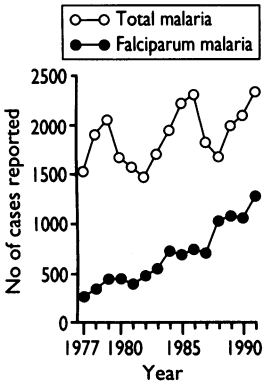
Prophylaxis against malaria for travellers from the United Kingdom

David Bradley on behalf of a meeting convened by the Malaria Reference Laboratory and the Ross Institute

To provide revised guidance on malaria prevention for the medical advisers of travellers from the United Kingdom going overseas to malarious areas, a committee of those most involved in giving advice and with specialist expertise in the United Kingdom agreed a policy document. There is a need for all travellers to be aware of the risk of malaria and to take measures to avoid being bitten by anopheline mosquitos, especially at night. Chemoprophylaxis is recommended also for most malarious areas. In view of the increasing prevalence of strains of *Plasmodium falciparum* resistant to chloroquine and proguanil, mefloquine is added to the list of recommended drugs for more areas than in the past, and is the preferred chemoprophylactic for east and central Africa. Chloroquine with proguanil continues to be widely appropriate. Detailed recommendations are given for each country. Travellers out of reach of prompt medical assistance are advised to carry treatment doses of a standby drug: halofantrine, Fansidar, or quinine. The need for full compliance with any regimen is emphasised. No prophylaxis is totally effective. Malaria must be considered in the differential diagnosis of any fever in someone who has visited an endemic area within the past year.



Malaria imported into the United Kingdom, 1977-91

Malaria continues to be a major hazard for travellers from the United Kingdom visiting tropical countries. Over 2000 cases are reported in the United Kingdom each year, and in 1991, 12 of these patients died. As resistance to the least toxic chemoprophylactic drugs increases and becomes more widespread, the choice of appropriate advice becomes more difficult. In November 1991 a meeting was convened at the London School of Hygiene and Tropical Medicine by the Malaria Reference Laboratory of the Public Health Laboratory Service to review developments since the last advice was published in October 1989. The meeting was attended by malaria specialists from throughout the United Kingdom, and the report of this meeting, modified to take account of data up to March 1993, has been reviewed by them. Those present or who had an opportunity to comment on the recommendations, though unable to attend, are listed in the appendix. The conclusions are a consensus; where this was not reached, the most limited range of options is set out. The tables are intended for easy reference; they should be used with the text, which discusses the options and the merits and defects of each prophylactic regimen in more detail, reflecting the range of opinons expressed.

Changing advice reflects, on the one hand, the high incidence of malaria in many tropical countries, the very widely distributed and spreading resistance of *Plasmodium falciparum* parasites to chloroquine, and increasing evidence in highly endemic areas of multiple drug resistance which even affects drugs recently introduced and increasingly used. On the other hand, the role of these newer drugs, particularly mefloquine and halofantrine, in the prevention and early treatment of malaria is gradually being defined. Information is already available on the advantages and disadvantages of these drugs, although much of it is anecdotal. The committee took these points into consideration when formulating its advice.

Key issues

Trends in malaria imported into the United Kingdom over the past decade show a steady rise in cases of potentially fatal *P falciparum* infection, even though total cases of imported malaria have reached a plateau (fig 1). Most cases of falciparum malaria seen in Britain have been acquired in Africa (92%), and 93% of those are from the four English speaking states of west Africa (Nigeria, Ghana, Sierra Leone, the Gambia), the three east African countries (Kenya, Uganda, Tanzania), and the three anglophone central African states (Malawi, Zambia, Zimbabwe). In all these areas chloroquine resistance is widespread, and resistance to compound antimalarials such as Fansidar (pyrimethamine and sulfadoxine) is found. The level of malaria risk for travellers from the United Kingdom who take few or no precautions is difficult to determine (for technical reasons involving the denominator) but is greatest in west Africa, where it may reach 1% per visit in Ghana and Papua New Guinea; it is high in east Africa and south Asia but orders of magnitude less in south east Asia.

However, compliance with prophylactic regimens remains an even greater problem than drug resistance for travellers. Most of those who died of malaria in the United Kingdom during the past two years had taken no prophylaxis or totally inadequate chemoprophylactic drugs. Others, however, had taken the recommended regimen and it is necessary to reiterate that no prophylaxis is totally effective and that malaria must be considered in the differential diagnosis of any fever in someone who has visited a malarious area within the past year. Travellers should be encouraged to seek medical advice if they develop a feverish illness and not only to tell their doctor of recent foreign travel but also to raise specifically the possibility that they might be suffering from malaria.

