

Malaria prophylaxis for long-term travellers

C Hughes, R Tucker, B Bannister, DJ Bradley, on behalf of the Health Protection Agency Advisory Committee on Malaria Prevention for UK Travellers (ACMP)

Summary: *These guidelines are designed to assist healthcare workers who are advising long-term travellers on malaria prophylaxis, defined for the purpose of this document as those travelling for longer than 6 months. The document focuses on long-term use of antimalarials for adults, but also identifies specific issues for women and children. However, data on the long-term use of antimalarials is limited for all travellers and few data are available on the incidence of malaria in travellers overseas or, indeed, deaths overseas from malaria. Whilst all available evidence is taken into account, the advice provided also reflects experienced professional opinion.*

This document has been written on behalf of the Health Protection Agency's Advisory Committee on Malaria Prevention for UK Travellers, and is designed to act as a supplement to the 'Guidelines for malaria prevention in travellers from the United Kingdom for 2003'³. The latter document contains a more complete description of antimalarials and additional preventive measures, together with recommendations for malaria chemoprophylaxis for individual countries. Decisions on the terms under which different drugs are licensed for use are the responsibility of the Committee on Safety of Medicines. This paper should also, therefore, be used in conjunction with Summary of Product Characteristics (data sheets).

Key words:
adverse reactions
antimalarials
chemoprophylaxis
malaria
long-term travel

Commun Dis Public Health 2003; **6**(3): 200-8

Introduction

International Passenger Survey (IPS) figures indicate that the majority of travellers to malarious regions are those on short-term visits of less than one month. However, data from the IPS on the number of travellers intending to visit malarious areas for longer than one month^{1,2}, combined with information from the Foreign Office regarding the estimated British community abroad

(unpublished) suggests that there is a need for advice on using malaria prophylaxis for longer periods.

Most of the advice currently available on malaria prophylaxis focuses on short-term use. These guidelines relate solely to the use of prophylactic drugs in the prevention of malaria in long-term travellers who, for the purpose of this document, will be defined as those travelling through, or visiting malaria-endemic countries for over six months. The document is intended to provide the best available evidence on which healthcare workers can base their advice on malaria prevention for long-term, non-immune travellers. This document acts as a supplement to the 'Guidelines for malaria prevention in travellers from the United Kingdom for 2003', pages 180-199 in this issue³, which should be referred to for a more complete description of antimalarials and other preventative measures.

The document is divided into three parts. Part A identifies the risks associated with long-term travel to a malarious area and examines the long-term use of malaria chemoprophylaxis in general. Part B discusses specific risks faced by women travellers and the use of malaria chemoprophylaxis in pregnancy and breastfeeding. Part C discusses the long-term use of chemoprophylaxis for children.

Part A: Advising the long-term traveller

It is essential that any pre-travel consultation with a prospective traveller involves the following:

C Hughes
Health Protection Agency, Colindale

R Tucker
National Travel Health Network and Centre
Hospital for Tropical Diseases, London

B Bannister
Royal Free Hampstead NHS Trust, Royal Free Hospital, London

DJ Bradley
Malaria Reference Laboratory
London School of Hygiene and Tropical Medicine

Address for correspondence:
Dr Barbara Bannister
Infections and Tropical Diseases Department
Royal Free Hospital
London NW3 2QG
tel: 020 7830 2648
fax: 020 7431 8845
email: barbara.bannister@royalfree.nhs.uk

- An assessment of the risk of the visit.
- Advice on the avoidance of mosquito bites.
- Recommendation of chemoprophylaxis appropriate to the risk and destination.
- Advice on seeking prompt medical attention in the event of a febrile illness whilst overseas, and within approximately a year of return, particularly within the first three months.

These four steps remain essential in preventing malaria.

Assessment of risk

Health risks for the long-term traveller will vary considerably, depending in part on the reasons for travel. These may include business/work related travel, those visiting friends and family in their country of origin, overseas study, aid work or those backpacking for extended periods. For the purpose of this paper, those living, working or studying overseas will be grouped together as 'expatriates' to differentiate them from backpackers and those visiting friends and relatives.

Visiting friends and relatives (VFR)

Individuals who originate from countries where malaria is transmitted, but who have settled in the UK may later visit their country of origin and remain there for long periods of time while working or visiting family. So too may their children who were born in the UK. Although these individuals are in an environment with which some of them may be familiar, the risk of malaria may be great. Their risk will depend on how much immunity to malaria they have retained since leaving their country of origin. This in turn will depend on how long they spent in the UK before their visit. Immunity to infection, which may have been acquired by long residence in an endemic area, but is always incomplete, tends to decrease if the individual is not regularly exposed to malaria.

Expatriates

Expatriates are usually based at a single location where the risk of malaria is known. They often have access to medical care, a good standard of accommodation and are usually more aware of the malaria risks.

However, this is not to imply that expatriates rarely contract malaria. It has been found that up to 30% of some expatriates develop malaria within two years and that despite their greater experience of overseas travel (or perhaps as a result) many cases can be attributed to poor compliance with prophylaxis (Schneider and Bradley, unpublished data). Low compliance in this group could be due to a loss of confidence in particular drugs following a febrile episode or suspected adverse effect whilst taking them. Expatriates may also mistakenly follow ill-judged local advice.

