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Esperança Sevene, Raquel González & Clara Menéndez

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Current knowledge and challenges of antimalarial drugs for treatment and prevention in pregnancy

Esperança Sevene[†], Raquel González & Clara Menéndez
[†]*Eduardo Mondlane University, Faculty of Medicine, Maputo, Mozambique*

Importance of the field: Malaria infection during pregnancy is a major public health problem worldwide, with 50 million pregnancies exposed to the infection every year. Approximately 25,000 maternal deaths and between 75,000 and 200,000 infant deaths could be prevented each year by effective malaria control in pregnancy. Antimalarial drug treatment and prevention has been hampered by the appearance of drug resistance, which has been a particular problem in pregnancy due to the inherent safety issues.

Areas covered in this review: New antimalarial drugs and combinations are being studied but there is not yet sufficient information on their efficacy or, more importantly, on their safety in pregnancy. This article provides an overview of the relevance of the topic and reviews the current antimalarial drugs recommended for pregnancy, as well as the guidelines for both treatment and prevention in women living in endemic areas and for travellers.

What the reader will gain: Updated information on the drugs currently used for malaria treatment and prevention in pregnancy, including new drugs under development, is provided. The gaps on efficacy and safety information for use during pregnancy are also discussed.

Take home message: Prevention and case management of malaria during pregnancy is based on risk–benefit criteria and poses one of the greatest challenges to current malaria control.

Keywords: drugs, malaria, pregnancy, prevention, treatment

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1. Introduction

1.1 Malaria global distribution

Malaria is the most important protozoan parasitic infection in humans, accounting for nearly one million deaths in 2006 [1]. The World Health Organization (WHO) estimates that half of the world's population is at risk of malaria, sub-Saharan Africa being the region where the infection exacts a major toll.

The parasite is transmitted by the bite of an infected female anopheline mosquito and, once in the body of its human host, migrates through the blood to the liver to invade hepatocytes (**Figure 1**). Five *Plasmodium* species can infect humans: *P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi* [2]; *P. falciparum* is the most virulent. Malaria transmission occurs in sub-Saharan Africa, South East Asia and South America (**Figure 2**). Most of the malaria burden in the world is focused on children younger than 5 years of age and on pregnant women.

1.2 Burden and effects of malaria in pregnancy

About 50 million pregnancies are thought to occur every year in malaria endemic areas [3], and more recent unpublished estimates suggest that this figure may reach

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Article highlights.

- The systematic exclusion of pregnant women from clinical trials has resulted in a lack of information on the safety and efficacy of most antimalarial drugs.
- The choice of antimalarial drugs for malaria treatment and prevention in pregnancy is based on risk–benefit criteria.
- Artemisinin-based combinations are the recommended drugs for treatment in the second and third trimesters of pregnancy; the recommendation for the first trimester has not yet been adequately resolved.
- The increasing emergence of parasite resistance to sulfadoxine–pyrimethamine requires the urgent evaluation of alternative drugs to be used as intermittent preventive treatment for malaria prevention in pregnancy in stable endemic areas.
- To solve the problem of malaria in pregnancy worldwide, research should be focused on the priorities specific for each endemic region. The recent effort from public and private health-funding agencies is going in this direction.

This box summarizes key points contained in the article.

up to 100 million pregnancies (ter Kuile, personal communication). Approximately 25 million pregnancies in the sub-Saharan region are exposed to malaria annually, most of them occurring in high-transmission areas where *P. falciparum* predominates. The rest of the estimated exposed pregnancies occur in regions with low malaria transmission where *P. vivax* infection co-exists with *P. falciparum,* or even predominates [1].

Pregnant women have been said to attract twice the number of mosquitoes than their non-pregnant counterparts and are more likely to develop malaria-related complications [4,5]. The deleterious consequences of malaria in pregnancy (MiP) on infant and maternal morbidity and mortality have been extensively described [6-13]. One of the consequences of MiP is the increased risk of low birth weight (< 2500 g), either through intrauterine growth retardation or preterm delivery [14,15]. As low birth weight is strongly associated with infant survival, it has been estimated that between 75,000 and 200,000 infant deaths could be prevented if MiP control was effective [9]. Furthermore, approximately 15.5% of maternal deaths can be attributed to malaria in endemic regions, and therefore an important impact in the reduction of maternal mortality could be achieved by implementing effective malaria control measures [16,17].

