Royal College of Obstetricians & Gynaecologists

The prevention of malaria in pregnancy

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This is the first edition of this guideline.

1. Purpose and scope

The aim of this guideline is to provide clinicians with evidenced based, up-to-date information about the prevention of malaria in pregnancy in situations that are likely to be encountered in UK medical facilities (that is, UK-based residents visiting malaria endemic areas). These guidelines are not necessarily appropriate for those residing in endemic areas.[1] This guideline covers malaria prevention travel recommendations in:

- women planning a pregnancy
- those already pregnant or breast feeding.

Drug recommendations for malaria prophylaxis can change, owing to resistance, and up-to-date information on drugs can be obtained using online resources as described in this guideline.

2. Background

Malaria can be life-threatening but it is preventable. Malaria is caused by the bite of the female *Anopheles* mosquito, which results in infection of the red blood cell. The species determines the pattern of the disease. The species of the 1370 imported infections reported in the UK in 2008 were: 79.3% (1087) *P. falciparum*, 12.9% (170) *P. vivax*, 5.5% (76) *P. ovale*, 2.1% (20) *P. malariae*, one unspecified infection and, of all these, nine were mixed infections.[2] In 2006, there was one case report of primate malaria (*P. knowlesi*) in a UK traveller returning from Brunei.[2] In 2008, there were six deaths reported in the UK from malaria.[2] By far the heaviest burden of malaria in travellers from the UK is *P. falciparum* from Africa (mainly West Africa, particularly Nigeria and Ghana).[3] *P. falciparum* is the most dangerous species of malaria and causes the vast majority of deaths worldwide. In UK travellers to Asia, particularly to the Indian subcontinent, infection with *P. vivax* is more likely and this can cause a relapsing type of malaria. *P. ovale* can also cause relapsing malaria and *P. malariae* is unique, owing to late recrudescence after many years. Other places where UK travellers have acquired malaria include South and Central America (including Great Exuma in the Bahamas), Hispaniola, Oceania and the Middle East.[2] In the UK, the majority of travellers with imported malaria report visiting friends and relatives in their families' country of origin, especially in West Africa.[4–7] The uptake of chemoprophylaxis among people residing in the UK who present with malaria in the UK is low.[8] Special effort to tailor malaria prevention messages to migrant groups could reduce the risk of travel-associated malaria significantly.[8]

Pregnant women are not specifically identified in the UK surveillance data.[2] A report published by the Health Protection Agency does not mention pregnancy.[8] Most of the literature on imported malaria worldwide is based on a few reports of isolated cases[9–11] with the most comprehensive series of 14 pregnant women reported by French investigators in Marseille.[12] Perhaps the message contained in this limited literature is found in surveillance from the USA: pregnant women comprised 1.6% of malaria cases (24/1505) during 2008 and none had adhered to a complete preventive drug regimen.[13]

3. Identification and assessment of the evidence

A literature search was performed using Medline (1983 to November 2009). The keywords used were 'malaria', 'prevention', 'travellers', 'UK', 'imported malaria', 'pregnancy' and 'breast feeding'. Reference lists of the articles identified were hand searched for additional articles. Other sources included malaria-related pages from the websites of the Health Protection Agency [www.hpa.org.uk/HPA], the National Travel Health Network and Centre [www.nathnac.org], European Network on Imported Infectious Disease Surveillance [www.tropnet.net], Centers for Disease Control and Prevention [www.cdc.gov/Malaria] and TOXBASE, the primary clinical toxicology database of the National Poisons Information Service [www.toxbase.org].

4. What are the medical complications of malaria in pregnancy?

Malaria infection in pregnancy carries significant risks to mother and baby. C

UK-based residents have low premunition and high susceptibility to malaria infection. B

Malaria infection in pregnancy may result in reduced birth weight in the fetus and this may have health consequences in later life. B

Malaria in pregnancy adversely affects the mother and fetus (Table 1).[14,15] Maternal mortality or pregnancy loss from miscarriage, stillbirth and premature labour are the main complications of malaria in women with low premunition and complications are likely to be equivalent or worse in women who are not immune.[16–18] The principal effect of malaria in pregnancy in women from endemic countries is low birth weight and this could have consequences on health in adulthood.[19] The extent of this effect in returned travellers has not been well documented.[12] In endemic areas, pregnant women are twice as likely to be bitten by anopheline mosquitoes[20,21] and to contract and die from malaria[22,23] than their non-pregnant counterparts.The clinical manifestations in pregnancy depend on premunition; that is, the degree of naturally acquired host immunity to malaria (Table 1).[14,18,24,25] Premunition depends on repeated exposure to infectious anopheline bites, so UK-based residents will have low or no premunition.

