose on each of three consecutive days
Co-artemether (Riamet)	20mg artemether plus 120mg lumefantrine	Six doses of 4 tablets over a period of 60 hours
Chloroquine*	150mg base	4 Tablets on days 1 and 2, 2 tablets on day 3

*Only in chloroquine sensitive areas.

as a standby drug.

Quinine alone can be used for seven days but few will complete the course because of increasing side effects. There is a risk of neuropsychiatric side effects with a therapeutic dose of mefloquine, but the hazards of untreated malaria are greater. Quinine plus doxycycline is appropriate if suspected malaria occurs in travellers taking prophylactic mefloquine and far from medical help.

In areas where there is a low risk of becoming infected but where the malaria is highly resistant to chloroquine and other drugs and no chemoprophylactic drug is being taken, either co-artemether, or quinine plus doxycycline (or other tetracycline) is the most suitable standby treatment. Atovaquone/proguanil is also suitable.

Pregnant women should avoid situations in which standby treatment may be needed; the only appropriate drug is quinine for seven days. Quinine in malaria therapeutic doses is safe and will not threaten the pregnancy nor promote premature labour.

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 (200mg 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 is an option, as is atovaquone/proguanil. 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. Weekly dapsone/pyrimethamine is an alternative drug in those taking phenytoin or phenobarbitone for epilepsy. It should be supplemented with folic acid (5 mg daily). It is likely that atovaquone/proguanil will prove suitable for travellers subject to epilepsy and visiting highly chloroquine-resistant areas. Dapsone/pyrimethamine is suitable for children with epilepsy.

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 3 of the *British National Formulary*⁴³. Atovaquone/proguanil contains proguanil and is

best avoided in moderate or 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 dialysis⁴⁴. Some 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 tends to be preferred in moderate impairment. More data are needed urgently on patients with cirrhosis or chronic hepatitis. All antimalarial drugs 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 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

TABLE 5 Doses of proguanil in adults with renal failure

Renal impairment grade	Serum Creatinine $\mu\text{mol/litre}$	Creatinine clearance $\text{ml}/\text{min}/1.73\text{m}^2$	Prophylactic dosage of Proguanil
(none)	<150	≥ 60	200mg daily (standard dose)
mild	150-300	20-59	100mg daily
moderate	300-700	10-19	50mg every second day
severe	>700	<10	50mg once weekly

TABLE 7 Features of antimalarials used in the prevention of chloroquine-resistant falciparum Malaria

Feature	Recommended regimens			Alternative regimen
	Mefloquine	Doxycycline	Atovaquone/proguanil (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
Efficacy against <i>P. vivax</i> and other malaria species	More limited	More limited	More limited	Good; Relapses can occur
Most notable adverse effects	neuropsychiatric	gastrointestinal, photosensitization	relatively low	gastrointestinal
Half-life of blood level	3 weeks	18 - 22 hours	Atovaquone 2-3 days Proguanil 17 hr	Chloroquine 30-60 days Proguanil 17 hr
Frequency of administration	1x 250mg tablet weekly	1x 100mg capsule daily	1 tablet daily	2 tablets Proguanil daily plus 2 tablets Chloroquine 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	[20.0 CU] **	2.4 CU
Number of tablets	15	91	[65]	212 (182+26)

* CU (cost units) are units of approximate relative cost, based on entries in the Monthly Index of Medical Specialities (April 2000)

** Not licensed for more than 28 days in a malarious area

folic acid daily. 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 these nor mefloquine should be used while breastfeeding.

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 7. 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 6)

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 south west of Cairo) and to Turkish tourist areas as far east as Antalya. Eastwards along the coast from Antalya

TABLE 6 Malaria chemoprophylaxis in North Africa and the Middle East

Risk	Country	Preferable Regimen*	Alternative regimen
Risk very low	Abu Dhabi Algeria Egypt (tourist areas) Libya Morocco Tunisia Turkey (most tourist areas)	Avoid mosquito bites	
Risk low	Armenia (June-October). No risk in tourist areas Azerbaijan (southern border areas and Khachmas, June-October) Egypt (El Faiyum only, June-October) Georgia (July-October) Iraq (rural north and Basrah Province, May-November) Syria (north border, May-October) Tajikistan (June-October) Turkey (plain around Adona, Side, south east Anatolia; May-October) Turkmenistan (June-October)	Chloroquine	Proguanil
Risk present, chloroquine resistance present	Afghanistan (below 2000m, May-November), Iran Oman (rural areas only), Saudi Arabia (except northern, eastern and central provinces, Asir plateau, and western border cities, where there is very little risk. United Arab Emirates (northern rural areas only) Yemen	Chloroquine plus proguanil	

