

## 8 - Frequently Asked Questions

### 8.1

What malaria prevention should be advised for travellers going on cruises? 85

### 8.2

What alternative antimalarial drugs can be used for India (and Sri Lanka) if chloroquine and proguanil are unsuitable for a traveller? 85

### 8.3

Which antimalarial can I give to a traveller with a history of psoriasis? 86

### 8.4

Which antimalarial can I give a traveller who is taking warfarin? 86

### 8.5

How long is it safe to continue a course of antimalarial tablets? 87

### 8.6

Which antimalarial drugs are suitable for women during pregnancy? 88

### 8.7

Which antimalarial drugs can be taken by breastfeeding women? 89

### 8.8

Which malaria drugs can be given to babies and young children? 89

### 8.9

What is the easiest way to calculate the correct dose of chloroquine for babies and young children? 90

### 8.10

Many travellers I see intend to travel through several areas where different anti-malarials are recommended as they progress through their journey. How do we advise these travellers? 90

### 8.11

Which antimalarial drugs can I advise for a traveller who has epilepsy? 91

### 8.12

What do I advise for the traveller with Glucose 6-phosphate dehydrogenase deficiency? 91

### 8.13

What do I advise people working on oil rigs? 92

### 8.14

What do I advise for the traveller on a stopover? 92



## 8. Frequently Asked Questions

### *Q1. What malaria prevention should be advised for travellers going on cruises?*

**A.** Cruises are a growing part of the holiday market. Most travellers on cruises are only ashore during daylight hours when the *Anopheles* vector of malaria is not feeding, and therefore do not require malaria chemoprophylaxis. Occasionally this is not the case and therefore the cruise itinerary must be reviewed to determine if there will be exposure to malaria.

As examples, cruises in the Caribbean may include several days travelling along the Amazon in Brazil, or Orinoco River in Venezuela. Cruises along the East African coast may include a stop for a night or more in the port of Mombasa, Kenya and passengers may be ashore or on deck after dusk. These itineraries will require malaria chemoprophylaxis.

In addition cruises that have an overnight stay in any other malaria endemic region of the world require malaria chemoprophylaxis. Risks in specific destinations can be determined by referring to the country tables 7-12 in chapter 4.

Based on the destination, duration of exposure, and health of the traveller, the choice of malaria chemoprophylaxis can be made using the advice in these guidelines. All travellers on cruises should use insect bite avoidance measures (see chapter 3).

### *Q2. What alternative antimalarial drugs can be used for India (and Sri Lanka) if chloroquine and proguanil are unsuitable for a traveller?*

**A.** Chloroquine plus proguanil are the recommended chemoprophylaxis for India (apart from Assam state in Northern India where either mefloquine, doxycycline or atovaquone / proguanil are the drugs of choice) and Sri Lanka. If a traveller is unable to take the combination of chloroquine plus proguanil, the alternative is a choice between one of three prescription drugs available: mefloquine, doxycycline or atovaquone / proguanil.

It depends on the reason why chloroquine and proguanil are not suitable as to which alternative is considered (e.g. those unable to take chloroquine due to epilepsy should not take mefloquine; if a traveller does not tolerate proguanil, then they should avoid atovaquone/ proguanil (Malarone<sup>®</sup>) as this also contains proguanil). For advice on malaria prevention in pregnant women there is a specific FAQ below.

Chloroquine plus proguanil remain the first choice agents in India and Sri Lanka because for most areas in these countries, *Plasmodium vivax* is the most prevalent species of malaria present and chloroquine is highly effective against this species. Because there is some *P. falciparum* present, the addition of proguanil to chloroquine provides additional protection against strains of *P. falciparum* that may be resistant to chloroquine alone. Where there is frequent or high level resistance, such as the Assam region discussed above, alternative agents are used.

### Q3. Which antimalarial can I give to a traveller with a history of psoriasis?

**A.** Proguanil, atovaquone / proguanil, doxycycline and mefloquine do not cause problems in those with psoriasis. Chloroquine and chloroquine-related drugs can exacerbate psoriasis and should be avoided in those with generalised psoriasis or a history of such. Travellers with mild psoriasis can consider chloroquine if they are aware of the possible risks. The benefit of chemoprophylaxis with chloroquine may outweigh the risk of exacerbation of psoriasis, but each case should be considered on an individual basis.

### Q4. Which antimalarial can I give a traveller who is taking warfarin?

**A.** Travellers on anticoagulants should ensure their clotting time is stable prior to departure. It should be noted that patients on warfarin may have underlying cardiac disease and may be on cardiac medication. Interactions with other medication together with the individuals' medical history should be taken into account when deciding on appropriate malaria chemoprophylaxis.