Evidence level 2++

5. Prevention of malaria infection in pregnancy

5.1 What advice should pregnant women be given if they are considering travel to a malaria endemic area?

Pregnant women should consider the risks of travel to malaria endemic countries and consider postponing their trip, unless travel is unavoidable. C

A health professional advising a prospective UK resident who is pregnant or thinking about becoming pregnant and who is intending to go to a malaria endemic area should suggest that the woman considers not going or postponing their trip until they are no longer pregnant (Table 1).[26]

Table 1. Summary of the main consequences of malaria in pregnancy in non-immune female UK-based residents, with different levels of premunition to malaria (severity indicated by + when known)

Consequence	Severity	Premunition	
		Low	High
Susceptibility to infection	++++	+++	++
Risk of illness	++++	+++	+
Severe anaemia	Not known	+++	+++
Severe/cerebral malaria	++++	+++	-
Maternal and fetal mortality (woman dies with the baby undelivered)	++++	+++	+
Reduction of birth weight	Not known	++	++
Miscarriage, premature birth, stillbirth	++++	++++	+
Gravida at risk	All	All	Primiparous
Placental parasitaemia	Not known	+	+++

5.2 If travel is unavoidable what advice should pregnant women receive about preventing malaria infection?

Advise the woman to seek guidance from a centre with expertise on malaria risks and avoidance strategies. B

Advise women that a fever or flu-like illness while travelling or upon returning home, up to 1 year or more, may indicate malaria and requires medical attention. B

Advise the woman on the risk of being exposed to malaria at her intended area of travel. B

There are no measures specific to pregnancy that can be taken to prevent malaria beyond those that non-pregnant travellers can apply.[27,28]

The 'ABCD' of malaria prevention is a useful formula to remember the components of malaria prevention:

- **A**wareness of risk (see Section 5.2.1)
- **B**ite prevention (see Section 5.3)
- **C**hemoprophylaxis (see Section 5.4)
- **D**iagnosis and treatment which must be prompt (see 5.5).

Women need to be educated about possible measures and, where possible, provided with written information in their own language.[1]

The Department of Health produces *Think Malaria* leaflets (order code MAL/1) which are available in 11 different languages and can be obtained from DH Publications by writing to: DH Publications Orderline, PO Box 777, London SE1 6XH, or by telephoning 03001231002, or by email to dh@prolog.uk.com or for further information see the Department of Health website [www.orderline.dh.gov.uk].

5.2.1 What needs to be done to raise pregnant traveller's awareness of the risk of malaria?

The risk of malaria is dependent on a variety of factors, including the level of transmission in the area(s) of travel and the time of year (rainy or dry season), the presence of drug resistant strains of *P. falciparum* or *P. vivax*, whether rural or urban sleepovers are planned, length of travel and the availability and the likelihood of uptake of malaria prevention interventions.[29] For example, if a woman proposes to go to urban tourist areas of Southeast Asia, such as Bangkok and Phuket, and stay in air-conditioned hotels, the risks are considered minimal for malaria, whereas urban travel in sub-Saharan Africa and New Guinea (Papua New Guinea and Papua) constitutes a significant risk of infection. For UK residents, the risk remains disproportionately high in the African Diaspora of travellers visiting friends and relatives in West Africa, particularly Nigeria, Ghana and Uganda.[8] The risk of contracting malaria during a 1 month stay without chemoprophylaxis (regardless of country of residence of the traveller) has been estimated from retrospective studies of large numbers of travellers (Table 2).[30–32]

Table 2. Risk of contracting malaria during a 1-month stay without chemoprophylaxis

Area	Risk
Oceania (Papua New Guinea, Papua, Solomon Islands and Vanuatu)	1:20
Sub-Saharan Africa	1:50
Indian subcontinent	1:500
Southeast Asia	1:500
South America	1:2500
Central America and the Caribbean	1:10 000

A suggested template of a comprehensive medical and travel history is available on Page 14 of the 2007 edition of the HPA Malaria Guidelines, available at [http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1203496943315]. Using this template will ensure that the physician is aware of background medical problems which may affect the choice of chemoprophylactic agent.[1]

Despite applying effective anti-mosquito measures and good compliance to chemoprophylaxis, women can still contract malaria. Education about the symptoms of malaria (such as a fever or flu-like illness) is beneficial to travellers: it enables them to realise that they need to seek medical attention without delay and to state that they have travelled to a malarious area. Worryingly, some migrant groups and their families do not access effective antimalarial prophylaxis.[8] Adults travellers born in Africa were reported to hold a belief that malaria was trivial or that they were protected from severe malaria.[33,34] It is important to challenge and advise on misconceptions. Awareness of the risk is vital. Women may find the websites listed in Box 1 useful to learn about malaria for travellers and to reinforce the points already made to them.