The beginning of effective malaria prevention is the traveller's awareness of the risk of malaria, and this depends on education by general practitioners, travel agents, and the media. This awareness is a particular problem for settled immigrants in Britain returning on visits, or sending their children to their country of origin, as malaria may have been well controlled there at the time of their original departure. The whole of any journey needs to be considered, not just the final destination, in case a stopover en route to a malaria free destination is malarious. There are thus three reasons for malaria breakthrough in people taking antimalarial drugs for prophylaxis: defective compliance with the regimen; resistance of the malaria parasites to the drug

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This report was prepared by Professor Bradley on behalf of the committee listed in the appendix.

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used; and a low level of circulating drug in spite of compliance. The latter may be due to temporarily defective absorption or to genetic variation in how drugs are handled in the body. The medical adviser, therefore, needs to emphasise the benefits of chemoprophylaxis (to encourage compliance) and also the limits to protection, so that any malaria, especially while the traveller is abroad and in the months following return to the United Kingdom, is not ignored or ascribed to "flu," with tragic consequences.

Equally neglected are measures for preventing infective mosquito bites. The introduction of mosquito nets impregnated with synthetic pyrethroid insecticides is a major advance in malaria control and well suited to the needs of travellers, especially infants. Repellents and other protection against bites in the evening can also provide considerble protection.

Available antimalarial drugs for prophylaxis

In the past two years experience with mefloquine (Lariam) has increased, and the new drug halofantrine (Halfan) has been introduced into the United Kingdom for treatment. This section describes key points of progress in understanding each major antimalarial prophylactic, old and new, which are set out before recommended regimens for different circumstances are given.

PROGUANIL AND CHLOROQUINE

The combination of 200 mg daily of proguanil and 300 mg weekly of chloroquine has continued to be recommended for use in most areas with falciparum malaria, so that experience is now extensive. This remains a very safe combination from which no mortality has been reported, and serious adverse reactions are perceived as very rare. Recent data from the Centers for Disease Control give comparable levels of serious neuropsychiatric toxicity with prophylactic proguanil plus chloroquine and with mefloquine, but the experience of members of the committee gave a substantially higher level from mefloquine. The reasons for this discrepancy remain unclear, but they have inevitably affected the conclusions. Compliance with proguanil with chloroquine is a problem, partly because of the larger number of tablets and daily dosage, though the relative merits of weekly versus daily medication for regular compliance remain more a matter of assertion than of established data. The incidence of mouth ulcers seems to be greater than with earlier regimens and is appreciable. Whether this is a consequence primarily of the raised dosage of proguanil or of the drug combination remains unclear, but it accentuates the problem of compliance. The absence of randomised controlled trials continues to make clear statements of prophylactic efficacy problematical. Its safety record is the main ground for the continued recommendation of proguanil with chloroquine; it continues to provide considerable protection, even in areas of chloroquine resistance in Africa.

Several travellers, mainly to Kenya, who died of malaria in the past five years claimed to have taken proguanil and chloroquine compliantly. The efficacy of this combination of drugs is known to be lower than in the past so an alternative option is given in the tables.

Mefloquine is preferable for male and non-pregnant female travellers on short visits of under three months to highly endemic areas with much high grade (R2-R3) chloroquine resistance, while proguanil with chloroquine is preferred for long term travellers and for women who are pregnant or likely to become pregnant within three months of stopping the drug. The efficacy of proguanil with chloroquine is low in areas of south east Asia.

MEFLOQUINE

Mefloquine is the focus of most interest and the most divergent opinions. Its key features are prophylactic efficacy against chloroquine resistant falciparum malaria and the dose of a single tablet once weekly for adults. But the main questions over the widespread use of mefloquine have been its severe neuropsychiatric toxicity in a few people, and whether to change dosage after a few weeks' use to avoid accumulation, together with uncertainty over its long term use and over possible teratogenicity. Up till now mefloquine has been sparingly recommended for use by travellers from the United Kingdom and only on short visits. The committee now extends recommendations for its use.

In many high transmission areas mefloquine has a high protective efficacy against malaria, including chloroquine resistant *P falciparum*. Mefloquine resistance is present in many populations of *P falciparum* at low frequency, and some breakthroughs occur in Africa. Mefloquine resistance is now frequently encountered in eastern Thailand. Much more extensive experience in continental Europe and the United States has now suggested that the dose can be maintained at one tablet weekly for months without toxic cumulation of the drug and that if side effects have not occurred in the first month they are unlikely to develop thereafter. On the basis of their experience some continental countries are using mefloquine extensively, as is the United States, whose experience with the Peace Corps volunteers over prolonged periods has been very favourable.