Backpackers

Backpackers are often younger than expatriates and may well be less careful of their personal safety and

less compliant with medical advice, in addition to having less experience of overseas travel in general. They have less control over their environment as they are constantly moving on and have to carry all their clothes, belongings and provisions with them. They may be unlikely to add an impregnated mosquito net to their pack, though they should be strongly urged to do so, and may well stay in mosquito infested areas with no house screening or vector control measures in place. In addition, backpackers may also pass through multiple countries where malaria transmission varies considerably, making advice on chemoprophylaxis difficult. It may not be possible for such travellers to take the recommended chemoprophylaxis for each country as this could involve a number of different regimens. It will therefore be important to ensure appropriate protection for areas of highest risk. These factors tend to make the backpacker at increased risk of malaria in comparison to the expatriate. Simple advice and a simple regimen will aid compliance and bite avoidance must be particularly emphasised for this group.

Access to medical care

One major problem for the long-term traveller is the variable access to and quality of medical care available overseas. It has been shown that health care is quite likely to be required at some time during a long stay overseas⁴ and that this is frequently more difficult to obtain for the overland traveller than for the expatriate. The provision of details of healthcare facilities or points of information could be crucial.

Chemoprophylaxis for long-term travellers

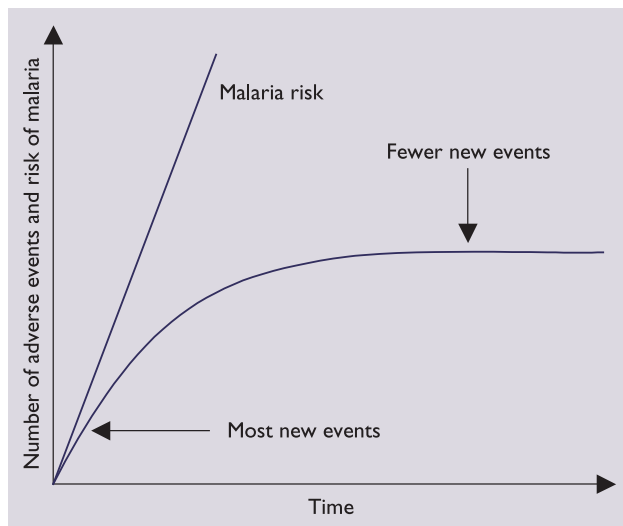
The main issues influencing the choice of malaria chemoprophylaxis on a long-term basis are the same as for short-term use, i.e. adverse events profile, compliance and efficacy. However, the specific problem relating to advice on chemoprophylaxis for the long-term traveller relates to current licensing restrictions.

Adverse events

The UK guidelines on malaria prevention emphasise the importance of balancing the risk of malaria and the risk of adverse reactions to antimalarial drugs³. The cumulative risk of contracting malaria is roughly proportional to the length of stay in a malarious area over the first few months. A three-month visit carries a risk around six times greater than a visit of two weeks³. The long-term traveller will therefore be at increased risk of malaria per visit compared with those on shorter visits.

Figure 1 gives a very simplified picture of the trends of malaria risk and of adverse events from chemoprophylaxis over time. The key issues are that while the risk of new adverse events falls off over time, the risk of contracting malaria continues to increase roughly linearly as exposure to malaria continues. In other words, chemoprophylaxis in highly malarious areas is even more important for long-term visitors

FIGURE 1 Cumulative risk of adverse events and of malaria



than for short-term travellers. For long-term travellers it is therefore more important to use a regimen with a higher protective efficacy.

The majority of product 'data sheets' (Summaries of Product Characteristics – SPC) state a time limit for the use of antimalarials. However, this is more often associated with a lack of experience in long-term use of the drug as an antimalarial than with any known new toxic effect of long-term or cumulative risk of drug adverse reaction. The guidance given here relates to the best evidence available on longer-term use of the drugs, whether for malarial prophylaxis or for other therapeutic purposes.

Compliance

Limited data are available on the long-term efficacy and tolerability of antimalarials in travellers. Often studies have been performed in a military setting where use of antimalarial chemoprophylaxis is usually closely supervised and adverse events monitored^{5,6}. A direct comparison of antimalarial use may therefore be difficult to make between the soldier, expatriate and backpacker.

Compliance is a key issue in the effectiveness of any chemoprophylactic regimen. A number of studies have illustrated that poor compliance is associated with an increased risk of malaria⁷⁻⁹. Compliance has been shown to be inversely related to the duration of travel¹⁰, except where military style discipline tends to support compliance. There is also evidence of weekly regimens having increased compliance over daily regimens¹⁰.

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

- Fear of long-term side effects.
- Actual adverse events to one or more regimens.
- Conflicting advice.
- Complex regime/daily tablets.
- Reduced confidence if intercurrent fever misdiagnosed as malaria.
- Chance of malaria (even with prophylaxis) cumulates over time, and if it occurs, reduces faith in prevention.