* See table 1 for details of regimens

to the Syrian border and inland in south east Turkey, and in parts of Syria and Iraq, as well as parts of the former USSR (see table 6). Chloroquine prophylaxis is recommended against vivax malaria. Falciparum malaria, often resistant to chloroquine, occurs in parts of Oman (Muscat itself is malaria-free), some Emirates, 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 8 Malaria chemoprophylaxis in sub-Saharan Africa

Risk	Country	Preferable regimen*	Alternative regimen*	
Risk very high, or locally very high. Chloroquine resistance very widespread	Angola Benin BurkinaFaso Burundi Cameroon Central African Republic Chad Comoros Congo Djibouti Equatorial Guinea Eritrea Gabon Ethiopia (below 2200m; no risk in Addis Ababa) South Africa (north east, low altitude areas of Northern Province and Mpumalanga, and eastern KwaZulu-Natal down to 100 km north of Durban. Risk present in Kruger National Park). Zimbabwe (areas in the Zambezi valley).	Gambia Ghana Guinea Guinea-Bissau Ivory Coast Kenya Liberia Madagascar Malawi Mali Mozambique Niger Nigeria Principe Rwanda São Tomé Senegal Sierra Leone Somalia Sudan Swaziland Tanzania Togo Uganda Zaire (Dem Rep Congo) Zambia	Mefloquine OR Doxycycline OR Atovaquone/ proguanil	Proguanil plus chloroquine (Limited Protection)
Risks in parts of country. Some chloroquine resistance	Botswana (only in the northern half of the country, November-June) Mauritania (year round in the south; in north July-October) Namibia (northern third only, November-June; all year along Kavango and Kunene rivers). Zimbabwe (areas below 1200m, November-June; all year in Zambezi valley where mefloquine or doxycycline or Malarone is preferable; risk negligible in Harare and Bulawayo).	Chloroquine plus proguanil	Mefloquine OR Doxycycline OR Atovaquone/ proguanil	
Low risk	Cape Verde (remember low risk exists if fever develops) Mauritius (except rural areas where chloroquine prophylaxis is appropriate)	Avoid insect bites		

* See table 1 for details of regimens

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.

Three drugs give good protection in areas of Africa south of the Sahara where there is much chloroquine resistance. They are mefloquine, doxycycline and atovaquone/proguanil. 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 is considered on the basis of trials outside Africa to give comparable protection to mefloquine and is now licensed for prophylactic use. 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 licenced for malaria prophylaxis. Experience so far suggests that adverse events are relatively minor, but long courses are very expensive. However, 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 is considered that atovaquone/proguanil should 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 the prophylactic drugs, which are active only against the bloodstream forms. Mefloquine, doxycycline and atovaquone/proguanil have similar overall value for malaria prevention in Africa, but have differing balances between efficacy, adverse events, and convenience. Their contra-indications for particular groups of people also differ. They are all summarized in table 7 (on page 95).

The forest zone of West Africa (table 8) has high rates of transmission of falciparum malaria throughout the year. 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. There is much transmission in areas visited by travellers from the UK. The recommended prophylaxis is mefloquine or doxycycline or atovaquone/proguanil. Proguanil plus chloroquine is an alternative, but 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, and 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 who encounter no significant adverse effects can continue to take them with relative safety. Atovaquone/proguanil is expected to prove 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

TABLE 9 Malaria chemoprophylaxis 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) Bhutan (southern districts only) India (no risk in mountain states of north) Nepal (below 1300m; no risk in Kathmandu) Pakistan (below 2000m) Sri Lanka (no risk in and just south of Colombo)	Chloroquine plus proguanil	Will vary locally
Risk high. Chloroquine resistance high	Bangladesh (only in Chittagong Hill Tracts)	Mefloquine OR Doxycycline OR Atovaquone/proguanil	Chloroquine plus proguanil

* See table 1 for details of regimens

against malaria and other mosquito borne diseases, and the appropriate chemoprophylaxis is proguanil plus chloroquine. The only areas in Bangladesh for which mefloquine or doxycycline or atovaquone/proguanil is required are the Chittagong Hill Tracts.

