

Case management of malaria in pregnancy

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In all malarious areas, infection by any of the main human plasmodial species during pregnancy is detrimental to the mother and the fetus. These potentially fatal infections must be prevented, but when they develop they require prompt diagnosis and treatment. Current tools to detect malaria parasites in pregnant women are often not used and remain too insensitive to detect a low parasitaemia. The kinetics, safety, and efficacy of available antimalarial drugs are poorly documented because pregnant women are systematically excluded from clinical trials. A considerable effort, involving clinical trials, is urgently required to improve the diagnosis and case management of malaria during pregnancy if the morbidity and mortality of maternal malaria is to be reduced.

Introduction

Malaria, the most common human parasitic disease, is both preventable and treatable, but continues to kill disproportionately children and pregnant women. In all malarious areas, infection by any of the main human plasmodial species during pregnancy is detrimental to the mother and the fetus. These potentially fatal infections must be prevented, but when they develop they require prompt diagnosis and treatment. The most deleterious effects on the mother are caused by *Plasmodium falciparum* and their nature depends in part on her background premunition: in areas of high transmission, severe anaemia is most common and associated with mortality, whereas in areas of low transmission or in epidemics, pregnant women are at high risk of severe and cerebral malaria and death.^{1–3} Millions of pregnant women are exposed to malaria and thousands die every

year as a direct or indirect consequence. In all endemic areas, babies born to mothers infected with malaria parasites (whether or not maternal symptoms are detected) have a lower birthweight and are therefore also at increased risk of death in infancy.⁴ Hence, to treat effectively pregnant women who are infected with plasmodium parasites is essential. Unfortunately, cheap, safe, and effective drugs (eg, chloroquine) have globally lost their efficacy against *P falciparum* and in some areas against *Plasmodium vivax* as well. Sulfadoxine-pyrimethamine is either already lost to resistance of *P falciparum* or increasingly compromised, even in Africa.⁵ There are few alternative drugs with known safety and efficacy because pregnant (and lactating) women are systematically excluded from treatment studies.

This paper addresses the questions of safety and efficacy of antimalarials used to treat malaria infection in the mother, whether it is detected actively or passively, for *P falciparum* and other plasmodial species. We discuss what is known and done about the diagnosis and treatment of malaria in pregnancy and what needs to be studied to improve case management on the basis of the new WHO treatment guidelines.⁶

Current knowledge and practices

Diagnosis of malaria in pregnancy

In most malaria endemic regions, pregnant women do not have access to parasitological diagnosis or even to treatment. In areas of high transmission, to leave parasitaemic but asymptomatic adults untreated is common practice. The assumption is that the natural immunity of such individuals will control the infection. However, in pregnant women, the presence of malaria parasites—even transient and without symptoms—is harmful for the mother and the fetus, whether or not placental malaria is detected at delivery.³ The biological diagnosis of malaria during pregnancy is also essential to avoid unnecessary exposure of the mother and the fetus to antimalarials drugs. New treatments for malaria are more expensive and to confirm the diagnosis of malaria before treatment is cost effective, especially if one takes into account the added risks—both morbid and iatrogenic—to the fetus.

The confirmation of malaria infection can be done either by microscopic examination (the current gold



Figure 1: Weekly antenatal clinic in a Karen refugee camp

standard) or by use of a rapid diagnostic test that detects a specific parasite antigen. An experienced and well equipped microscopist can detect 15 parasites per μL of blood. In most non-pregnant cases of malaria, this is well below the pyrogenic density threshold above which patients present with symptoms. However during pregnancy, asymptomatic low parasite densities and parasites sequestered in the placenta are harmful to the mother and the fetus, so the sensitivity of microscopy is insufficient in these cases. Together with the practical constraints of microscopy, this lack of sensitivity impairs the detection of pregnant women who need treatment and the assessment of the efficacy of antimalarials. More recently, rapid diagnostic tests have been developed. Such tests are practical but do not have the sensitivity needed in pregnancy. PCR is used in research settings for genotyping and detection of malaria parasites and is marginally more sensitive than microscopy.