Compliance in long-term travellers may also be eroded by anecdotal evidence accumulated whilst overseas. Such anecdotes may encourage the perception that chemoprophylaxis is unnecessary¹¹ and, in addition, long-term travellers may overlook personal protective measures against mosquitoes¹². This situation has been further compounded by the confusion that has surrounded malaria chemoprophylaxis since chloroquine-resistant *Plasmodium falciparum* (CRPF) became widespread.

It is therefore particularly important that, as far as practicable, and considering the need to tailor recommendations to the specific requirements of the long-term traveller, instructions should be clear and simple and the risks associated with malaria must be emphasised.

A decision on whether chemoprophylaxis is continued on a long-term basis may partly depend on the overall length of stay, seasonal risk in the area, and access to medical facilities. Those travellers living or backpacking in rural areas may well be further from appropriate medical attention and the need for standby emergency medication should also be considered³. The continued use of chemoprophylaxis will also depend on current personal health, current medication, previous medical history, pregnancy, and relevant family medical history.

Efficacy of regimens

It is important to stress that no chemoprophylactic regimen is 100% effective and that anti-mosquito measures should be observed. Also, failures of prophylaxis are not necessarily due to drug resistance. They may be due to inadequate blood concentrations, as a result of non-compliance, or variations in drug absorption and elimination. Travellers should be encouraged to continue chemoprophylaxis despite suffering what they believe to be a malaria episode. Chemoprophylaxis can only be effective if taken regularly at the correct dosage and will usually reduce the severity of a malaria attack in the event of a 'breakthrough' infection.

Licensing restrictions

The specific problem relating to prophylaxis advice for long-term travellers is that long-term use of many of the currently advised malaria drugs falls outside the terms of their current Marketing Authorisation (Licence).

Until now there have been a number of approaches in response to this time limit:

- Switching from one chemoprophylactic regimen to another as the time limit is reached.
- Using chloroquine and proguanil, the only regimen licensed for long-term use but considered to give sub-optimal protection in areas of markedly chloroquine-resistant falciparum malaria.
- Discontinuing prophylaxis in favour of access to local advice and standby or physician-guided treatment
- Continuing with one prophylactic regimen beyond its licensed length of use.

The Health Protection Agency Advisory Committee on Malaria Prevention for UK Travellers (ACMP) has examined the available evidence, which is limited and in some cases anecdotal, regarding the consequences of taking antimalarial drugs outside their current licence. It is thought unlikely that manufacturers will mount trials looking at the long-term use of these drugs in the future. As a result, long-term use outside licensing restrictions is based on cumulative evidence of lack of harm rather than positive evidence of safety, and this situation is unlikely to change.

General advice for all regimens

- Once a client is compliant on one prophylactic regimen and is tolerating it well, transfer to another regimen increases the likelihood of the development of side effects due to the introduction of a different drug.
- There is no evidence of new side effects from long-term use of any currently available prophylactics (except from the exceedingly long-term use of chloroquine, and very rarely).
- Evidence for safety in long-term use comes more from an accumulating lack of evidence of harm than from scientific evidence of safety.
- In areas where malaria transmission is high the risk of disease greatly exceeds the risk of adverse drug effects.
- Individual risk assessments are important when deciding what advice should be given. In particular the other measures that will be used by those staying long-term in an area where the risk varies with the season may influence the advice.
- Simplicity in regimen can, as always, be expected to improve compliance. The safest option is compliance with one of the most effective regimens.
- Minimising exposure to infection is important, especially protection from being bitten whilst asleep.
- It is essential to seek medical advice promptly if symptoms develop.

Specific advice relating to individual regimens

Chloroquine

Travellers have used the combination of chloroquine plus proguanil extensively, although its efficacy of protection against falciparum malaria has decreased in many places in recent years. Chloroquine has been taken safely for periods of many years at a dose used for malaria chemoprophylaxis.

Much concern has been expressed about the possible development of retinal toxicity with long-term use of chloroquine. Retinal toxicity has been described in those on daily chloroquine dosage for rheumatic disorders and as a result, two thresholds for the risk of retinopathy have been suggested:

- A total cumulative dose of 100g of chloroquine base.
- A daily dose of 250mg (4mg/kg)¹³.

The first threshold would require an adult to take chloroquine continuously, weekly for six years, and the second threshold is far in excess of the prophylactic dosage. It is therefore possible to conclude that risk of

retinopathy from prophylactic dosage alone is negligible¹⁴. Further reassurance can be gained from the fact that retinopathy has very rarely been reported in patients taking weekly prophylactic doses^{13,15}. However, if travellers are concerned, an ophthalmological examination on a six-month to yearly basis after several years of use is recommended¹⁴.

Proguanil

Proguanil seems to be well tolerated, with no serious side effects. Gastrointestinal problems and mouth ulcers are reported to occur in 25% of users and may well be more frequent in those taking the combination of proguanil plus chloroquine^{13,16}. There is no time limit specified for the use of proguanil, and so, as long as it is tolerated, there is no reason to believe that it cannot be used for a period of several years on a continuous basis.

ACMP advice regarding chloroquine and proguanil: no problems with long-term use but considerable concern regarding level of protective efficacy in certain geographical areas where the regimen used to be useful.