Documented interactions between warfarin and antimalarial tablets

#### *Chloroquine*

There is no interaction between warfarin and chloroquine documented in the BNF, although there is a caution in the Summary of Product Characteristics for Nivaquine.

#### *Proguanil*

There has been an isolated report of an enhanced effect of warfarin when taken together with proguanil<sup>58</sup>.

#### *Mefloquine*

Mefloquine is not considered to be a problem for those taking warfarin. The manufacturer states that '*although no drug interaction is known with anticoagulants, effects of mefloquine on travellers should be checked before departure.*'

Please see below for how this can be monitored.

#### *Atovaquone / proguanil (Malarone®)*

It is unknown whether there are interactions between Malarone and warfarin, although there have been isolated reports of an enhanced effect of warfarin when taken together with proguanil (see above under proguanil).

#### *Doxycycline*

The anticoagulant effect of coumarins (including warfarin) is possibly enhanced by tetracyclines<sup>59</sup>.

Advice for travellers needing malaria chemoprophylaxis who are taking warfarin

Travellers should start taking their malaria tablets at least 1 week (and ideally 2-3 weeks in the case of mefloquine) prior to their departure. A baseline INR should be checked prior to starting chemoprophylaxis, and re-checked after 1 week of taking chemoprophylaxis. If a traveller is away for a long period of time the INR should be checked at intervals at the destination. However, the sensitivity of thromboplastin reagent used by some laboratories in different countries may vary<sup>60</sup>.

### *Q5. How long can a traveller take different antimalarial drugs?*

**A.** Guidelines for the long term use of malaria tablets are summarised in chapter 7 and were originally published in 2003 by the ACMP<sup>55</sup>.

The main issues influencing the choice of malaria chemoprophylaxis on a long-term basis are the same as for short-term, i.e. adverse event profile, ease of compliance and efficacy. However, the specific issue relating to advice on chemoprophylaxis for the long-term traveller relates to current licensing restrictions. Long term use of malaria chemoprophylaxis outside licensing restrictions is based on the cumulative evidence of lack of harm rather than positive evidence of safety. This situation is unlikely to change.

#### *Chloroquine*

Chloroquine has been taken safely for periods of many years at doses used for malaria chemoprophylaxis. However, there has been concern expressed about the possible development of retinal toxicity with long term use of chloroquine (or hydroxychloroquine, often used to treat rheumatologic disorders). Retinal toxicity has been described in those on daily chloroquine dosage for rheumatic disorders. 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 base (4mg / kg)<sup>80</sup>.

The first threshold would require an adult to take chloroquine continuously, weekly, for a period of six years. The second threshold is far in excess of the prophylactic dosage. It has been concluded that the risk of retinopathy from prophylactic dosage alone is negligible<sup>29</sup>. Further reassurance can be gained from the fact that retinopathy has only rarely been reported in patients taking weekly prophylactic dosages<sup>80,81</sup>.

ACMP advice suggests that chloroquine can be taken on a long-term basis. However, physicians should consider an ophthalmologic examination every 6-12 months, beginning at 6 years' cumulative use for those on long-term chloroquine.

#### *Proguanil*

There is no time limit specified for the use of proguanil. Therefore, it can be taken continuously for several years.

#### *Mefloquine*

There are few data on the use of mefloquine for periods exceeding two years, although there is no evidence of cumulative toxicity, and mefloquine taken for over 1 year is well tolerated. The product licence suggests mefloquine can be taken continuously for a period of up to 12 months. However, advice from the ACMP indicates that there is no evidence of harm in long term use if the drug is tolerated in the short term, and suggests that mefloquine can be used safely for up to three years in the absence of side effects.

### *Doxycycline*

Doxycycline is licensed for up to two years or more in the treatment of acne in the same dose as is used for malaria prophylaxis. The ACMP have concluded that there is no evidence of harm in long-term use of doxycycline and it may be taken safely for periods of at least up to two years.

### *Atovaquone / proguanil (Malarone®)*

Both components of Malarone® have been used individually on a long term basis, although there is little experience of long-term use of the combination. Many countries do not restrict the length of time atovaquone/proguanil can be taken although the UK product license states it can only be taken for travel up to 28 days.

There is a report of atovaquone/proguanil use for periods from 9 to 34 weeks, in which there was no excess of adverse effects and no appearance of unexpected adverse effects<sup>82</sup>. The ACMP concludes that there is no evidence of harm in long-term use and suggests that it can be taken confidently for travel up to one year or longer. Nevertheless, long-term use of atovaquone/proguanil should be prescribed with careful consideration until additional post licensing experience is available.