Adverse effects involving the central nervous system are associated with mefloquine use. The prevalence of serious effects is low, around 1:10 000, during prophylactic use but 10-fold higher when therapeutic doses are used. The adverse effects include fits, hallucinations and delusions, paranoia, severe anxiety, depression, and other symptoms. The boundary between the very unpleasant and truly psychotic reactions is difficult to delineate. Forty per cent of these events during prophylaxis occurred after the first dose and 75% by the third dose. The incidence is not age dependent but there is some predominance of female patients among those with side effects on prophylactic doses. No deaths have been reported, but some of the neurological and psychiatric effects were severe and alarming.

Practical problems with mefloquine are two. First is the occurrence of these serious neuropsychiatric side effects in a small proportion of users. They pass off if the drug is withheld, and they usually occur early in its use. Surveys suggest that severe effects during mefloquine prophylaxis are rare, but the frequency with which British physicians have encountered them, in the absence of precise population data, seemed to exceed that rate substantially, and it is the type of effect which, once it occurs in a patient, tends to deter the physician from further use of the drug, whether or not this reaction is rational. The second problem is the long half life of mefloquine, combined with uncertainties about its teratogenic potential. The safety of mefloquine in the first trimester of pregnancy is not established at present, but common prudence and the maufacturer's recommendations both point to avoidance of its use in pregnancy. The long half life means that patients are recommended to avoid pregnancy for three months after stopping mefloquine. In younger people travelling for holiday purposes this may be difficult and could lead to the preferred antimalarial differing for a man and woman travelling together to Africa, which would be relatively impractical.

Mefloquine prophylaxis should not be given to those with a history of convulsions (or a history of convulsions in close family members) or of major psychiatric disorders. Nor is it appropriate for people, such as

airline pilots, who undertake precision activities. Those experiencing severe adverse effects during prophylaxis should not use mefloquine subsequently. On current evidence, mefloquine should not be given to pregnant women nor to those liable to become pregnant within three months of stopping the drug. Other contraindications include concurrently taking quinidine. Concern expressed over concurrent use of β blockers, digoxin, or calcium channel blockers seems to have a doubtful basis. Mefloquine is not recommended as a standby drug for treatment as the incidence of side effects is higher than in prophylaxis, nor should quinine be used for standby treatment for failed mefloquine prophylaxis because there is sufficient chemical similarity that mefloquine may reduce the dose of quinine needed. (Standby treatment is for self medication in an emergency by travellers; these comments do not apply to treatment by doctors.)

Mefloquine is, in the absence of contraindications, suitable and highly protective as a chemoprophylactic agent for malaria in areas of high malaria transmission and chloroquine resistance. It is of special value for short term visitors, such as tourists, to east Africa and other parts of sub-Saharan Africa, and as experience grows it is likely to be used for longer periods.

Priority antimalarial for sub-Saharan Africa

Opinions differ on the priority antimalarial for use in Africa where chloroquine resistance is present (effectively, all of sub-Saharan Africa). It is agreed that the two available options are proguanil plus chloroquine, and mefloquine. The former is safer in itself, and cheaper, but compliance may be reduced and protection is incomplete. Mefloquine is more effective, of easier compliance, but rather expensive; it raises problems in women of child bearing age if pregnancy is sought, and it is perceived to have a higher level of neuropsychiatric side effects.

The committee therefore recommends either option, with a preference for mefloquine for visits of up to three months or so to highly endemic, chloroquine resistant areas for men and for women not intending to become pregnant. Chloroquine and proguanil are recommended for long term visitors and when pregnancy is a possibility. Travellers with renal or hepatic impairment may well need a reduced dosage of any antimalarial drugs, but there is insufficient information on the disposition of the main prophylactic drugs in renal or hepatic failure on which to make precise recommendations.

OTHER PROPHYLACTIC DRUGS

Maloprim (a fixed proportion combination of dapsone and pyrimethamine) retains its utility in some areas of chloroquine resistant falciparum malaria. In combination with chloroquine to cope with *P vivax* it is one of the recommended regimens for Oceania, where many Australian tourists use it. Maloprim also has a role for those unable to take the primary regimens. The therapeutic ratio is narrow and the recommended dosage of one tablet weekly for adults must not be exceeded because of the risk of serious adverse reactions, including haemolytic anaemia and agranulocytosis.