Mefloquine

Weekly mefloquine has been shown to be a highly effective regimen in preventing *Plasmodium falciparum* infections. However, concern has been raised over the use of mefloquine in terms of toxicity and side-effect profile. Despite this, mefloquine was found to be generally well tolerated when taken in prophylactic dosages^{5,17-19}.

The overall levels of mild to moderate adverse events experienced by travellers taking mefloquine have been found to be comparable to those experienced when taking proguanil plus chloroquine. The discontinuation rate due to side effects in a population taking malaria prophylaxis for between one and four weeks was found to be lower for mefloquine (1.7%) than chloroquine plus proguanil combination (3%)²⁰. This was also found to be the case in a study on Italian soldiers in Somalia and Mozambique taking prophylaxis for over three months, although in this instance a larger proportion of those over 26 years of age discontinued than did younger people¹⁹. The frequency and type of adverse events was also found to be comparable in a study on Peace Corps volunteers taking either weekly mefloquine or chloroquine alone for over four months^{17,21}. In addition these studies by Lobel indicated that minor side effects with mefloquine declined in frequency with continued use; most occur within the first three weeks of weekly doses. However side effects can develop later, and those developing them should not persist with the course of medication.

There are few data on the use of mefloquine for a period greater than two years, although there is no evidence of cumulative toxicity^{14,17,22}. Studies of both Peace Corps workers and the military found that long-term prophylaxis (over one year and anecdotal evidence up to two and a half years) is well tolerated^{5,17}.

ACMP advice regarding mefloquine: no evidence of harm in long-term use if tolerated in the short term, suggest can be used safely for up to three years in the absence of side effects.

Doxycycline

Doxycycline is known to cause photosensitivity and may predispose to vaginal yeast infections (candidiasis)^{13,23}. Women using doxycycline may carry a one-dose treatment for this in case of need. Doxycycline causes diarrhoea in rare instances, but may also protect against some bacterial causes of traveller's diarrhoea. It is licensed for use for up to two years or more in the treatment of acne in the same dose as is used for malaria prophylaxis. Doxycycline has also been used daily for four months in troops deployed to Somalia, and for 12 months in troops stationed in Cambodia, without increased adverse events²⁴.

ACMP advice regarding doxycycline: no evidence of harm in long-term use. Evidence suggests that it may be used safely for periods of at least up to two years.

Atovaquone plus proguanil (Malarone)

This is the most recent antimalarial to be licensed in the UK for malaria chemoprophylaxis. Both components have been used individually on a long-term basis, and both components have a relatively short half-life, so there should not be a problem with use beyond the current 28-day restriction. However, experience of the combination is not prolonged. It should be noted that the USA has licensed Malarone for unrestricted long-term use, and many countries do not limit the length of course in their licensing requirements. Cost may become prohibitive for some travellers.

ACMP advice regarding atovaquone plus proguanil: no evidence of harm in long-term use, suggest can be used confidently for travel up to three months, and possibly up to six months or longer, but only with caution until more post-licensing experience is available. All adverse events (including attacks of malaria) should be reported.

Part B: Specific considerations for women

Data suggests that around 45% of all UK residents travelling abroad are women¹. It is perhaps more likely that women expatriates will be either travelling with their family or planning to have children whilst living overseas. Advice on malaria chemoprophylaxis that is safe for both mother and baby at conception, during pregnancy and whilst breastfeeding will therefore be necessary. Expatriates do not necessarily have access to appropriate information whilst overseas.

There are a small number of studies on women in areas where malaria is either endemic or epidemic^{18,25-31}. In regions where malaria transmission is seasonal and erratic, the population may be regarded as non-immune, so that parallels can be drawn with non-immune travellers.

Risks associated with malaria in pregnancy

Pregnant women are relatively immunosuppressed and are therefore at greater risk of developing severe malaria, which is more likely to be fatal than in non-

pregnant women. Diagnosis can be difficult, as peripheral parasitaemia may be absent because numerous parasites are lodged in the placenta. Complications include severe haemolytic anaemia, hypoglycaemia, fever, jaundice, renal failure, hyperpyrexia and pulmonary oedema. These complications can result in miscarriage, premature delivery, and maternal and/or neonatal death³². Congenital malaria, especially due to *Plasmodium vivax*, is a rare occurrence in pregnant women with untreated or incompletely treated parasitaemia.

Advice to female travellers

For the above reasons, pregnant women or those reluctant to avoid pregnancy are usually advised against travel to malarious areas. However, where travel is unavoidable it is essential that the patient is made fully aware of the risks that malaria presents and also the risks and benefits of chemoprophylaxis. The importance of reducing contact with mosquitoes cannot be overemphasised. If at all possible, pregnant women should remain indoors between dusk and dawn; however, if they are outdoors at night they should wear clothing that covers both legs and arms. Screens and/or permethrin-impregnated bed nets should be used. Insect repellents containing DEET (N, N diethyl-*m*-toluamide) (<50%) can be used sparingly although nursing mothers should wash repellents off their hands and breast skin carefully before handling infants³³. Concern over the use of DEET appears to be due to the rare but widely publicised reports of encephalopathic reactions in children³⁴. A review of the toxicity of DEET revealed only two cases of systemic toxicity in adults after topical application and 13 cases of encephalopathic toxicity in children despite 40 years of extensive use³⁵.