1.3 History of malaria treatment

The first reported antimalarial treatment dates back to the seventeenth century and was based on the powder obtained from the bark of the cinchona tree. This tree is found on the slopes of the Andes and Jesuit priests introduced the use of its bark to Europe. However, it took nearly two centuries to isolate the active principle of the cinchona bark powder: the alkaloid quinine (QN) [18]. In the twentieth century, the development of antimalarial drugs ran in parallel with the military history. QN remained the drug of choice for treating malaria until the end of World War II, when chloroquine (CQ) became the mainstream treatment of the disease due to its effectiveness, safety profile and low cost. CQ was first synthesized in Germany in 1934 and was extensively used worldwide until the spread of CQ-resistant *P. falciparum* parasites in the late 1950s. CQ resistance to *P. falciparum* was first observed in Thailand and around the Colombian–Venezuelan border [19]. Other antimalarial drugs, such as proguanil (PG), amodiaquine (AQ), primaquine (PQ), sulfadoxine–pyrimethamine (SP), halofantrine and mefloquine (MQ), were developed to counter malaria CQ-resistant parasites. Piperaquine (PIP) was discovered in the 1960s and replaced CQ as first-line treatment in China for *P. falciparum* and *P. vivax* malaria in 1978 [20]. CQ resistance was widespread in sub-Saharan Africa by 1989.

Despite the efforts made in the 1950s and 1960s to support the WHO Malaria Eradication Programme, the infection remained neglected by the scientific research community and of the 1393 new chemical entities marketed in the last 25 years of the twentieth century only four were antimalarial drugs [21]. One of the oldest Chinese herbal medicines for treating fevers, the wormwood *Artemisia annua,* has recently been added to the global antimalarial drugs collection. Its active ingredient, artemisinin (or *Qinghaosu*), was isolated in 1971 by Chinese scientists. However, widespread availability of the semi-synthetic derivates of this plant was delayed until the last decades of the twentieth century.

1.4 Current recommendations for malaria control in pregnancy in endemic areas

Current WHO recommendations for the control of MiP in areas of stable transmission rely on: i) prompt and effective case management of malaria illness; ii) intermittent preventive treatment (IPT) with at least two treatment doses of SP; and iii) the use of insecticide-treated nets (ITNs) [3]. There are no specific recommendations in areas of low endemicity and treatment depends on each country's guidelines.

The following antimalarial drugs have been recommended for its use in pregnancy: quinine, chloroquine, amodiaquine, mefloquine, sulfadoxine–pyrimethamine, proguanil, artemisinins and clindamycin [22]. The choice of the most suitable drug to be used is based on the severity of the malarial episode, the gestational age of the pregnant woman and the pattern of drug resistance and local availability of antimalarials in the region.

1.5 Review justification and search limits

Pregnant women are systematically excluded from drug trials for ethical, legal and sociological concerns, and for fear of toxicity to the fetus, but issues concerning the liability of pharmaceutical companies dominate the others. This has resulted in a lack of information on safety, efficacy and even correct dosage of most drugs, including antimalarials, in pregnancy.