5.3 How should bites be prevented?

Inform women about bite prevention measures, including skin repellents, knock-down mosquito sprays, insecticide-treated bed nets, clothing and room protection. **A**

The anopheline mosquito has different preferred biting times in different parts of the world but making the assumption that the risk period is from dawn to dusk will suffice.[35,36] In pregnancy, other mosquito-borne diseases, such as dengue, which is caused by a daytime-biting mosquito, should be prevented, so applying mosquito bite prevention measures 24 hours a day is advisable.

Repellents – the evidence favours skin repellents containing 50% DEET

A solution of 20% DEET (N,N-diethyl-m-toluamide or N,N-diethly-3-methyl-benzamide) was applied to the exposed areas of the arms and legs twice daily in pregnant women (second and third trimesters) as part of a randomised controlled trial of prevention of malaria.[37,38] Pregnancies were followed prospectively and there were no adverse effects noted for the woman or fetus but DEET was detected in 8% of cord bloods examined after spontaneous birth. There are no specific data on the safety of DEET in the first trimester of pregnancy but it is estimated to have been used by millions since 1956 and about 30% of the American population every year with no apparent adverse effects.[39,40] In addition, there is no evidence of reproductive or developmental toxicity in rats.[41] As the consequences of malaria in pregnancy can be devastating and higher concentrations

Evidence level 1+

Box 1. Websites for pregnant (or intending to become pregnant) travellers to learn about malaria

Patient UK [www.patient.co.uk/health/Malaria-Prevention.htm]
Supports the measures recommended by the Advisory Committee on Malaria Prevention in UK Travellers and the Health Protection Agency and is available in a patient friendly format with printouts.

Health Protection Agency [www.hpa.org.uk/HPA/Topics/InfectiousDiseases/InfectionsAZ/1191942128239]
General information, news and guidelines.

Centers for Disease Control and Prevention, USA [www.cdc.gov/malaria]
Various informative resources. The website also presents a realistic cautionary tale of a pregnant woman of 19 weeks on a trip from USA to Sierra Leone for a family crisis. [http://www.cdc.gov/malaria/stories/malaria_travel_pregnancy.html]. There is also an interactive malaria map [https://www.cdc.gov/malaria/travelers/about_maps.html]

Health Link British Columbia [www.healthlinkbc.ca/healthfiles/hfile41f.stm]
Gives good general advice on travel for pregnant women and is available in English, French, Chinese, Punjabi, Spanish, Vietnamese.

Malaria Hotspots [www.malariahotspots.co.uk/facts-maphotspots.asp]
Dynamic website with interactive malaria world map, malaria myths, FAQs and even a test of knowledge. Not specific for pregnancy but good general principles.

Nobel Prize.org [http://nobelprize.org/educational_games/medicine/malaria]
An interactive malaria games and a brief about malaria. Not specific to pregnancy.

give longer protection, 50% DEET is recommended.[1] In a sweaty environment, the effect of repellent is lowered and more frequent applications are required. There are few alternatives when 50% DEET is not tolerated, including PMD [p-methane 3,8 diol], IR3535 [3-ethlyaminopropionate], picaridin 20% [KBR3023(2-(2-hydroxyethyl)-1-piperidinecarboxylic acid 1-methylpropylester)] and these are all less effective than DEET and require more frequent applications.[42–45] Evidence demonstrates that not wearing repellent in a group where others do puts a person at more risk of being bitten.[46]

Evidence level 1+

Knock-down mosquito sprays: permethrin and pyrethroids sprays kill resting and flying mosquitoes

Whether women stay in air-conditioned hotel rooms or tents, a can of insect spray active against mosquitoes is useful to help clear the room of mosquitoes. Pyrethroids will quickly kill mosquitoes and are the preferred ingredient in sprays,[47–50] while permethrin will both repel and kill mosquitoes when used regularly in the same room.[51–54]

Evidence level 2+

Insecticide treated bed nets: long lasting pyrethroid-impregnated bed nets offer significant protection