Chemoprophylaxis prior to conception

If women or their doctors wish to estimate the time taken for a malaria drug to be excreted prior to conception, the CDC supplies information on the half-lives of selected antimalarial drugs (see table 1 or consult the CDC website <http://www.cdc.gov/travel/pregnant.htm> for up-to-date information).

The half-life of antimalarial drugs has been used to estimate the time to wait before attempting to conceive, after ceasing to take the drug.

Mefloquine

Women wishing to become pregnant should allow three months after finishing mefloquine before attempting to conceive.

Doxycycline

Women wishing to become pregnant should allow one week after finishing doxycycline before attempting to conceive.

Malarone

Women wishing to become pregnant should allow

TABLE 1 Half-lives of selected antimalarial drugs

Drug	Half-life
Chloroquine	Can extend from 6 to 60 days
Mefloquine	2 to 3 weeks
Doxycycline	12 to 24 hours
Atovaquone	2 to 3 days
Proguanil	14 to 21 hours
Primaquine	4 to 7 hours
Sulfadoxine	150 to 200 hours
Pyrimethamine	80 to 95 hours

two weeks after finishing Malarone before attempting to conceive.

Chemoprophylaxis during pregnancy

Chloroquine-proguanil

The chloroquine-proguanil regimen is considered to be safe when taken during pregnancy^{23,36} but is not as effective as mefloquine in areas with CRPF^{20,37}. However, it is more effective than chloroquine alone or no prophylaxis.

Mefloquine

Recommendations on the use of this drug in pregnancy have recently been revised based on the results of a double-blind, placebo-controlled study¹⁸ and on increasing experience with mefloquine during pregnancy. It now seems unlikely that mefloquine is associated with adverse foetal outcomes. WHO and CDC now recommend that, for travel to areas with CRPF, chloroquine-proguanil should be used during the first three months of pregnancy and that mefloquine prophylaxis may be taken thereafter³⁸.

However, there is concern over the possible association of stillbirths and miscarriages with the use of mefloquine prophylaxis in pregnancy^{18,39,40}. Animal toxicology studies involving the administration of doses at least ten-times higher than that recommended for use in humans, led to a decision by pharmaceutical companies not to recommend the use of mefloquine during pregnancy. However, a study by Phillips-Howard et al. (1998) showed that, in a traveller cohort of 236 pregnant women, there was no significant difference in the rates of adverse outcomes when taking chloroquine-proguanil, sulfadoxine-pyrimethamine or mefloquine throughout pregnancy⁴¹. In addition, there is evidence from a database established by Roche, of women exposed to either mefloquine or sulfadoxine-pyrimethamine during pregnancy, suggesting that the rate of adverse outcomes is comparable to background rates⁴¹. However, a study by Nosten and colleagues in Thailand showed that mefloquine treatment of malaria during pregnancy was associated with a significantly

increased stillbirth rate with a relative risk of 4.72⁴². This prompted reconsideration of their earlier, two-phase prophylactic study¹⁸ using mefloquine during pregnancy. The first phase showed a strong association between mefloquine treatment and loss of pregnancy but the second stage showed no significant association. The combined phases gave a combined relative risk of 2.63, which did not reach statistical significance. However, Steketee, working in Malawi, failed to demonstrate an association with stillbirth³⁹.

The lack of conclusive data has encouraged caution and women have been advised to use contraceptive precautions while taking mefloquine and for three months after the last dose. However, the risk of adverse effects in pregnancy should be balanced against the risk of contracting malaria and the complications this can involve. Women should be reassured that taking mefloquine inadvertently prior to and/or during the first trimester is not regarded as an indication to terminate.

Adequately powered studies of mefloquine use in pregnancy in non-immunes would be so large as to be impractical and could be regarded as unethical. Therefore, evidence of safety will inevitably be limited to the cumulative experience of exposures, as in the Phillips-Howard study, and will be slow to accumulate. The CDC plans to collect data about outcomes of pregnancy in women exposed to mefloquine during the first trimester⁴³.

Inevitably, a certain number of women will fail to comply with a recommended chemoprophylactic regimen whilst travelling long-term or working abroad. In the event that conception occurs in this instance, women should be advised to consider a number of factors:

- the level of malaria transmission in the area,
- the prevalent species of malaria and whether it is chloroquine resistant,
- whether any other form of prevention (e.g. bite-avoidance) is being used.

If the risk of malaria is low, advice may be limited to urging comprehensive avoidance of mosquito bites and emphasising the need to seek urgent assessment of any febrile illness as though it may be malaria. However, in areas of medium to high transmission it would be foolish not to take any prophylaxis. Even if chloroquine resistance exists, a regimen of chloroquine weekly and proguanil daily can still offer some degree of protection. If residence in remote areas cannot be avoided, stand-by emergency medication may be carried, but the options for effective drugs are limited in pregnancy (please refer to the 'Guidelines for malaria prevention in travellers from the United Kingdom for 2003', p180-199 in this issue³).