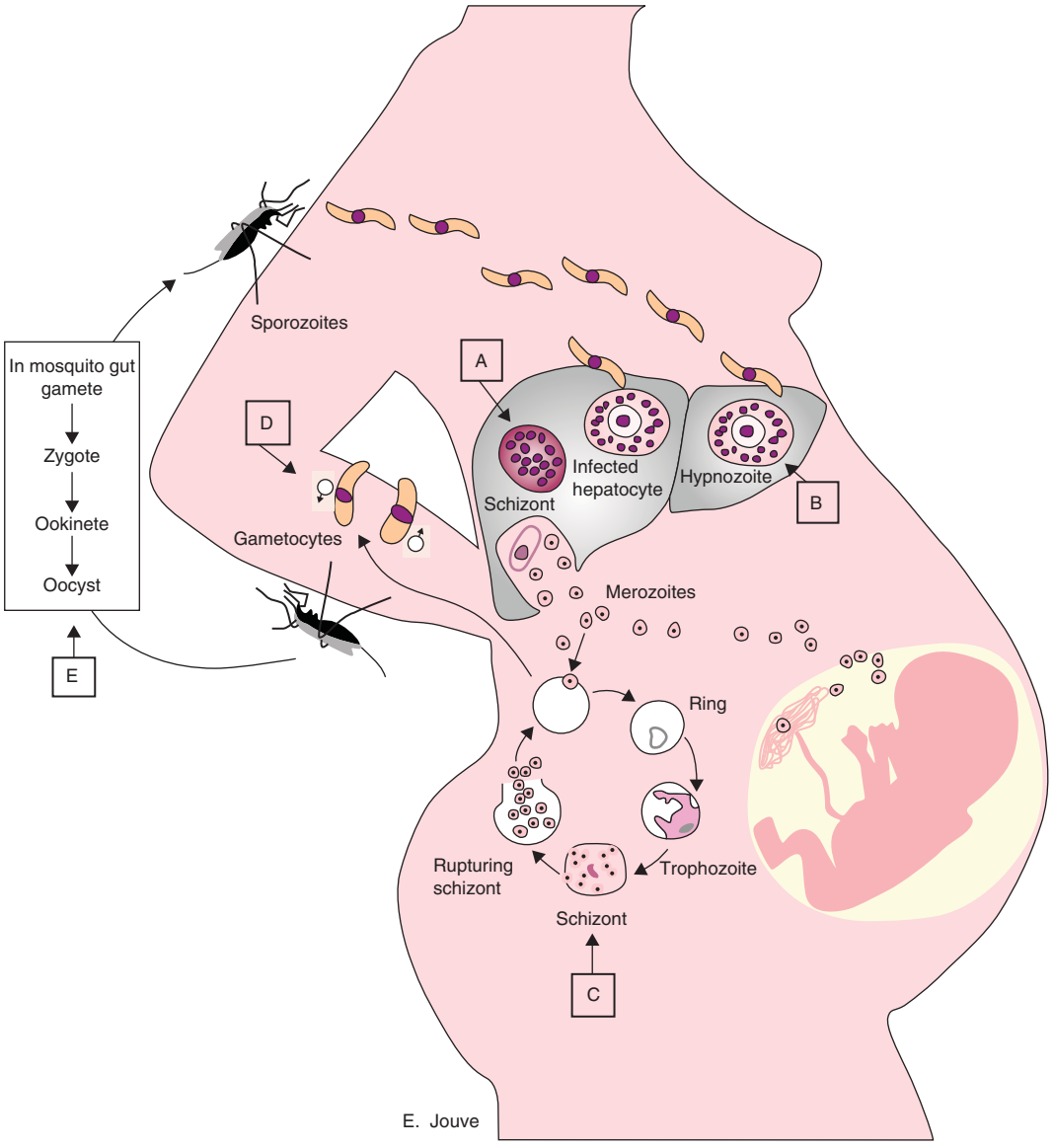

Figure 1. Malaria life cycle and antimalarial drug *Plasmodium* stage targets. *Plasmodium* sporozoites travel from the salivary glands of the anopheline mosquito through the bloodstream of the human host to the liver, where they invade hepatocytes and divide to form multinucleated schizonts. Hypnozoites can be found in *P. vivax* and *P. ovale* infections as a quiescent stage in the liver. Liver schizonts rupture and release merozoites into the circulation, where they invade red blood cells. Within the red cells, merozoites mature from ring forms to trophozoites to multinucleated schizonts. Some merozoites differentiate into male or female gametocytes that can then be ingested by the anopheline mosquito. The *Plasmodium* cycle is completed in the mosquito gut. Capital letters indicate the *Plasmodium*-stage targets of antimalarial drugs.
A: Tissue schizonticides; B: Hypnozoiticides; C: Blood schizonricides; D: Gametocytocides; E: Sporontocides.

Thus, the administration of antimalarial drugs to pregnant women is frequently based on risk–benefit criteria without the drugs going through adequate clinical reprotoxicity or teratologic evaluation. For MiP, safe and effective antimalarial drugs in a context of widespread CQ resistance of *P. falciparum* (and, to a lesser extent, of *P. vivax* parasites) are needed more than ever.