Doxycycline has been recommended for use on short visits by some overseas agencies, particularly for business people. It also gives some protection against diarrhoea, typhus, and leptospirosis. However, it may cause skin photosensitivity, is unsuitable for children or in pregnancy, and is expensive. Rarely it may cause diarrhoea, and vaginal candidiasis is a particular problem in women. It has a specialised role in patients unable to take the first line prophylactics.

The following drugs are not recommended for chemoprophylaxis against malaria: pyrimethamine alone because it is ineffective; amodiaquine because of bone marrow toxicity; and Fansidar (pyrimethamine with sulfadoxine) because of cutaneous toxic reactions. Prophylaxis with quinine, the sheet anchor of prophylaxis before 1940, is clumsy, unpleasant, and not completely effective. Halofantrine is neither licensed nor recommended for malarial prophylaxis. Several of these drugs are used as standby drugs for emergency treatment.

Drugs for standby treatments

The increasing prevalence of multidrug resistant *P falciparum* in many parts of the world means that, in spite of careful choice of chemoprophylaxis and prudent measures to avoid mosquito bites, increasing numbers of travellers will contract malaria. Travellers need to be made aware of this and of the need to consult a doctor immediately in case of fever. However, some travellers are likely to be far from medical advice or aid and others may be in countries where advice can be sought but medicines are likely to be scarce. Such travellers are wise to carry with them a standby emeregency treatment for use in case of fever. The preferred standby treatment should be safe and easy for the traveller to take; it should not interact with common prophylactic agents and should be speedily effective against malaria parasites, which may be resistant to these prophylactic agents. No medicine completely fits these criteria, but three are considered as suitable standby drugs by the committee.

Halofantrine—This drug has been recently introduced, and as yet resistance is uncommonly encountered. It is taken orally (as are the others recommended) in three doses over 12 hours. There is a low but real recurrence rate of *P falciparum* after this, and a second treatment one week later is recommended. The advantages of halofantrine are efficacy and a low reported toxicity. As the drug has been in use for only a short time there is limited experience of its use and no good data on the incidence of rare but major side effects. Halofantrine absorption is improved by taking the drug with fats. Some Asian patients have shown substantial cardiotoxicity, and the drug should be used with caution in patients with underlying cardiac problems, and in those previously treated with mefloquine. It is better tolerated than mefloquine and as yet no adverse central nervous system effects have been reported, though it may sometimes cause diarrhoea. Currently the balance of known advantages and disadvantages makes halofantrine the preferred standby drug in the opinion of many, though this view may have to be modified in the light of experience. It is very expensive. Halofantrine should not be used during pregnancy; pregnancy should also be avoided for one month after the final dose of the drug.

Fansidar—This fixed proportion mixture of sulfadoxine and pyrimethamine was highly effective against chloroquine resistant falciparum malaria. Now resistance to it, too, is common in the highly chloroquine resistant areas of east Africa and south east Asia, and in other areas, so that in many areas it is less efficacious than halofantrine. The main serious toxic side effects are Stevens-Johnson syndrome and toxic epidermal necrolysis, with a death rate around 1/18 000 of those using the drug for prophylaxis, for which it is no longer recommended. The standby treatment is taken as a single dose so the risk of side effects is less. Moreover it is being taken for presumptive malaria, not merely to prevent it.

Quinine—Quinine is the longest established antimalarial and though resistance is developing in parts of Asia in *P falciparum*, that resistance is only partial and quinine provides a proved efficacy for standby purposes. Its main disadvantages for this purpose are

that the course lasts seven days and not the single day of other standby drugs, and the relatively high prevalence of unpleasant (but not dangerous) side effects.

Quinine is the only one of these three standby drugs that is completely safe for pregnant women, who should nevertheless also seek medical advice if they get a fever. Quinine at therapeutic dosages does not cause abortion. To prevent recurrence of fever, quinine, in those not pregnant, as a standby drug may be combined with tetracycline, 250 mg four times daily, or three days of quinine may be followed by a single dose of three Fansidar tablets for adults.

Travellers carrying one of the above standby drugs should also carry the following written instructions: "If you develop a fever of 38°C or more (use a thermometer) seven days or more after arriving in a malarious area, seek medical advice at once. If medical help cannot be obtained that day or the condition is deteriorating, self treatment is indicated." Otherwise there is a danger of excessive self medication. In any case a doctor should be consulted as soon as feasible; if the fever does not begin to fall within a day or if it recurs then seeing a doctor is urgent.