A microscopic blood examination or a rapid diagnostic test can be done either because a pregnant woman presents with symptoms (or a history of symptoms) compatible with malaria, or as part of a systematic antenatal screening (bearing in mind the limitations in detection). In all malarious areas, every time a pregnant woman is seen in an antenatal consultation, a blood test for malaria should be done and positive cases treated appropriately (figure 1). In areas of intense and stable transmission, the absence of evidence of plasmodia in the peripheral blood on a single occasion does not exclude infection. Parasitaemia can fluctuate and be kept under the level of detection (total biomass about 10^8 parasites) by acquired immunity or self-medication, and *P. falciparum* can sequester in the placenta. These factors complicate the assessment of the efficacy of antimalarial drugs and underline the need for more sensitive diagnostic tools. The earlier in the pregnancy and the more frequent the antenatal consultations and blood screening, the more likely a malaria parasitaemia will be detected and treated. This early detection and treatment have been shown to reduce the placental malaria burden, a key step in reducing the harmful effects on the fetus.⁷ In the presence of a well implemented, effective, and safe prevention strategy (intermittent preventive treatment and vector control), the frequency of antenatal visits could be limited. Only four antenatal visits are recommended in the newly introduced approach⁸ of focused antenatal care in sub-Saharan Africa, and this new strategy should include parasitological diagnosis. Pregnant women can still develop malaria between focused antenatal care visits, and the health system must allow them access to prompt, reliable diagnosis and safe, effective treatment.

Treatment of non-falciparum species

Little is known about the effects of non-falciparum plasmodial species on the mother and the fetus except

for *P. vivax*; however, to assume that the other two species have similar effects is reasonable.^{9,10} Pregnant women infected with *P. vivax*, *Plasmodium ovale*, or *Plasmodium malariae* must be treated with an effective drug. Chloroquine (25 mg/kg base) is safe in all trimesters and effective to treat episodes of non-falciparum malaria,¹⁰ with the exception of *P. vivax* in south Asia (Indonesian archipelago) where there is high grade resistance.¹¹ Evidence for the safety of chloroquine during pregnancy comes from studies of systemic diseases^{12,13} rather than from studies of malaria treatment,¹⁴ and over 700 first trimester exposures have been reported without apparent adverse effects.¹⁵ The main adverse effect attributable to chloroquine in pregnancy in Africans is pruritus,¹⁶ but overall the drug is deemed to be safe for pregnant women. Chloroquine was effective against *P. vivax* in a recent double-blind placebo controlled trial in Thailand.¹⁷ Weekly chloroquine was well tolerated by the mothers and had no adverse effect on pregnancy outcomes and the development of infants in the first year of life. Amodiaquine is also effective against non-falciparum species but data on efficacy and safety in pregnancy are insufficient,¹⁸ although a recently published large trial provided reassuring evidence of the safety of amodiaquine in pregnancy.¹⁹ However, this drug must not be given as prophylaxis because of the risk of agranulocytosis.²⁰ Primaquine—the only available drug effective on the liver stages of the parasite—is contraindicated in pregnancy and in lactating women because of the susceptibility of fetal red blood cells to haemolysis.²¹

Treatment of falciparum infections

Infections caused by *P. falciparum* are mostly responsible for the excessive malaria-related mortality and morbidity in mothers and infants, especially when not treated adequately. The choice of antimalarials is made difficult because of the spread of drug resistance in *P. falciparum* (figure 2) and also because most drugs carry a contraindication warning for pregnancy in the labelling of the manufacturer.

Uncomplicated infections

Pregnant women infected with *P. falciparum* must be treated without delay, whether or not they are symptomatic. This approach stops the progression of malaria to symptomatic or severe infection and reduces—but does not completely eliminate—maternal anaemia. By clearing the placenta of parasites, prompt treatment also reduces the insult to the fetus. Chloroquine (and, in some areas, sulfadoxine-pyrimethamine) is no longer effective but it is still widely prescribed and used because it is cheap and easily available. Like chloroquine, sulfadoxine-pyrimethamine is generally regarded as a safe drug despite evidence of toxicity in preclinical studies.^{22,23} The most common side-effects associated with sulfadoxine-pyrimethamine are gastrointestinal and



Figure 2: Karen pregnant women with multidrug-resistant *P falciparum* malaria

cutaneous (when used as a prophylactic).²⁴ In pregnancy, sulfadoxine-pyrimethamine is used for treatment and in the intermittent preventive treatment strategy.^{25–27} The drug has not been associated with adverse effects on the fetus and is well tolerated by mothers. The efficacy of sulfadoxine-pyrimethamine is reduced by folate (5 mg daily).²⁸ Although the drug has been used for decades, there are no data on the pharmacokinetics in pregnancy, so the optimum dose is unknown.