This review examines the available efficacy and safety information on the current antimalarial drugs recommended for treatment and prevention of MiP. We conducted a comprehensive literature search of medical databases (Medline, the Cochrane library, WHO) and non-medical search engines using the following keywords: pregnancy, malaria, treatment, antimalarial, control, prevention, drugs.

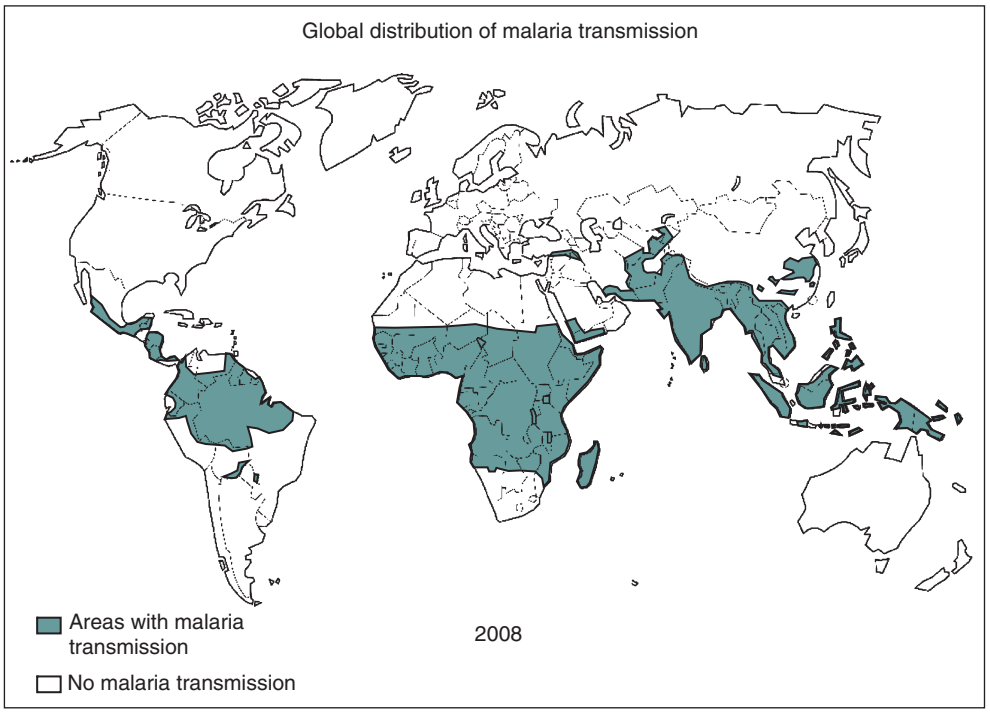

Figure 2. Global malaria distribution 2008.
Adapted from WHO.

2. Clinical manifestations of malaria in pregnancy

The frequency and severity of the effects of MiP depend on the pre-pregnancy level of acquired malaria immunity, which mainly depend on the intensity of malaria transmission. In areas of stable malaria transmission, where women are considered to be semi-immune with regard to malaria infection, it is assumed that most *P. falciparum* infections are asymptomatic [23]. However, in high transmission areas, infected women have an increased risk of maternal anaemia, low birth weight and premature delivery [15,24]. In areas of low transmission, pregnant women with malaria parasitaemia frequently present symptoms and signs such as fever, headache, vomiting and malaise. If untreated, the infection may develop into severe complications, such as cerebral malaria and pulmonary oedema, and may be a cause of maternal mortality [22,25,26].

3. Classification of antimalarial drugs

Antimalarial drugs can be classified according to their chemical structure and pharmacologic mechanism of action (**Table 1**). Antimalarial drugs target different stages in the life-cycle of the *Plasmodium* parasites and the following groups of drugs can be distinguished (**Figure 1**):

- Tissue schizonticides: act against pre-erythrocitic schizonts (e.g., primaquine, atovaquone–proguanil, pyrimethamine).
- Hypnozoiticides: act against quiescent liver stage hyponozoites from *P. ovale* and *P. vivax* infections (e.g., primaquine).
- Blood schizonticides: suppress infection symptoms by elimination of erythrocytic forms; also called 'clinically curative' (e.g., atovaquone–proguanil, sulfadoxine, sulfones, tetracyclines, halofantrine, quinine, mefloquine and chloroquine).
- Gametocytocides: eliminate gametocytes forms in the blood, preventing mosquito infection (e.g., primaquine has activity against all *Plasmodium* spp, chloroquine and quinine against *P. vivax* and *P. malariae*).
- Sporontocides: prevent the development of oocyst and multiplication of parasites in the mosquito gut when ingested with the blood of the human host (e.g., primaquine, chloroguanide, pyrimethamine).