TABLE I—*Prophylactic regimens*

Regimen	Generic name(s)	Trade names	Usual amount per tablet	Dose for chemoprophylaxis
	Prophylaxis in areas of chloroquine resistant P falciparum			
Mf	Mefloquine*	Lariam	250 mg (228 mg in United States)	1 Tablet once weekly
CqP	Proguanil plus chloroquine	Paludrine Nivaquine; Avloclor	100 mg 150 mg (base)	2 Tablets daily plus 2 Tablets weekly
MaCq	Dapsone with pyrimethamine plus chloroquine	Maloprim† Nivaquine; Avloclor	100 mg+12·5 mg 150 mg (base)	1 Tablet weekly plus 2 Tablets weekly
	Prophylaxis in areas without drug resistance			
P	Proguanil	Paludrine	100 mg	2 Tablets daily
Cq	Chloroquine	Nivaquine; Avloclor	150 mg (base)	2 Tablets weekly
	Procedure for some areas of limited risk			
O	No chemoprophylaxis but be aware of risk, avoid mosquito bites, and carry standby treatment(s) where indicated in the text			

All antimalarial drugs to be avoided in severe hepatic and renal impairment. Chloroquine dosages are given as the base.
*Avoid during pregnancy and lactation; possible risk of interactions with cardioactive agents (β blockers, digoxin, calcium channel blockers). Metoclopramide accelerates the absorption of mefloquine. Do not prescribe if there is a history of epilepsy or of psychiatric disorder. Not usually recommended to be taken for over three months abroad, but there is increasing evidence of long term safety.
†Contraindicated in the first trimester of pregnancy. Give folate supplements if Maloprim is prescribed during second or third trimester.

TABLE II—*Standby treatment*

Generic name (trade name)	Usual amount per tablet (No of tablets per adult course)	Dose for treatment
Halofantrine (Halfan)	250 mg (6+6)	2 Tablets in one dose, another 2 tablets after 6 hours, and 2 more tablets 6 hours after that. Repeat course 7 days later
Sulfadoxine with pyrimethamine (Fansidar)	500 mg+25 mg (3)	3 Tablets in one dose
Quinine*	300 mg (42)	2 Tablets three times a day for 7 days* or for 3 days followed by 3 tablets of Fansidar once

*Not a suitable standby if mefloquine is used as a prophylactic.

TABLE III—*Doses of prophylactic antimalarial drugs for children**

Age	Weight (kg)†	Fraction of adult dose: Chloroquine with proguanil	Maloprim (pyrimethamine and dapsone)	Mefloquine
0-5 Weeks		1/8	Not recommended	Not recommended
6 Weeks-11 months		1/4	1/8‡	Not recommended
1-5 Years	10-19	1/2	1/4	Not recommended under age 2 years; 1/4 (2-5 years)
6-11 Years	20-39	3/4	1/2	1/2 (6-8 years); 3/4 (9-11 years)
≥12 Years	>40	Adult dose	Adult dose	Adult dose

*For children aged under 2 years in areas of chloroquine resistance the appropriate medication is chloroquine plus proguanil. Chloroquine is available as a syrup but the proguanil has to be powdered on to jam or food. Measures against mosquito bites are specially important.
†When both are available weight is a better guide than age for children over 6 months old.
‡Not feasible to prepare unless a paediatric formulation is available.

Paediatric dosage

The committee hoped to bring uniformity into recommendations on paediatric dosage from the United Kingdom, World Health Organisation, and the data sheets on each drug. This cannot easily be achieved because of the different but slow procedures to effect change. In theory, the current World Health Organisation recommendations lead to low dosage on a surface area basis for young children, while the guidance in the United Kingdom tends to high doses in later childhood. Rather than confuse matters further by a unilateral change, the committee has left the recommendations on paediatric dosage unchanged in the present document and will seek a consensus with the other agencies before publishing changes. There is no clear practical or empirical evidence to favour any one of the present sets of recommendations on grounds of either efficacy or toxicity.

For children under the age of 2 years going to an area where chloroquine resistant falciparum malaria occurs, protection against mosquito bites is specially important. It is relatively easy to screen a sleeping baby's cot with netting impregnated with insecticide. The appropriate antimalarial drugs for these young children are proguanil (powdered onto jam or other food) together with chloroquine, which can be obtained in syrup form.

Pregnancy

Pregnant women intending to visit areas where malaria is endemic and *P falciparum* is resistant to chloroquine should be aware of the risk and consider whether to make the journey. Proguanil plus chloroquine is a suitable prophylactic regimen and Maloprim can also be used, but both regimens should be supplemented with folic acid in pregnancy. Neither gives complete protection in areas of multiple drug resistance.