The fast expansion of resistant isolates has compromised the use of sulfadoxine-pyrimethamine in many areas. Instead, quinine with clindamycin has a proven high efficacy against multidrug-resistant strains of *P falciparum*.²⁹ Clindamycin has a good safety record³⁰ and its pharmacokinetic properties are unchanged by pregnancy.³¹ This combination is recommended in the first trimester, while an effective artemisinin-based combination therapy (ACT) in the second and third trimesters should be the preferred first-line treatment, in line with WHO guidelines (panel 1).⁶

Evidence for the safety of quinine in pregnancy is mostly historical and there are few clinical trials published. The most common adverse effects of quinine are tinnitus, dizziness, and hypoglycaemia,^{32,33} and the experience with first-trimester exposure is restricted to 368 published cases.¹⁵ The decline of quinine efficacy in pregnancy in southeast Asia is worrying^{29,33} and could be caused by altered kinetics of quinine in pregnancy as well as decreased parasite sensitivity.

Panel 1: Current recommendations for case management⁶

Uncomplicated falciparum malaria

First trimester

- First episode: quinine 10 mg/kg three times a day for 7 days, preferably with clindamycin 5 mg/kg three times per day for 7 days.
- Subsequent episodes: repeat treatment with quinine and clindamycin (as above); ACT that is locally effective; or artesunate 2 mg/kg per day for 7 days with clindamycin (as above).

Second and third trimesters

- First episode: ACT that is locally effective or artesunate plus clindamycin (as above).
- Subsequent episodes: artesunate plus clindamycin as above; or quinine plus clindamycin as above.

Prevention

- Intermittent preventive treatment with sulfadoxine-pyrimethamine where efficacy remains.

Severe malaria

- Artesunate 2–4 mg/kg intravenously at hour 0, 12, and 24 and continued every 24 h until the patient can tolerate oral artesunate 2 mg/kg per dose, for a total of 7 days, and clindamycin 5 mg/kg three times daily for 7 days.

Or

- Intravenous quinine: loading dose 20 mg/kg given over 4 h, then 10 mg given 8 h after the loading dose was started, followed by 10 mg/kg every 8 h for 7 days. Once the patient has recovered sufficiently to tolerate oral medication both quinine 10 mg/kg and clindamycin 5 mg/kg, three times daily should be continued for 7 days.

Non-falciparum malaria

- Chloroquine phosphate (one tablet contains 250 mg salt, equivalent to 155.3 mg base). Dose is 10 mg/kg base once a day for 2 days followed by 5 mg/kg base on third day. For chloroquine-resistant *P vivax*, amodiaquine, quinine, or artemisinin derivatives can be used.

Prevention

- Chloroquine phosphate 600 mg base on admission followed by 300 mg base per week.

The use of ACT is supported by clinical evidence of the safety and efficacy of artemisinin derivatives in over 1000 pregnant women.^{29,34–41} However, there are only 124 reported cases of first trimester exposures and there are concerns from animal data on the safety of artemisinin derivatives in the first weeks of gestation.⁴² In the largest reported series of artesunate in pregnant women (539 treatments) there were remarkably few adverse effects attributable to artesunate (mild pruritus in 0.20% of treated women³⁶). Doses of artesunate given in pregnancy vary from 4 mg/kg single dose³⁵ to multiple 12–16 mg/kg total dose treatments given over 3–7 days, within the same pregnancy,³⁷ with no adverse effects seen to the mother or the fetus. However, the pharmacokinetics

of artesunate are altered in pregnancy, which could have a negative effect on efficacy.⁴³ Data on adherence to artesunate in pregnant women remains scarce but, in the reported series, non-compliance could not be related to drug side-effects.³⁶

Mefloquine is effective against chloroquine-resistant parasites and has been used extensively in Asia for over 20 years. The drug's most common side-effects are neurological and gastrointestinal.²⁴ Resistance to mefloquine has emerged in Asia and South America, and it is now recommended for use in combination with artesunate. Mefloquine has been used in pregnancy and was shown to be effective for the prevention of *P falciparum* and *P vivax* malaria.⁴⁴ In treatment, mefloquine was also effective and well tolerated by pregnant women either as monotherapy⁴⁴ or combined with artesunate,³⁴ but in one retrospective study it was associated with an increased risk of stillbirth.⁴⁵ However, this was not found in a study in Malawi.⁴⁴ The long elimination of mefloquine makes it a good candidate for intermittent preventive therapy, but the pharmacokinetics of the drug are altered in pregnancy and the doses might have to be adjusted.⁴⁶