## *Q6. Which antimalarial drugs are suitable for women during pregnancy?*

**A.** Malaria during pregnancy is a serious illness for both the mother and the fetus. Pregnant women should be advised against travel to an area with malaria, particularly if there is chloroquine resistant *Plasmodium falciparum*.

Doxycycline and atovaquone / proguanil (Malarone®) are both unsuitable for use during pregnancy.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing foetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy (SPC).

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. Animal studies showed no evidence for teratogenicity of the combination. The individual components have shown no adverse effects on parturition or pre- and post-natal development (SPC). Women should be reassured that taking Malarone inadvertently prior to or during the first trimester is not an indication to terminate a pregnancy.

The data available from studies on the prophylactic use of mefloquine in pregnancy is generally reassuring. Most experts recommend that mefloquine is avoided during the first trimester, but can be offered to women during the second and third trimesters. The risk of adverse effects of mefloquine use in pregnancy should be balanced against the risk of contracting malaria and the complications that can result. The decision on whether to recommend mefloquine should be carefully discussed with the traveller.

Women of childbearing age should take contraceptive precautions while taking mefloquine and for three months after the last dose. However, they should be reassured that taking mefloquine inadvertently prior to or during the first trimester is not an indication to terminate a pregnancy.

Both chloroquine and proguanil have been taken safely during pregnancy for many years although this combination offers insufficient protection in areas with chloroquine resistant *P. falciparum*. Folic acid supplements should be taken if proguanil is used in those who are pregnant or seeking to become pregnant.

### **Q7. Which antimalarial drugs can be taken by breastfeeding women?**

**A.** Breastfeeding women should not take doxycycline or atovaquone / proguanil (Malarone®). Chloroquine plus proguanil can be used during breastfeeding although this combination provides suboptimal protection for the mother in areas of chloroquine resistant *Plasmodium falciparum* malaria.

There is little data on the use of mefloquine during breastfeeding (see Breastfeeding section in chapter 6). Although mefloquine is excreted in breast milk in small amounts there is not enough data to draw conclusions regarding potential harmful effects on the infant.

Mefloquine may be considered for breastfeeding mothers travelling to areas of chloroquine resistant *P. falciparum*. Each traveller should be assessed individually, weighing the potential risks and benefits of taking mefloquine whilst breastfeeding, and taking into consideration the risk of malaria at the destination.

The small amounts of antimalarials that pass into breast milk are not enough to protect the baby. Breastfeeding infants therefore need to take their own prophylaxis. If both mother and infant are taking mefloquine there is a concern that the amount of mefloquine the infant may receive will exceed the recommended maximum, particularly in infants in the lower weight range. However, this possible effect is likely to be short lasting as the weight of the child increases and the contribution of mefloquine in breast milk to the total prophylactic dose becomes relatively small.

### **Q8. Which antimalarial drugs can be given to babies and young children?**

**A.** Both chloroquine and proguanil can be given from birth. Chloroquine is available as syrup but proguanil will need to be crushed and given with jam or food.

Mefloquine can be given to infants weighing 5 kg or more (see Summary of Product Characteristics). Atovaquone / proguanil (Malarone®) can be given to infants weighing 11 kg or more; paediatric tablets are available.

Doxycycline is unsuitable for children under 12 years.

One of the main challenges in giving malaria tablets to babies and young children will be the practical aspects of administration.

All dosages for malaria chemoprophylaxis in children are found in tables 4-6 in chapter 4, and in the British National Formulary (BNF). The dose for children will be dependent on the weight / age of the infant or child.

Mosquito bite avoidance is extremely important for this age group.

**Q9. What is the easiest way to calculate the correct dose of chloroquine for babies and young children?**

**A.** The dose steps for chloroquine syrup are not the same as for chloroquine tablets and a child may be prescribed a different dose of chloroquine depending on whether they take tablets or syrup (see tables 4 and 5, chapter 4). The main reason for any differences is due to the different amount of chloroquine base within the syrup and the tablets. The chloroquine syrup formulation contains 50 mg chloroquine base / 5 mls syrup. The amount of chloroquine base contained within the tablets is 150mg (Nivaquine) and 155mg (Avloclor).

An additional factor which might be confusing is that the packet insert for chloroquine phosphate (Avloclor) gives different dosages (usually lower) for children than in these guidelines and the BNF. The ACMP guidelines and BNF dosages should be used.

While there is an optimum dose of chloroquine base for children of every weight, the final dosage given to the child will depend, in part, on the practicality of administering the formulation of chloroquine available (i.e. either tablet or syrup). E.g., when dividing tablets for children, it is not possible to break a tablet into thirds, so the dosages will involve either a half or a quarter of a tablet.