Women sleeping outdoors or in unscreened accommodation should use long-lasting pyrethroid-impregnated nets. If the net is not long-lasting it needs reimpregnating every 6 months, starting from the first date on which the net is used after purchase. The use of bed nets by pregnant women in endemic areas has been studied for both efficacy and safety in large numbers of women,[55–61] with reassuring results. Nets are now recommended by the World Health Organization for all pregnant women in malaria-endemic areas.[62] Long pyrethroid insecticide treated bed nets, without tears and well tucked in under mattresses or mats, are estimated to offer a protective efficacy of 50%.[63] Again, travellers in groups where some have nets and others in the room do not are likely to be at higher risk of being bitten.[64] Permethrin-impregnated hammocks are another possibility.[65,66]

Evidence level 1++

Clothing that covers the body and forms a barrier from biting mosquitoes will reduce the risk of malaria

After sunset, long sleeves, long trousers, loose-fitting clothing and socks, regardless of colour, are recommended. Clothes can be impregnated with permethrin or permethrin or DEET can be sprayed on to the clothes.[67–72] Studies by the military demonstrate absorption of permethrin from clothes but levels are within safe limits.[73]

Evidence level 1-

Room protection: electrically heated mats will kill mosquitoes in the room

If electricity can be relied upon, an electrically heated device that vaporises synthetic pyrethroids from a mat tablet can kill mosquitoes.[74,75] A supply of mats is required, as new mat is needed each night. While mosquito coils could be used as an alternative, they are not as effective and not recommended indoors.

Evidence level 2+

There is a growing trend among pregnant women to use herb-based remedies for many aspects of pregnancy care.[76–78] There is no evidence that any of the following offers sufficient protection from malaria to advocate their use: herbal remedies, homeopathy, buzzers, wrist and ankle bands, vitamin B1, garlic, yeast extracts, tea tree oil and bath oils.[1,29] While citronella has repellent properties, the effects are too short-lasting to recommend its use.[79]

5.4 Which drug can be recommended for malaria prevention in pregnancy?

Inform women (and their general practitioner) of the risks and benefits of chemoprophylaxis versus the risks of malaria. **A**

Remind women that there is no malaria prophylaxis regimen that is 100% protective. **A**

The choice of drug and advice about chemoprophylaxis in pregnant women depends on the level of chloroquine-resistant *P. falciparum* and *P. vivax* malaria and the trimester of pregnancy. There are malaria prevention guidelines produced for travellers who are UK residents and these are detailed: by country and popular destination and updated regularly.[1] It is not the aim of this guideline to reproduce these guidelines here. They can be directly accessed on the Health Protection Agency website [www.hpa.org.uk/HPA/Topics/InfectiousDiseases/InfectionsAZ] and clicking on malaria. Updates to guidelines, such as change in resistance or transmission, can be found at the same place.

Chemoprophylaxis for malaria can be causal or suppressive. Causal prophylaxis is directed against liver schizont stage, which takes approximately 7 days to develop so these drugs (for example, atovaquone-proguanil (Malarone®) need to be continued for 7 days after leaving a malarious area.[80] Suppressive prophylaxis (such as mefloquine) is directed against the red blood cell stages of the malaria parasite and so should be continued for 4 weeks after leaving a malarious area.[81] The full listings of drug actions, dosages, adverse effects, interactions and contraindications is contained in the British National Formulary [www.bnf.org] and will not be repeated here. Women should be warned that drugs purchased in endemic countries or over the internet may be cheaper but they may be fake.[82-84]

Evidence level 1+

5.4.1 Chemoprophylaxis for women planning a pregnancy

Women planning pregnancy and travelling to a destination where there is a risk of contracting malaria should be advised there may be harmful consequences for the pregnancy. Prophylaxis is not 100% effective and malaria is associated with increased risk of miscarriage. Women should be advised not to travel or to choose an alternative destination. If it not possible to delay either the pregnancy or the travel plan, advice from a specialist with current experience of malaria should be sought (Box 2). Chloroquine and proguanil are not efficacious in chloroquine-resistant areas and cannot be recommended because of this.[85] There are very few chloroquine-sensitive areas remaining.

To avoid completely any potential adverse drug effects from preconceptual and first-trimester exposure, it is advisable to wait for complete excretion of the drug, if it was taken for prophylaxis, before becoming pregnant (Table 3). Nevertheless, unplanned conception while taking malaria prophylaxis is not considered a reason to recommend termination of pregnancy, owing to the low risk of teratogenicity.