Atovaquone-proguanil (malarone) is an effective—albeit very expensive—treatment for falciparum infections. The drug is well tolerated and has been shown to be effective as prophylaxis.⁴⁷ The main weakness of this drug is the rapid emergence of resistance in *P falciparum* caused by a single mutation, and it should be combined with an artemisinin derivative.⁴⁸ This triple combination was used to treat multidrug-resistant infections in pregnancy, without apparent deleterious effects to the mothers and infants, but numbers of women treated were small.^{37,49} As with other antimalarials, the pharmacokinetics of atovaquone are modified by pregnancy and the doses will have to be adjusted.⁵⁰ The hormone-induced reduction in the biotransformation of proguanil to the metabolically active cycloguanil in pregnancy might not be crucial since it is the parent compound (proguanil) that increases the activity of atovaquone.

Chlorproguanil-dapsone (Lapdap) is a newly developed antimalarial active against chloroquine-resistant parasites. Both drugs have been used separately and in combination and are generally well tolerated. Their main side-effects are gastrointestinal (proguanil) and haematological (dapsone). In pregnancy, proguanil is deemed to be safe but there are insufficient data on dapsone to estimate the risk or benefit to the mother and the fetus.⁵¹ There is only one published trial on the use of chlorproguanil-dapsone in pregnancy. The drug was safe and more effective than chloroquine to treat Kenyan pregnant women but the outcomes of pregnancy were not reported.⁵² In view of the changes in the metabolism of proguanil during pregnancy and the need to increase its dose by 50%,⁵⁰ there are concerns over the toxicity of dapsone in a fixed combination.

Severe and complicated malaria

Pregnant women with weak natural immunity are particularly at risk of severe and complicated malaria caused by *P falciparum*. Maternal mortality is higher than in non-pregnant patients. Major complications often seen in pregnant women include hypoglycaemia, adult respiratory distress syndrome, and fetal loss is usual. Intensive care and prompt parenteral antimalarial treatment are crucial to the mother's survival. For decades the recommended drug has been parenteral quinine (with a loading dose) but this drug frequently causes hyperinsulinaemia and hypoglycaemia in pregnant women with severe malaria.⁵³ Artesunate and artemether are now recommended to treat pregnant women with severe malaria because they are faster acting and do not cause hypoglycaemia.⁶ In a randomised trial, intravenous artesunate (2.4 mg/kg initial dose and at 12 h, followed by 2.4 mg/kg daily) reduced mortality in Asian adults (including 49 pregnant women) by 34%, compared with quinine.³⁹ Intramuscular artemether can also be used to treat severe malaria, but absorption is less predictable than that of artesunate, especially in patients with cardiovascular collapse.

Other aspects of case management

Severe anaemia without evidence of parasitaemia

In 2002, the Strategic Framework for Malaria Control during Pregnancy in the Africa Region⁵⁴ recommended that pregnant women with severe anaemia from a malaria-endemic area be treated presumptively with an effective antimalarial, whether or not peripheral parasitaemia is present or whether or not there is a history of fever. The recommended drugs were chloroquine in chloroquine-sensitive areas and sulfadoxine-pyrimethamine in areas with chloroquine resistance. Quinine is an alternative in areas where both chloroquine and sulfadoxine-pyrimethamine are not effective, but adherence is poor. Unfortunately, within a few years of this recommendation being made, drug resistance to both chloroquine and sulfadoxine-pyrimethamine had increased and spread dramatically, and WHO now recommends ACT for malaria treatment.⁶ Pregnant women with severe anaemia and who live in areas where the risk of *P falciparum* infections is high should receive an ACT (even in the absence of parasitaemia) in the last two trimesters and quinine (or another effective antimalarial) in the first trimester.