The tables in chapter 4 have been calculated based on weight and surface area and the most accurate dose according to the weight is recommended. Although differences occur, all recommended dosages in the tables fall within accepted limits of toxicity. It is important not to overdose children with chloroquine as severe toxicity can occur.

A practical approach when calculating children's dosages for chloroquine is to decide on the most appropriate preparation (either tablet or syrup) for the child and calculate the dose appropriate to that preparation, according to the tables in chapter 4.

**Q10. Many travellers I see are travelling through areas where different anti-malarials are recommended as they progress through their journey. How do we advise these travellers?**

**A.** Travellers planning extensive journeys across continents will often travel into areas which have different malaria chemoprophylaxis recommendations. In these situations it is important that the traveller is protected in all areas of risk and the choice of medication needs to reflect the overall risk.

It may be possible to move from one regimen to another, although for shorter trips this may not be practical. For example, a traveller visiting parts of India for 2 weeks (where chloroquine plus proguanil may be recommended) and then going on to areas in Myanmar and Cambodia for 6 weeks (where mefloquine, doxycycline or atovaquone/proguanil may be recommended) would be advised to take either mefloquine, doxycycline or atovaquone/proguanil for the whole of the visit rather than change from chloroquine and proguanil to one of the other agents.

**Q11. Which antimalarial drugs can I advise for a traveller who has epilepsy?**

**A.** Both chloroquine and mefloquine are unsuitable for those with epilepsy. For areas with a high risk of chloroquine resistant *Plasmodium falciparum*, doxycycline or atovaquone / proguanil can be used. However for children under the age of 12 the only suitable antimalarials under these circumstances will be atovaquone / proguanil (Malarone®) (bearing in mind the length of travel). Proguanil alone can be given for malarious areas without chloroquine resistance.

Phenytoin, carbamazepine and barbiturates reduce the half life of doxycycline; in theory the dose should be increased for those taking these drugs. However, there is no evidence that this is necessary, and a dose adjustment is not recommended.

**Q12. What do I advise for the traveller with Glucose 6-phosphate dehydrogenase deficiency?**

**A.** Glucose 6-phosphate dehydrogenase (G6PD) is an enzyme in the hexose monophosphate shunt of the glycolytic pathway. This shunt supports the red cell's protection against oxidative damage. Absence of G6PD renders the red cell liable to haemolysis in the presence of some drugs.

The most common G6PD deficiency allele in Africa (G6PD A-) has been shown to confer some resistance to malaria in both hemizygous males and heterozygous females<sup>61</sup>. Nevertheless, all G6PD-deficient travellers to malarious areas still require appropriate chemoprophylaxis.

*Chloroquine*

There is a theoretical risk of haemolysis in some G6PD-deficient individuals who receive chloroquine. This risk is acceptable in acute malaria<sup>59</sup> and G6PD levels are not usually checked before using chloroquine in treatment doses. Haemolysis does not appear to be a problem when chloroquine is given in the dose recommended for malaria chemoprophylaxis so there is no need to withhold chloroquine prophylaxis from those known to be G6PD-deficient.

*Primaquine*

This drug is not currently recommended as a first line agent for malaria prevention in UK travellers, but may be considered in special circumstances on expert advice<sup>27</sup>. There is a definite risk of haemolysis in G6PD-deficient individuals. The traveller's G6PD level must be checked before primaquine is prescribed and G6PD deficiency contraindicates its use for prophylaxis.

*Q13. What do I advise people working on oil rigs?*

**A.** There is a large number of staff employed in the oil industry predominantly based around West Africa. Employees commonly travel to these areas every 4-6 weeks, followed by a similar period of leave back in the UK. Oil rigs may be based in river estuaries or many miles offshore. Therefore the level of risk may be difficult to assess until one period of work has been completed and antimalarial chemoprophylaxis should be taken for the whole of this first trip.

Antimalarial chemoprophylaxis is advised for those workers on oil rigs based in river estuaries.

Offshore rigs pose little risk and antimalarial chemoprophylaxis may only be needed if staying overnight onshore during transit.

*Q14. What do I advise for the traveller on a stopover?*

**A.** Many stopovers are in urban or tourist areas (particularly in Asia) and have minimal malaria risk. They are often situated in countries which may have malaria transmission in parts. Therefore, in order to assess risk it is essential to establish where overnight accommodation will be.

Stopovers in most of sub-Saharan Africa, including main cities, present a risk of malaria and antimalarial prophylaxis should be recommended.