Doxycycline

Doxycycline is contraindicated in pregnancy (e.g.³).

Malarone

The safety of atovaquone and proguanil hydrochloride when administered concurrently for use in human

pregnancy has not been established and the potential risk is unknown (SPC, Malarone). Animal studies have not shown evidence of teratogenicity of the combination.

Proguanil has been used for malaria chemoprophylaxis in pregnant women for many years with no evidence of toxic effects on the foetus⁴¹. Animal studies have revealed no teratogenicity for atovaquone.

Chemoprophylaxis and breastfeeding

This is an area where there is very little helpful evidence. The excretion of chloroquine, dapson, pyrimethamine⁴⁴ and mefloquine in breastmilk⁴⁵ has been documented, although both studies were based on the administration of a single dose. Research on the effects of continuing prophylactic dosage has not been published. Experience suggests that mefloquine is safe during lactation although there is concern that an infant over three months (or 5 kg) being given mefloquine prophylaxis and being breastfed by a mother also taking mefloquine could receive a dose above the recommended maximum, based on the child's weight. This effect would be short lasting, as the weight of the child increases and the contribution of breastfeeding to the total prophylactic dose becomes relatively small.

Nursing mothers should be advised to take the usual adult dose of antimalarial appropriate for the country to be visited, except that doxycycline is contraindicated and atovaquone/proguanil is not recommended because of the absence of data. The amount of medication in breast milk will not protect the infant from malaria. Therefore, the breastfeeding child needs his or her own prophylaxis²³, which for children of breastfeeding age will be either chloroquine plus proguanil or mefloquine.

Part C: Specific considerations for infants and older children

Harries et al. (1988) found that the incidence of malaria in expatriate children was comparable to that in adults⁴⁶. This could be partly related to inappropriate dosage regimens due to errors in calculating paediatric doses⁷. Children are at particular risk of severe and fatal malaria; therefore, parents are advised against taking infants and young children to malarious areas, especially if CRPF is present³⁸. If travel is unavoidable, infants and children should be well protected against mosquito bites and receive appropriate malaria chemoprophylaxis³⁸. A study by Peppiatt and Byass (1990), in which no malaria was found in expatriate children, suggests that such comprehensive measures can be highly effective⁴⁷. Parents must however be cautious not to exceed maximum recommended doses, since antimalarials can be particularly toxic to children. Details of dosages are provided in the malaria guidelines³.

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

same as for adults. Unless otherwise indicated the recommendations below are based on the best evidence available, supplemented with general information in adults. It is assumed that a parent will supervise children's chemoprophylaxis, as some regimes can be difficult even for adults to follow.

Chemoprophylaxis

Chloroquine

Chloroquine is safe for both infants and young children^{3,38}. However, particular care must be taken when giving tablets to children, to ensure that they are actually swallowed, as they have a bitter taste. Chloroquine syrup, which is sweetened, is widely available in both developed and tropical countries. It is important to ensure that chloroquine is stored safely away from children since an overdose can be fatal.

Proguanil

As with chloroquine, this drug has been used since the 1940s and is suitable for use by infants and young children^{3,38,48}. As for adults, the combination of proguanil daily with weekly chloroquine is more effective than taking either drug alone, particularly in areas where CRPF has been reported. However, this can be a difficult regimen to use for children since proguanil is only available in adult formulations and, dependent on the weight of the child, the adult-dose tablets must be broken and powdered into food³. This, combined with its incomplete effectiveness, makes it a viable option only when mefloquine or doxycycline or atovaquone/proguanil cannot be used.

Mefloquine

A study of mefloquine use in more than 500 children aged less than five years indicates that it is well tolerated⁴⁹. Long-term use of mefloquine is reported to be safe, well tolerated and not associated with an increase in adverse effects^{5,17,19}. The main problem lies in the administration of the correct dosage because there is currently no suspension available.

Doxycycline

There are no data available on the long-term use of doxycycline; however, long-term use of other tetracyclines for other indications is generally well tolerated⁵⁰. Doxycycline is only licensed in the UK for children over the age of 12 years due to the bone damaging effects of the drug. This age limit varies between countries.

Atovaquone plus proguanil (malarone)

A 12-week randomised placebo-controlled study on children aged between four and 16 in a hyperendemic area for *P. falciparum* showed that prophylaxis with atovaquone plus proguanil was both highly effective and safe⁵¹. Atovaquone-proguanil may be a valuable addition to the prophylactic antimalarials available for use in children.

Malarone Paediatric tablets are available in the UK for malaria prophylaxis in children from 11 kg

TABLE 2 Long-term chemoprophylaxis for adults

Malaria chemoprophylaxis	ACMP advice on long-term use
Chloroquine	No problem with long-term use*
Proguanil	No problem with long-term use*
Mefloquine	No evidence of harm in long-term use if tolerated in the short term. Suggest can be used safely for up to three years in the absence of side effects.
Doxycycline	No evidence of harm in long-term use. Evidence suggests that it may be used safely for periods of at least up to two years.
Atovaquone/Proguanil (Malarone)	No evidence of harm in long-term use. Suggest can be used confidently for travel up to 3 months, and possibly up to 6 months or longer, but only with caution until more post-licensing experience is available.