Supportive treatments

Pregnant women with moderate anaemia should receive folic acid and iron. However, there are concerns that this practice could increase the risk of malaria,⁵⁵ including infections caused by *P vivax*.⁵⁶ This effect was not confirmed for *P falciparum* in a study in the Gambia,⁵⁷ but pregnant women with the haemoglobin genotype AS might not benefit from iron supplementation.⁵⁸ Pregnant

women with severe anaemia living in a high transmission area should be treated for malaria as well as receiving screened blood.

WHO recommends the systematic use of anthelmintics in pregnancy (in the second and third trimesters), even though the supportive evidence is limited.^{59,60}

Estimating gestation before treatment

The relative efficacy and safety of antimalarials during pregnancy are poorly documented; therefore, most antimalarials (with the exception of quinine, proguanil, chloroquine, and clindamycin) must be avoided during the first trimester unless there is a clear benefit for the mother. Any female of child-bearing age, in any country, should be asked about the possibility of pregnancy before receiving antimalarial drug treatment as part of normal routine case management. If there are doubts, palpating for a fundus, or doing a urine or blood pregnancy test are useful. To estimate correctly the gestational age is essential. Gestational age can be estimated with the last normal menstrual period, ultrasound scanning, fundal height, or a combination of these methods.

Critical gaps in knowledge

Diagnosis of malaria (and of pregnancy): can the sensitivity of biological testing be improved?

As long as we are unable to reliably confirm that a pregnant woman is infected with malaria parasites, the approach to case management in pregnancy will be difficult. Except when the treatment occurs near delivery, to know whether the current antimalarial regimens are able to clear placental parasites will be impossible.

Another critical question is whether pregnant women with placental malaria (and an effective natural immunity) become transiently parasitaemic during pregnancy. Longitudinal cohort studies are required to answer this question, and more sensitive diagnostic tools must be developed.

Treatment of non-falciparum malaria

The dispositions of chloroquine and amodiaquine in the treatment of non-falciparum malaria in pregnancy are not documented. Whether these drugs can be used as intermittent preventive therapy for *P vivax* in pregnancy is unknown. For chloroquine-resistant *P vivax*, the optimum treatment is unclear. Quinine, mefloquine, amodiaquine, dihydroartemisinin-piperaquine, or artesunate are probably effective, but there are no studies reported and there are concerns about the safety of mefloquine and the artemisinins. Also unknown is the treatment of the hepatic stages of *P vivax* and *P ovale* infection, since primaquine cannot be used. This drug mainly affects fetal red blood cells and is found in breast milk. Primaquine's efficacy, kinetics, and safety in the postpartum period and in lactating women need to be studied.

Uncomplicated falciparum malaria

Because of parasite resistance and the absence of clinical trials in pregnancy, there is currently no satisfactory (ie, safe and effective) antimalarial that can be used for prevention, which represents a serious gap in knowledge and makes the detection and treatment of infected pregnant women even more crucial. Even when effective treatments exist, the question is: how effective are these treatments in pregnancy? This question is difficult to answer because of placental sequestration of parasites and the modified pharmacokinetics of most (if not all) antimalarials. The correct doses of all antimalarial drugs need to be established for pregnant women, given that pregnancy alters their dispositions and blood concentrations tend to be substantially lower than in non-pregnant patients. The safety for the fetus of most antimalarials is unknown, especially when the exposure occurs in the first trimester—ie, during organogenesis—which is of particular concern for artemisinin derivatives and for mefloquine. These uncertainties make the choice of a second-line treatment or the choice of a drug for intermittent preventive treatment difficult in the early stages of pregnancy, because the data to determine the risk–benefit to the mother and fetus are non-existent.

Treatment of severe and complicated malaria

The optimum maintenance therapy, once the patient has recovered consciousness, is still to be determined. Whether pregnancy termination or exchange transfusion improves the chances of survival of a woman with cerebral malaria remain controversial. The knowledge of pharmacokinetics of parenteral artesunate is urgently needed.

Antimalarial drug	Number of documented* treated cases in pregnancy	Remark	Data on pharmacokinetics (number of women)
Artesunate	1000	Need studies in severe malaria	No
Artemether	100	Need studies in severe malaria	No
Artemisinin	<10	..	No
Di-hydroartemisinin	0	Will be widely use in combination with piperaquine	Yes (24) ⁶³
Piperaquine	0	Candidate for intermittent preventive treatment if safe	No
Mefloquine	1000s	Suitable for intermittent preventive treatment	Yes (29) ^{66,61}
Artemether-lumefantrine	100	On-going assessment	Yes (24) ⁶²
Amodiaquine	<100	Can be used in combination with artesunate	No
Quinine	500	For severe malaria and resistant cases	Yes (10) ⁶³
Sulfadoxine-pyrimethamine	2000	For intermittent preventive treatment	No
Chloroquine	1000s	For non-falciparum malaria	No
Atovaquone-proguanil	100	Very expensive	Yes (50) ^{60,64}

*Published.