Malaria treatment should ideally include drugs with tissue and blood schizonticide, as well as gametocytocide activities.

4. Antimalarial drugs recommended or with potential use in pregnancy

Malaria treatment during pregnancy has traditionally followed the Hippocratic principle of *prima non nocere* (i.e., 'first do not harm'). The labelling of most of the antimalarial drugs refers to pregnancy risk category C. This means that animal reproduction studies have shown an adverse effect on the fetus

Table 1. Classification of antimalarial drugs according to the chemical structure.

Group	Drug
4-Aminoquinolines	Chloroquine, amodiaquine
8-Aminoquinolines	Primaquine, tafenoquine (WR238605)
Arylaminoalcohols	Quinine, quinidine, mefloquine, halofantrine, lumefantrine, pyronaridine
Antifolates	Type 1: competitive inhibitors of dihydropteroate synthetase – sulfones, sulfonamides Type 2: inhibit dihydrofolate reductase – biguanides: proguanil, chloroproguanil; diaminopyrimidine: pyrimethamine
Peroxides	Artemisinin derivatives
Inhibitors of the respiratory chain	Atovaquone
Antibiotics	Tetracycline, doxycycline, clindamycin, azithromycin, fluoroquinolones

and there are no adequate and well-controlled studies in humans, but that potential benefits may warrant use of the drug in pregnant women despite potential risks. The choice of the antimalarial drug to treat pregnant women is based on risk–benefit criteria and individual assessment due to lack of human data. The available antimalarial drugs that are currently recommended in pregnancy are outlined below.

4.1 Aminoquinolines

4.1.1 *Chloroquine*

Apart from its schizonticidal and gametocytocidal activities, CQ also has antipyretic and anti-inflammatory properties [27]. The drug is effective against, *P. ovale, P. malariae, P. vivax* and sensitive *P. falciparum* parasites. CQ alone or in combination with proguanil is recommended for chemoprophylaxis for travellers to endemic areas. A CQ-resistant *P. falciparum* parasite has been described worldwide and resistance to *P. vivax* has been reported in areas of south-east Asia and the Pacific [28,29]. However, even today CQ remains effective in some areas of Central America and south-western Asia. CQ efficacy could be improved by its combination with other antimalarial drugs, while recovery of *P. falciparum* sensitivity to CQ has been reported in an area where previous parasite resistance to the drug was documented [30].

Safety: CQ is usually well tolerated although mild side effects such as nausea, dizziness and headache can occur. CQ-induced pruritus has been described to be particularly frequent in black-skinned populations [31]. Long-term use of high doses of CQ may induce retinopathy and neuromyopathy. Malaria prophylactic recommended doses can difficulty result on retinopathy. The drug is considered to be safe in all trimesters of pregnancy and can be given to breast-feeding mothers [32-34].

Pharmacokinetics: CQ is efficiently absorbed when administered orally, peak plasma concentrations being achieved within 3 h (range 2 – 12 h). Chloroquine is slowly eliminated and detected in blood for up to 56 days, with an elimination half-life of around 10 days, and is predominantly excreted as the parent drug. CQ readily crosses the human placenta [35]. A study among African pregnant women suggested that CQ clearance is increased in the third trimester of pregnancy [36]. On the other hand, blood concentrations of CQ were not significantly affected among pregnant women with *P. vivax* malaria [37].

4.1.2 *Amodiaquine*

Amodiaquine (AQ) is another 4-aminoquinoline similar in structure and activity to CQ. It also presents antipyretic and anti-inflammatory effects [38]. It is generally effective against CQ-resistant *P. falciparum* infections. The role of AQ in the treatment of CQ-resistant *P. vivax* malaria has not been adequately evaluated.