Recommendations

Four components of protection are essential.

(1) Awareness of risk. In all countries where malaria is transmitted there is a risk, large or small, of contracting malaria and this possibility must be borne in mind in all cases of fever in those who have travelled abroad recently, even if antimalarial precautions have been taken, as no prophylactic is 100% effective. Early malaria can be easily treated but is a medical emergency requiring prompt action, whereas late, severe, or complicated malaria is life threatening and requires immediate specialised management.

(2) Avoiding being bitten by anopheline mosquitoes. All travellers to malarious areas should protect themselves against biting mosquitoes by

- Sleeping in properly screened rooms and using a knockdown flyspray to kill any mosquitoes that may have entered the room during the day
- Using mosquito nets round the bed at night, checking that there are no holes, and tucking the edges under the mattress before nightfall; protection may be enhanced by impregnating the netting with permethrin, 0·2 g/m² of material, every six months
- Using an electric mat to vaporise synthetic pyrethroids overnight or burning mosquito coils; electronic buzzers are ineffective
- Wearing long sleeved clothing and long trousers when out of doors after sunset

TABLE IV—*Malaria in north Africa and the Middle East*

	Risk extremely low (Remember remote chance of malaria if fever)	Risk present, usually low; risk very low in major cities	Risk present; chloroquine resistance present
Regimen*	O	Cq or P	CqP
Countries	Algeria	Egypt (rural, June-October)	Afghanistan
	Egypt (tourist areas)	Iraq (rural, North, May-November)	Iran
	Libya	United Arab Emirates (rural)	Oman
	Morocco	Syria (rural, May-October)	Saudi Arabia (rural)
	Tunisia	Turkey (rural, May-November, and Side town)	Yemen
	Turkey (most tourist areas)		
		Also (outside this area)	
		Mauritius (rural)	

*See table I.

TABLE V—*Malaria in sub-Saharan Africa*

	Risk very high; chloroquine resistance very widespread	Risk sometimes very high; chloroquine resistance widespread	
Regimen*	Mf (CqP regimen needed for longer term, for pregnant travellers, or when Mf is contraindicated)	CqP OR Mf	
Countries†	Kenya	Angola	Madagascar
	Malawi	Benin	Mali
	Tanzania	Botswana	Mauritania
	Uganda	Burkina Faso	Mozambique
	Zambia	Burundi	Namibia
		Cameroon	Niger
		Central African Republic	Nigeria
		Chad	Principe
		Comoros	Rwanda
		Congo	São Tomé
		Dijibouti	Senegal
		Equatorial Guinea	Sierra Leone
		Ethiopia	Somalia
		Gabon	South Africa (parts of Natal and Transvaal only)
		Gambia	Sudan
		Ghana	Swaziland
		Guinea	Togo
		Guinea-Bissau	Zaire
		Ivory Coast	Zimbabwe
		Liberia	

*See table I. †See table IV for Mauritius.

TABLE VI—*Malaria in south Asia*

	Risk variable; chloroquine resistance usually moderate
Regimen*	CqP
Countries	Bangladesh
	Bhutan
	India
	Nepal
	Pakistan
	Sri Lanka

*See table I.

- Using repellents such as diethyl toluamide on exposed skin or on appropriate garments (30 ml diethyl toluamide in 250 ml water used to impregnate a garment makes it repellent).

(3) Under most circumstances travellers to malarious areas should start taking antimalarial prophylactic drugs a week before departure and continue for four weeks after returning to the United Kingdom, as well as taking them throughout the time overseas. It may be helpful to start mefloquine two weeks before departure, to check for absence of adverse reactions.

(4) Compliance with protective measures is the main determinant of their efficacy. The main impetus towards compliance will be an informed awareness of risk by the patient.

Recommendations by area

Advice is set out for each continent in tables IV-IX. The regimens refer back to table I for chemoprophylaxis and table II for standby treatments. Paediatric dosages are given in table III. The country specific tables indicate where transmission is confined to rural areas.

TABLE VII—*Malaria in south east Asia*

	Risk very low; remember chance of malaria if fever	Risk substantial; drug resistance common
Regimen*	O	Mf OR CqP (for longer term, pregnant travellers, or when mefloquine is contraindicated)
Areas	Tourist areas and cities in:	Cambodia (seek specialist advice)
	Bali	China (rural, some areas)
	Brunei	Indonesia (outside Bali)
	China (main tourist areas)	Laos
	Hong Kong	Myanmar (Burma)
	Peninsular Malaysia	Philippines (rural, some areas)
	Philippines	Sabah
	Sarawak	Thailand (no chemoprophylaxis in rural areas but urgent need for treatment of fever; specialist advice for border areas)
	Singapore	Vietnam
	Thailand (Bangkok and main tourist areas)	West Malaysia (some rural areas only)

*See table I.