5.4.2 Chemoprophylaxis for pregnant or breastfeeding women

Mefloquine (5mg/kg once a week) is the recommended drug of choice for prophylaxis in the second and third trimesters for chloroquine-resistant areas. With very few areas in the world free from chloroquine resistance, mefloquine is essentially the only drug considered safe for prophylaxis in pregnant travellers (Table 4).[7]

The majority of observational and clinical data, mostly second and third trimesters, suggest that the drug does not result in an increased risk of stillbirth or congenital malformation at prophylactic doses.[104,108,109] One study found an association with increased risk of still birth at treatment doses (25 mg/kg) for chloroquine-resistant *P. falciparum* malaria[110] but other studies where the drug has been

Evidence level 1-

Box 2. Expert centres in the UK on chemoprophylaxis

Malaria Reference Laboratory [www.malaria-reference.co.uk]
Possible to send risk assessment via fax (template available on website) and receive results in 3 days.
Tel: 020 763 70248.

National Travel Health Network and Centre [www.nathnac.org]
Advice line for healthcare professionals.
Tel. 0845 602 6712.

Liverpool School of Tropical Medicine [www.liv.ac.uk/lstm]

TRAVAX: the A–Z of Healthy Travel (Health Protection Scotland and NHS Scotland) [www.travax.nhs.uk]

Table 3. Suggested waiting times before becoming pregnant, with animal and human first-trimester data on teratogenicity

Drug	Estimated half life	Excretion time	Data	
			Animal	Human
Mefloquine	14–21 days	3 months	Skeletal and muscular malformation in rats at 5–20 times the therapeutic dose[87]	Post-marketing surveillance system of the manufacturer (Hoffman-LaRoche) or case reports focusing on the effects of mefloquine prophylaxis[88–90] do not support the hypothesis that mefloquine is associated with embryo toxicity even in the first trimester [Evidence level 1–]
Doxycycline	12–24 hours	1 week	Chick embryos: abnormal skeletal development and reduced fetal growth;[91] rats: discolouration of the lens[92]	Disturbances of bone growth of the fetus; congenital cataract[92] [Evidence level 3]
Malarone ® Atovaquone	2–3 days	2 weeks	No teratogenicity shown in animal studies with the combination of both drugs[93]	Three women inadvertently exposed at the time of conception, all with normal pregnancy outcomes[94] [Evidence level 3]
Proguanil	14–21 hours	1 week		Proguanil as chemoprophylaxis in pregnant women demonstrated no evidence of toxic fetal effects after decades of use;[95] cycloguanil, the active metabolite of proguanil, is toxic at the stage of cleavage of the ovum[96] [Evidence level 3]
Chloroquine	1–2 months	Not applicable	Embryotoxicity in rat culture at doses close to therapeutic range, including developmental abnormalities of neural tube; micro-ophthalmia and optic primordium;[97] altered cranial neural tube development and morphology of neural crest cells[98,99]	No adverse effects in first trimester reported from malaria literature[100-107] nor from a meta-analysis on women treated with high doses of hydroxychloroquine for autoimmune disease[108] Evidence level 1++]

used for treatment or intermittent preventive treatment or in combination with artesunate have not reported this association.[109-114] The use of mefloquine in the first trimester may still be justified in areas of high risk of acquiring falciparum malaria. In the UK, this can be discussed with a specialist with current experience of managing malaria (Box 2). There are strict contraindications to mefloquine, including current or previous history of depression, neuropsychiatric disorders, epilepsy or hypersensitivity to quinine or mefloquine.[1]

Evidence level 1-

Table 4. Dosing regimen for chemoprophylaxis in pregnancy

Regimen	Dose for chemoprophylaxis	Usual amount/tablet (mg)	P. falciparum resistance n
Mefloquine	1 tablet weekly	250	Chloroquine resistant
Atovaquone-proguanil[a]	1 tablet daily	250 atovaquone + 100 proguanil	Chloroquine resistant & mefloquine not tolerated or contraindicated **OR** Mefloquine resistant
Proguanila plus chloroquine	2 tablets daily plus 2 tablets weekly	100 proguanil + 150 (chloroquine; base)	No chloroquine resistance

[a] Folic acid supplements (5 mg daily) need to be taken if proguanil is used in those who are pregnant or seeking to become pregnant