Safety: Adverse reactions to AQ are generally similar to those of chloroquine, being itching probably less common with AQ. However, in contrast, amodiaquine can induce toxic hepatitis and fatal agranulocytosis following its use for prophylaxis [31,39,40]. AQ is contraindicated for chemoprophylaxis and in persons with haematological and hepatic disorders. Recent studies suggest that AQ is safe during second and third trimester of pregnancy [41].

Pharmacokinetics: Oral AQ is rapidly absorbed, peak plasma concentrations are reached after a mean of 1.5 h in malaria patients. It is extensively metabolized in the liver to desethylamodiaquine, the main antimalarial compound. AQ and its metabolites have more than 90% protein bound and have a mean terminal half-life of 5.2 (± 1.7) [42]. There are no data of AQ pharmacokinetics in pregnancy [43,44].

4.1.3 *Piperaquine*

The extensive use of piperaquine (PIP) as monotherapy, in mass treatment and in prophylactic campaigns in China, led to the development of resistance to the drug, so that its use was abandoned during the 1980s. Recently, interest in PIP has revived and it is now proposed to use it in combination with artemisinin derivatives. PIP is currently used in Asia combined with dihydroartemisinin (DHA) and is under registration by the European and USA regulatory authorities for its use in children and non-pregnant adults [45]. To date, there have not been studies in pregnant women with this drug combination.

Safety: PIP is usually well tolerated with a safety profile similar to that of CQ.

Pharmacokinetics: PIP is a highly lipid-soluble drug with a large volume of distribution at steady state/bioavailability, long elimination half-life and a clearance that is markedly higher in children than in adults.

4.2 Arylaminoalcohols

4.2.1 Quinine

QN sulphate is administered orally for the treatment of uncomplicated malaria and QN hydrochloride as intravenous infusion for the treatment of severe or complicated malaria. In areas of multi-drug-resistance in south-east Asia, Western Oceania and South America, QN is combined with tetracyclines or clindamycin. The efficacy of QN monotherapy has been evaluated in pregnant women and ranges from 66 to 90% depending on the drug resistance in the area [46-49]. QN is not indicated for chemoprophylaxis.

Safety: QN is a potentially toxic drug and most of its adverse effects are dose-related. 'Cinchonism' is a characteristic syndrome associated with QN treatment that consists of tinnitus, headache, nausea and dizziness [31]; most of these adverse effects are reversible. QN also has arrhythmogenic potential (QT interval prolongation) and can cause hypotension. In addition, it stimulates insulin secretion and in patients with G6PD deficiency may occur haemolytic anaemia [46,50]. Although QN is generally thought to be safe during pregnancy, pregnant women have an increased risk of hypoglycaemia [51]. Glycaemia monitoring and parenteral dextrose supplementation are thus critical recommendations in the case management of pregnant patients with complicated malaria receiving QN [52]. According to the available documented exposures to QN during pregnancy (including 368 in the first trimester) it has recently been concluded that the drug does not increase the number of birth defect outcomes and, thus, can be considered safe for the treatment of malaria in pregnancy [53,54].

Pharmacokinetics: QN is absorbed rapidly when orally administered. Peak plasma concentrations are achieved within 1 – 3 h of an oral dose. QN is extensively metabolized in the liver and its plasma half-life is 10 – 12 h. The pharmacokinetics of QN in non-pregnant adults [55-57] and in pregnant populations [43,58] have been examined. A recent study on pregnant and non-pregnant Sudanese women found no differences between the two groups regarding QN metabolism and concluded that there is no need to adjust QN doses during pregnancy [59].

4.2.2 Mefloquine

MQ is recommended for malaria prophylaxis in travellers and for treatment in areas of drug resistance. Most of the experience of MQ as malaria treatment during pregnancy comes from south-east Asia, where increasing MQ resistance has been reported [60,61]. In these areas of multi-drug-resistance, MQ is combined with AS for malaria treatment. In Thailand, this combination (MQ + AS) has been found to be more effective than QN in clearing parasites and fever in pregnant women with uncomplicated malaria [48,62]. In a study conducted in eastern Sudan, 25 mg/kg dose of MQ was found to be safe and effective for treating CQ-resistant malaria episodes in pregnant women [63].