South east 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 and 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 risk of malaria, however, and should take any attack of fever very seriously⁴⁵. The risk in Ko Chang in Thailand is substantial and chemoprophylaxis is recommended. 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 who go backpacking in northern Thailand and go near the Myanmar border for a night or two face a low but significant risk of malaria. Such travellers need either to take doxycycline or atovaquone/proguanil, (with the slight risk of adverse reaction) or to 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 rate of transmission is high, mefloquine or doxycycline or atovaquone/proguanil is recommended, as it is for East Timor, 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 most of China and 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 south east Asia. In south east 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.

TABLE 10 Malaria chemoprophylaxis in South East Asia

Risk	Country	Preferred regimen*
Risk very low, remember malaria possible if fever	Bali, Java Brunei† China, main tourist areas Hong Kong Korea (both Democratic People's Republic and Republic) Malaysia (except Sabah, see below, where mefloquine, and deep forests where chloroquine plus proguanil) Sarawak Singapore† Thailand, Bangkok, and main tourist centres	Avoid mosquito bites
Risk substantial, drug resistance common	Cambodia (except no risk on Phnom Penh, and see below) China (only in Yunnan and Hainan; chloroquine in other remote areas of China) East Timor Irian Jaya and Lombok Laos (except no risk in Vientiane) Myanmar (formerly Burma) Sabah (proguanil plus chloroquine also acceptable for short visits) Vietnam (except no risk in cities, Red River delta area, coastal plain north of Nha Trang)	Mefloquine OR Doxycycline OR Atovaquone/proguanil
Risk variable, some chloroquine resistance	Indonesia (other than Bali, Java and cities where low risk, and Irian Jaya, Lombok and East Timor where mefloquine recommended) Philippines (rural below 600m; no risk in Cebu, Leyte, Bohol, Catanduanes, Metropolitan Manila) Deep forests of peninsular Malaysia and Sarawak	Chloroquine plus proguanil
Risk great, mefloquine resistance prevalent	Cambodia, western provinces Thailand, borders with Cambodia and Myanmar, Ko Chang	Doxycycline OR Atovaquone/proguanil

* See table 1 for details of regimens

† No risk in these countries

TABLE 11 Malaria chemoprophylaxis in Oceania

Risk	Country	Preferable regimen*	Alternative regimen*
Risk high. Chloroquine resistance high.	Papua New Guinea, below 1800m Solomon Islands Vanuatu	Doxycycline OR Mefloquine OR Atovaquone/proguanil	Pyrimethamine/dapsone plus Chloroquine

* See table 1 for details of regimens

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 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.

Latin America and Caribbean (Table 12)

A high risk of highly chloroquine resistant malaria exists in the basin of the river Amazon⁴⁶, 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.

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

TABLE 12 Malaria chemoprophylaxis in Latin America and the 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) French Guiana Guyana (all interior regions, sporadic cases on coast) Surinam (except Paramaribo and coast) Amazon basin area of Bolivia and Venezuela and Peru Ecuador: Esmeraldas Province - see below for elsewhere	Mefloquine OR Doxycycline OR Atovaquone/proguanil for short visits	Chloroquine plus proguanil
Risk variable or high, chloroquine resistance present	Bolivia (rural areas below 2500m) Ecuador (areas below 1500: no malaria in Galapagos Islands nor Quito. See above for Esmeraldas Province) Panama, east of canal Peru (rural areas below 1500m) Venezuela (rural areas other than coast; Caracas free of malaria)	Chloroquine plus proguanil	Mefloquine OR Doxycycline OR Atovaquone/proguanil
Risk variable to low, no chloroquine resistance	Argentina (small area in north west only) Belize (rural except Belize district) Costa Rica (rural below 500m) Dominican Republic El Salvador Guatemala (below 1500m) Haiti Honduras Mexico (in some rural areas less often stayed in by tourists) Nicaragua Panama (west of canal) Paraguay (rural)	Chloroquine	Proguanil

* See table 1 for details of regimens

No malaria risk in Uruguay or Chile

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 (CCDCs) and public health may be able to help in this by copying reports to MRL and sending MRL blue forms to notifying doctors.

All adverse events believed to be related to use of antimalarial regimens should be reported to the Medicines Control Agency on a standard yellow card. 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 monitoring carefully.

Future prospects

While the chemoprophylactic options against chloroquine-resistant falciparum malaria have long been far from ideal, the situation is improving, with the 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 future. Some promising candidate vaccines provided inadequate protection in controlled trials while a few have shown some action and newer candidates are entering trials. 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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