Atovaquone and proguanil (Malarone®) is potentially a good candidate for prophylaxis in the second and third trimesters but it is not recommended, owing to insufficient data on its safety in pregnancy.[115] To date, only treatment data on pregnant women have been published; the drug was effective and well tolerated with no adverse effects detected.[93,116–119] If travel to a chloroquine-resistant area is essential in pregnancy and mefloquine cannot be tolerated or is contraindicated, atovaquone and proguanil use can be considered in consultation with a specialist with current experience of managing malaria (Box 2).[7]

Evidence level 3

Doxycycline and primaquine are contraindicated as chemoprophylaxis in pregnant women. Doxycyline has been reported to disturb bone growth of the fetus[120] and to cause irreversible teeth coloration when given in the third trimester[121] and congenital cataract has been reported.[122] Primaquine can cause haemolysis, particularly in G6PD deficiency. Fetal red blood cells are more sensitive to haemolysis and the G6PD status of the fetus cannot be determined.[123,124]

While chloroquine and proguanil are safe, they are no longer efficacious in areas of chloroquine resistance and provide women with suboptimal prophylaxis if recommended.[1]

Evidence level 1+

Recommendations for breastfeeding mothers are the same as for pregnancy. There are few data on the use mefloquine during breastfeeding[125] and, while it is excreted into breast milk in small amounts, there are not enough data to draw conclusions regarding harm.[126]

Evidence level 3

Atovaquone and proguanil may also be considered in consultation with an infectious diseases physician for a pregnant woman travelling to a mefloquine-resistant area.[7]

5.5 Emergency standby treatment in pregnancy?

Written instructions should be given to a pregnant traveller regarding emergency standby malaria treatment in the event of suspected malaria without access to medical care. **D**

Suspected malaria is a medical emergency and women should seek diagnosis and treatment at a health facility at the earliest opportunity.[1,28] Early diagnosis and stand-by emergency treatment have been promoted in the event of remote travel without access to medical care within 24 hours of symptoms. In theory, this should be an extremely rare situation in pregnant women, as this type of travel could be hazardous in pregnancy. Owing to reports of the misuse of standby treatment[127,128] and the importance that it is given correctly, written instructions should be issued. An example template is available from the Health Protection Agency Malaria Guideline, on page 54 of the 2007 edition [www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1203496943315?p=1249920576136].[1]

Evidence level 3

Standby treatment should be started if malaria is suspected (flu-like illness) and temperature is 38°C or above. Medical treatment for a full medical evaluation and, in the event that the fever has another cause, must be sought at the earliest possibility. Antipyretics should be used for fever. The only recommended treatment in the UK for pregnant women is quinine (300 mg tablets, two tablets three times a day for 7 days) and clinda-mycin (150 mg capsules, three capsules three times a day for 5–7 days). If a dose is vomited within 30 minutes, the full dose should be repeated and if the dose is vomited after 30–60 minutes, half the dose should be repeated. The treatment should be finished and mefloquine should be commenced 1 week after the last treatment dose.

Drugs that are highly efficacious and well tolerated are likely to be the best candidate drugs for stand-by emergency treatment. Quinine may be efficacious in most parts of the world but it is not well tolerated. Co-artem (Riamet®) or atovaquone-proguanil (Malarone®) (if not used as prophylaxis) could be used as stand-by emergency treatment and evidence to support the use of these drugs in uncomplicated malaria in pregnancy is detailed in Part B of this guideline.[129]

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APPENDIX

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Development of RCOG Green-top Guidelines* (available on the RCOG website at **www.rcog.org.uk/womens-health/clinical-guidance/development-rcog-green-top-guidelines-policies-and-processes**). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated within the appropriate health services.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme. Once adapted for local use, these guidelines are no longer representative of the RCOG.

Classification of evidence levels

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies; e.g. case reports, case series

4 Expert opinion

Grades of recommendations

A At least one meta-analysis, systematic reviews or randomised controlled trial rated as 1++ and directly applicable to the target population; or
A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

Good practice point

✓ Recommended best practice based on the clinical experience of the guideline development group

This Guideline was produced on behalf of the Guidelines Committee of the Royal College of Obstetricians and Gynaecologists by: Dr R McGready PhD Dip RANZCOG, Mae Sot, Thailand; Dr EA Ashley PhD, London; Professor F Nosten MD PhD, Mae Sot, Thailand; Dr M Rijken MD PhD, Mae Sot, Thailand.

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The Guidelines Committee lead peer reviewers were: Dr ALM David MRCOG, London, and Professor F McAuliffe FRCOG, Dublin.

The final version is the responsibility of the Guidelines Committee of the RCOG.

The guideline review process will commence in 2013
unless otherwise indicated