When prophylaxis is needed for part of the year only, the months with risk are indicated.

NORTH AFRICA AND THE MIDDLE EAST (TABLE IV)

Malaria risk is low or extremely low throughout the greater part of this area. In the countries with higher risk, chloroquine resistance is also recorded.

SUB-SAHARAN AFRICA (TABLE V)

No traveller visiting malarious sub-Saharan Africa should travel without adequate protection against biting mosquitoes and chemoprophylaxis cover. One of the two regimens in the first part of table I is recommended. Mefloquine is appropriate for shorter visits (up to three months and possibly longer, see above) and gives a greater degree of protection, but note contraindications. Proguanil with chloroquine is very safe and appropriate for those on long visits or when a woman is pregnant or likely to become pregnant within three months of stopping chemoprophylaxis; its protective efficacy is less than with mefloquine. The possibility of breakthrough malaria must be borne in mind, whatever the chemoprophylaxis being taken. Where travellers will be away from medical advice or in places where access to medicines may be difficult, a standby treatment should be carried. Halofantrine is probably the most convenient and widely effective.

Visitors to the east African coast and to west Africa are at particular risk and several fatalities occur annually, both among those who neglect precautions and now also among those taking prophylactic drugs whose fevers are not investigated and treated appropriately. Mefloquine is particularly recommended for those visiting the highly malarious countries of east and central Africa (table V). For the remaining countries of sub-Saharan Africa the alternatives of mefloquine or proguanil with chloroquine are recommended, but there are variations in the intensity of transmission. Some highland areas of Ethiopia and Kenya are free of malaria, as are most parts of South Africa with the exception of parts of Natal and the Transvaal, while in some arid areas of Africa malaria is seasonal. It is best to assume that antimalarial drugs are needed, especially as most visitors are likely to travel outside their main destination.

In Zimbabwe and some adjacent countries, Maloprim (sold widely as Deltaprim) is widely used as a chemoprophylactic by local residents, sometimes in conjunction with chloroquine. This gives some protection, but the committee has sought to recommend as few variations as feasible for travellers from the United Kingdom, especially as many visit more than one country in Africa.

SOUTH ASIA (TABLE VI)

Visitors to all countries of the Indian subcontinent are at risk of malaria. It is a particular problem for settled immigrants and their children who may be visiting relatives in an area of south Asia that was not malarious when they originally left. Thirty per cent of malaria imported into Britain is from the Indian subcontinent. *P vivax* is overwhelmingly predominant, but the risk of *P falciparum* is real and chloroquine resistance is reported. Proguanil with chloroquine is recommended. Urban malaria is a problem in many cities of south Asia.

SOUTH EAST ASIA (TABLE VII)

Malaria endemicity varies greatly, but multidrug resistant *P falciparum* is common. Some countries, such as Malaysia (apart from Sabah), have a high degree of malaria control, so that the risk of malaria in most areas is very low and no chemoprophylaxis is necessary but travellers should be aware of the risk,

TABLE VIII—*Malaria in Oceania*

	Risk high; chloroquine resistance present
Regimen*	Mf OR MaCq
Countries	Papua New Guinea Solomon Islands Vanuatu

*See table I.

avoid mosquito bites, and carry standby treatment. In Thailand the major tourist cities such a Bangkok, Pattaya, Phuket, and Chiangmai are malaria free. The rural areas around them have a risk of malaria but resistance to all the commonly used prophylactics is common. Under these circumstances where the protective efficacy is so low the recommendation is also to take no chemoprophylaxis but to seek immediate medical advice in the event of a fever. Those travelling extensively overland or to the eastern or western borders of Thailand, where transmission is high, or to Cambodia should seek specialist advice before travelling, as mefloquine resistance is now a considerable problem on the eastern border of Myanmar (Burma), the east and west borders of Thailand, and the western and northern borders of Cambodia.

TABLE IX—*Malaria in Latin America*

	Risk variable; no chloroquine resistance	Risk variable or high; chloroquine resistance present
Regimen*	Cq	CqP
Countries	Argentina (a few areas only) Belize Costa Rica (rural) Dominican Republic El Salvador Guatemala Haiti Honduras Mexico (rural, little visited areas) Nicaragua Paraguay (rural, October to May) Peru (below 1500 m)	Bolivia (below 2500 m) Brazil (rural, some areas)† Colombia Ecuador French Guiana Guyana Panama Surinam Venezuela (rural; Caracas and main cities free of malaria)

*See table I.
†Amazonia region of Brazil has high risk of chloroquine resistance and mefloquine is recommended for short term travellers (up to three months abroad) without contraindications.