* No problem with long-term use but considerable concern regarding level of protective efficacy of the combination of chloroquine plus proguanil in certain geographical areas where the regimen used to be useful

upwards. The tablets are a quarter of the strength of adult tablets and, as stated in the Summary of Product Characteristics, they can be crushed if necessary for ease of administration.

References

- Office for National Statistics. Travel trends: a report on the 2001 international passenger survey. 2002.
- Office for National Statistics. International migration: migrants entering or leaving the United Kingdom and England and Wales, 1999. Series MN no.26, 2001.
- Bradley D, Bannister B. Guidelines for malaria prevention in travellers from the United Kingdom for 2003. *Commun Dis Public Health* 2003; **6**(3): 180-99.
- Stenbeck JL. Health hazards in Swedish field personnel in the tropics. *Travel Med Internat* 1991; **9**: 51-9.
- Hopperus Buma A, van Thiel P, Lobel HO, et al. Long-term malaria chemoprophylaxis with mefloquine in Dutch marines in Cambodia. *J Infect Dis* 1996; **173**: 1506-9.
- Ohr C, Richie TL, Widjaja H, Shanks GD, Fitriadi J, Fryauff DJ, et al. Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers. A randomized double-blind, placebo-controlled trial. *Ann Int Med* 1997; **126**: 963-72.
- Adera T, Wolfe WS, McGuire-Rugh K, Calhoun N, Marum L. Risk factors for malaria among expatriates living in Kampala, Uganda: the need for adherence to chemoprophylactic regimens. *Am J Trop Med Hygiene* 1995; **52**(3): 207-12.
- Phillips-Howard PA, Radałowicz F, Mitchell J, Bradley DJ. Risk of malaria in British residents returning from malarious areas. *BMJ* 1990; **300**: 499-503.
- Basco LK, Le Bras J, Charmot G, et al. Chloroquine and proguanil prophylaxis in travellers to Kenya. *Lancet* 1992; **339**: 63.
- Steffen R, Heusser R, Machler R, et al. Malaria chemoprophylaxis among European tourists in tropical Africa: use, adverse reactions and efficacy. *Bull WHO* 1990; **68**: 313-22.
- Janosi M. Advice to long-term travellers. *Travel Med Internat* 1988; **6**: 110-2.
- Lobel HO, Phillips-Howard PA, Brandling-Bennett AD, et al. Malaria incidence and prevention among European and North American travellers to Kenya. *Bull WHO* 1990; **68**: 209-15.
- Luzzi GA, Peto TEA. Adverse effects of antimalarials. An update. *Drug Safety* 1993; **8**: 295-311.
- Hill DR. Issues for long-term and expatriate travellers. In: Cook GC, editor. *Travel Associated Disease*. Royal College of Physicians, London: 1995. P101.
- Lange WR, et al. No evidence for chloroquine-associated retinopathy among missionaries on long-term malaria chemoprophylaxis. *Am Journal Trop Med Hygiene* 1994; **51**(4): 389-92.
- Drysdale SF, Phillips-Howard PA, Behrens RH. Proguanil, chloroquine and mouth ulcers. *Lancet* 1990; **i**: 164.
- Lobel HO, Miani M, Eng T, Bernanrd KW, et al. Long-term malaria prophylaxis with weekly mefloquine. *Lancet* 1993; **341**: 848-51.
- Nosten F, ter Kuile FO, Melankiri L, et al. Mefloquine prophylaxis in pregnancy: a double blind placebo controlled trial. *J Infect Dis* 1994; **169**: 595-603.
- Peragallo MS, et al. Compliance and tolerability of mefloquine and chloroquine - proguanil for long-term malaria chemoprophylaxis in groups at particular risk (the military). *Trans R Soc Trop Med Hyg* 1999; **93**: 73-7.
- Steffen R, Fuchs E, Schildknecht J, et al. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting East Africa. *Lancet* 1993; **341**: 1299-303.
- Lobel HO, Bernard KW, Williams SL, Hightower AW, Patchen LC, Campbell CC. Effectiveness and tolerance of long-term malaria prophylaxis with mefloquine. Need for a better dosing regimen. *J Am Med Assoc* 1991; **16**; **265**(3): 361-4.
- Pennie RA, Koren G, Crevoisier C. Steady state pharmacokinetics of mefloquine in long-term travellers. *Trans R Soc Trop Med Hyg* 1993; **87**: 459-62.
- Centers for Disease Control. Health Information for International Travel, 2001-2002. Atlanta 2001.
- Shanks GD, et al. Doxycycline for malaria prophylaxis in Australian soldiers deployed to United Nations missions in Somalia and Cambodia. *Mil Med* 1995; **160**(9): 443-5.
- Bouvier P, Doumbo O, Breslow N, et al. Seasonality, malaria and impact of prophylaxis in a west African village I. Effect on anemia in pregnancy. *Trans R Soc Trop Med Hyg* 1997; **56**(4): 378-83.
- Bouvier P, Breslow N, Doumbo O, et al. Seasonality, malaria and impact of prophylaxis in a West African village II. Effect on birth weight. *Trans R Soc Trop Med Hyg* 1997; **56**(4): 384-9.
- Greenwood BM, Greenwood AM, Snow RW, et al. The effects of malaria chemoprophylaxis given by traditional birth attendants on the course and outcome of pregnancy. *Trans R Soc Trop Med Hyg* 1989; **83**: 589-94.
- Greenwood AM, Menendez C, Todd J, Greenwood BM. The distribution of birthweights in Gambian women who received malaria chemoprophylaxis during their first pregnancy and in control women. *Trans R Soc Trop Med Hyg* 1994; **88**: 311-2.
- Ndyomugenyi R, Magnussen P. Chloroquine prophylaxis, iron-folic acid supplementation or case management of malaria attacks in primigravidae in western Uganda: effects on maternal parasitaemia and haemoglobin levels and on birth weight. *Trans R Soc Trop Med Hyg* 2000; **94**: 413-8.
- Schultz LJ, Steketee RW, Macheso A, et al. The efficacy of antimalarial regimens containing sulfadoxine-pyrimethamine and/or chloroquine in preventing peripheral and placental *Plasmodium falciparum* infection among pregnant women in Malawi. *Am J Trop Med Hygiene* 1994; **51**: 515-22.
- Shulman CE, Dorman EK, Cutts F, et al. Intermittent sulphadoxine-pyrimethamine to prevent severe anaemia secondary to malaria in pregnancy: a randomised placebo controlled trial. *Lancet* 1999; **353**: 632-6.
- Shulman CE, Dorman EK, Brabin B. Malaria in pregnancy. In: MacLean A, Regan L, Carrington D, editors. *Infection in Pregnancy*. RCOG Press; 2001.
- Centers for Disease Control. Health Information for International Travel, 2003-2004. Atlanta 2003.