Table: Candidate drugs

Discussion

For most of the modern history of malaria therapeutics, to leave pregnant women with malaria untreated was considered acceptable if they did not have symptoms (mostly fever). We now know that this “case mismanagement” has probably resulted, over the years, in tens of thousands of maternal and fetal deaths, especially in Africa. The simple presence of plasmodial parasites in a pregnant woman’s body affects her health and the health of her fetus, regardless of the presence of detectable symptoms. However, detection of a small parasite biomass in a human organism is difficult and sometimes impossible. For this reason, emphasis must be on the prevention of malaria infection. Unfortunately, two independent events have concurred, leading to today’s situation in which no antimalarial drug can reliably and safely protect pregnant women from malaria parasites. On the one hand, the reluctance to treat pregnant women with antimalarials or include them in clinical trials, for fear of adverse consequences on the fetus, means that there is virtually no data on the safety and efficacy of these drugs in this vulnerable group. On the other hand, mutant parasites capable of resisting the cidal activity of many drugs have spread over the malarious world. This vicious circle must be broken.

Before new antimalarials can be used to prevent malaria in pregnant women who are not yet infected, there must be sufficient evidence of their safety and efficacy in women who already have malaria, hence the need for a proper case management strategy. Large multicentre clinical trials are needed to study the kinetics, efficacy, and safety of drugs such as quinine, mefloquine, amodiaquine, and ACTs. The development of stand-

ardised ways of doing such trials (including studies in severe malaria, in lactating mothers, and in non-falciparum infections) is an important research priority. The table shows candidate drugs for use in pregnancy.

At the same time, unnecessary exposures in the first trimester should be avoided and all women of child-bearing age should be asked about the possibility of pregnancy before being prescribed an antimalarial drug. Antimalarials have documented safety profiles for product registration but the extent to which post-marketing surveillance has been mounted varies. Such surveillance is essential for antimalarials since it allows an opportunity to identify rare or unexpected adverse reactions that were not reported during the drug registration process. Since the safety of these products remains a concern, especially during the first trimester of pregnancy, there is an urgent need to concert efforts to mount post-marketing surveillance. These efforts should focus on the outcome of pregnancy in pregnant women exposed to antimalarials during the first trimester. Considering the fact that most African countries adopt malaria treatment policies without a formal approval for use during pregnancy, and that every year millions of women become pregnant, that large numbers of women will be exposed to antimalarials in the first trimester is evident. Therefore, well-coordinated and efficient systems for post-marketing surveillance should be able to generate useful safety data; nevertheless effective post-marketing surveillance is extremely difficult to establish even in developed countries.

Ultimately, the case management of malaria during pregnancy will depend mainly on our ability to diagnose malaria and the best use of the tools currently at our disposal. Improving the quality of malaria diagnosis should therefore also be a research priority (panel 2).

Panel 2: Research priorities and strategies

- 1 Improve and adapt the diagnostic tools to pregnancy (clinical and laboratory studies, involves the industry)
- 2 Establish standard methodology for in-vivo tests in pregnancy (expert/consensus opinion)
- 3 Study the safety and efficacy of antimalarials for the mother and fetus (multicentre clinical trials)
- 4 Study the pharmacokinetics of antimalarials (multicentre clinical trials)
- 5 Drug interactions between antimalarials and highly active antiretroviral therapy (multicentre clinical trials)

Search strategy and selection criteria

For this Review, papers on the treatment of malaria were identified by searching Pubmed with search terms “malaria” AND “pregnancy” AND [treatment OR diagnosis] AND “antimalarials” OR “pharmacokinetics” NOT “preventive”. The references were then searched by individual antimalarial drugs. For treatment trials, particular attention was given to papers reporting pregnancy outcome. Articles in English and French were included, from 1966 to 2006.

Conflicts of interest

We declare that we have no conflicts of interest.

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