OCEANIA (TABLE VIII)

In Papua New Guinea, the Solomon Islands, and Vanuatu transmission of malaria is intense, and in Papua New Guinea multiply drug resistant malaria is a major problem. The advice given here is consistent with that given to the many Australian visitors to those islands.

LATIN AMERICA (TABLE IX)

In Central America there is a low to moderate risk of malaria without chloroquine resistance (except in south Panama). This is also the case in part of the west of South America. Elsewhere in South America malaria is highly endemic in patches and chloroquine resistance is common. This is especially the case in the Amazonia region.

Appendix

Contributors to the recommendations are: Dr R H Behrens, Professor D J Bradley (chairman), Dr A D M Bryceson, Dr P L Chiodini, Dr P D Clarke, Brigadier G O Cowan, Dr C Dow, Dr J Dunlop, Dr C J Ellis, Professor A Geddes, Professor H M Gilles, M P Golightly, Squadron Leader A D Green, Dr M Janosi, Wing Commander F Jones, Dr G Lea, Dr J Leese, Dr J Levine, Brigadier C J Lewthwaite, Professor K McAdam, Surgeon Commander A R O Miller, Professor G Pasvol, Professor W Peters, Dr T Peto, Dr P Phillips-Howard, Sister F Rayside, Dr J Stewart, Dr R Stanwell-Smith, Dr E Walker, Professor D A Warrell, Dr W R C Weir, Dr G B Wyatt, Mrs M Blaze, Dr M J Colbourne, Mrs V Smith, Dr B A Southgate, Professor G A T Targett, Dr D A Warhurst, Dr R H Webber.

Thomas McKeown and Archibald Cochrane: a journey through the diffusion of their ideas

Carlos Alvarez-Dardet, María Teresa Ruiz

In the 1970s Thomas McKeown and Archibald L Cochrane were two of the most influential voices in criticising the dominance of medical thinking. A bibliometric study of the citations to McKeown's *The Role of Medicine: Dream, Mirage or Nemesis* and Cochrane's *Effectiveness and Efficiency: Random Reflections on Health Services* was performed from the publication of each book until 1988 to study how their ideas have been disseminated. During the study period 430 papers in the *Science Citation Index* or the *Social Sciences Citation Index* cited Cochrane's book, 133 cited McKeown's, and 166 cited both. The citations came mainly from original papers published in journals of internal medicine or public health and epidemiology (35%) and written by authors from the United States or the United Kingdom. Cochrane's book was cited most frequently in medical journals, suggesting a higher degree of penetration of his ideas among medical scientists. Although the dominance of original papers among the citations suggests that these books have been important in stimulating new knowledge, the main problems that McKeown and Cochrane identified—namely, the relatively small impact of clinical medicine on health outcomes and the poor use of scientific methods in clinical practice—are still with us.

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The 1970s were dominated by a world crisis in medical thinking and in health service policies. This crisis was produced by accumulative arguments about the relative lack of effectiveness of medical practice and the inappropriateness of medical thinking to deal with health matters.[1-3] In the years of economic shortage following the rising price of crude oil these criticisms acquired more relevance in challenging health systems mainly orientated towards expensive therapeutic, biological, and technological objectives. Even the World Health Organisation was affected by this wave of criticism and at the end of the 1970s produced a profound redefinition of objectives in the meeting at Alma Ata which coined the term "health for all."[4]

Thomas McKeown and Archibald Cochrane were two of the more influential voices in the 1970s, and both provided theoretical support to the critical side of the debate through their books: *The Role of Medicine: Dream, Mirage or Nemesis* by McKeown[5] and *Effectiveness and Efficiency: Random Reflections on Health Services* by Cochrane.[6] Their criticisms of the medical establishment were different, and both of them were keen to emphasise the differences. McKeown's more radical hypothesis can be summarised as follows: the erroneous interpretation of the effect of medicine in improving health in the past and, as a result, unrealistic expectations for the future have led to a distorted appreciation of the role of medicine. In Cochrane's reformist view the lack of effectiveness of medical services and the imbalance between financial inputs into health services and outcomes in terms of health status were attributed to the poor use of scientific method in medicine, especially in evaluating therapeutic interventions, and, in particular, the failure to use experimental designs like randomised control trials.