34. Durrheim DN, Leggat PA. Preventing mosquito bites is also effective. *BMJ* 1999; **318**: 1139.
35. Fradin MS. Mosquitoes and mosquito repellents: a clinician's guide. *Ann Int Med* 1998; **128**: 931-40.
36. Ryan ET, Kain KC. Health advice and immunisations for travellers. *New Engl J Med* 2000; **23**: 1716-25.
37. Lewis SJ, Davidson RN, Rose EJ, Hall AP. Severity of imported falciparum malaria: effect of taking antimalarial prophylaxis. *BMJ* 1992; **305**: 741-3.
38. World Health Organization. International travel and health: vaccination requirements and health advice 2002. Geneva, Switzerland; 2002.
39. Steketee RW, Wirima JJ, Hightower AW, et al. The effect of malaria and malaria prevention in pregnancy in offspring birthweight, prematurity and interuterine growth retardation in rural Malawi. *Am J Trop Med Hygiene* 1996; **55**: 33-41.
40. Steketee RW, Wirima JJ, Slutsker L, et al. Malaria treatment and prevention in pregnancy: indications for use and adverse events associated with use of chloroquine or mefloquine. *Am J Trop Med Hygiene* 1996; **55**(Suppl 1): 50-6.
41. Phillips-Howard PA, et al. Safety of mefloquine and other antimalarial agents in the first trimester of pregnancy. *J Trav Med* 1998; **5**: 121-6.
42. Nosten F, Vincenti M, Simpson J, et al. The effects of mefloquine treatment in pregnancy. *Clin Infect Dis* 1999; **28**: 808-15.
43. Wilson ME. Malaria prophylaxis in young children and pregnant women. *Pediatr Infect Dis J* 1996; **15**(1): 101-2.
44. Edstein MD, Veenendaal JR, Newman K, Hyslop R. Excretion of chloroquine, dapsone and pyrimethamine in human milk. *Br J Clin Pharmacol* 1986; **22**(60): 733-5.
45. Edstein MD, Veenendaal JR, Hyslop R. Excretion of mefloquine in human breast milk. *Chemotherapy* 1988; **34**: 165-9.
46. Harries AD, Forshaw CJ, Friend HM. Malaria prophylaxis amongst British residents of Lilongwe and Kasungu districts, Malawi. *Trans R Soc Trop Med Hyg* 1988; **82**: 690-2.
47. Peppiatt R, Byass P. Risk factors for malaria among British missionaries living in tropical countries. *J Trop Med Hygiene* 1990; **93**: 397-402.
48. Bruce-Chwatt LJ, Bruce-Chwatt JM. Antimalarial drugs in West Africa with particular reference to proguanil. *BMJ* 1950; **II**: 7-14.
49. Luxemburger C, Price RN, Nosten F, et al. Mefloquine in infants and young children. *Ann Trop Paediatr* 1996; **16**(4): 281-6.
50. Delaney TJ, Leppard BJ, MacDonald DM. Effects of long-term treatment with tetracycline. *Acta Derm Venereol* 1974; **54**: 487-9.
51. Lell D, et al. Randomised placebo-controlled study of atovaquone plus proguanil for malaria prophylaxis in children. *Lancet* 1998; **351**: 709-13.