Safety: MQ can cause mild gastrointestinal and neurological adverse effects. Severe CNS effects occur in 1:10,000 patients taking MQ as chemoprophylaxis [31,64]. Rare cardiac (bradycardia, hypotension, arial flutter) and pulmonary (alveolar damage, pneumonia) toxic effects have also been described after its use [65-69]. The incidence of adverse events is higher when administered as treatment, indicating a dose-related pattern. Most of the safety data for the use of MQ in pregnant women come from the post-marketing surveillance system of the manufacturer and from retrospective studies [54,70,71]. A retrospective study evaluating antimalarial exposure during pregnancy in Thailand showed an increased risk of stillbirths in the group of pregnant women treated with MQ [72]. However, in a study conducted in Malawi, no differences were found in abortion and stillbirth rates between the group of pregnant women treated with CQ and the group treated with MQ [33]. From the clinical data available, MQ can be considered a safe drug to be administered during pregnancy, even in the first trimester [43,73].

Pharmacokinetics: MQ is highly protein bound (98% in plasma) and has a long elimination half-life, varying between 10 and 40 days in adults but tending to be shorter in pregnant women. The pharmacokinetic parameters of MQ are changed in acute *P. falciparum* malaria, reaching a higher C_{max}, probably due to a contraction of the apparent distribution volume. MQ clearance was found to be increased during late pregnancy in a study conducted in 20 women from an area of multi-drug-resistance in south-east Asia. MQ is considered to be one of the best characterized antimalarial drugs from a pharmacokinetic point of view in pregnancy [59].

4.2.3 Lumefantrine (or benflumetol)

Lumefantrine is used in association with artemisinins derivatives in patients with uncomplicated *P. falciparum* malaria. Lumefantrine is only available in combination with artemether (AL). The drug clears parasites rapidly and results in fewer gametocyte carriers [74]. AL is not indicated for chemoprophylaxis.

Safety: Lumefantrine is usually well tolerated, with minor and reversible events such as nausea, abdominal pain, diarrhoea, pruritus and skin rashes. It has been found to prolong the QTc interval at the standard recommended dose but no adverse events attributable to QTs prolongation have been reported in patients treated with AL [75,76]. In comparison to halofantrine, the incidence and degree of QTc prolongation are significantly lower in the combination of lumefantrine with artemether. In animal studies, no evidence of mutagenicity was detected but teratogenicity and embryotoxicity occurred with the combination of both drugs. AL was well tolerated and safe in a study conducted in Thailand among 125 pregnant women [77,78].

Pharmacokinetics: Lumefantrine pharmacokinetic data show a considerable variation of all parameters, except for the terminal half-life. This is also mainly ascribed to the variability of absorption. The estimated mean absorption half-life was 3.2 h (range 2 – 7 days), showing little variation between ethnic groups and fat food intake. The terminal half-life of lumefantrine seems to differ between healthy

subjects (2 – 3 days) and malaria patients (3 – 6 days). Reduced concentrations of the drug have been described in late pregnancy suggesting that drug-adjustment may be needed [79]. Elimination of lumefantrine is via liver and faeces, and the drug is eliminated very slowly.

4.2.4 Pyronaridine

Pyronaridine is an acridine derivative, a synthetic drug widely used in China that may have utility for multi-resistant *P. falciparum* malaria [80]. It seems likely that drug resistance would emerge rapidly if pyronaridine is used as monotherapy; therefore, it has been studied in combination with other antimalarials as artesunate [81]. No data on its use in pregnancy are available.

4.3 Antifolates

4.3.1 Sulfadoxine and pyrimethamine

Sulfadoxine and pyrimethamine (SP) are used in fixed combination only in the treatment of malaria. This combination is a highly active blood schizontocide against *P. falciparum* but is less effective against other species. There is no cross-resistance with the 4-aminoquinolines, mefloquine, quinine, or the artesiminin derivatives. The drug does not have gametocytocidal activity but has been shown to be sporontocidal in animal models. There is extensive experience with the use of SP in pregnancy, as it is the recommended drug for malaria prevention in pregnant women in stable transmission areas and has also been used for treatment in combination with other antimalarial drugs [22].

Safety: The SP combination is generally well tolerated when used at the recommended doses for malaria therapy. The most serious events are associated with hypersensitivity to the sulfa component, involving the skin and mucous membranes and include life-threatening erythema multiforme (Stevens–Johnson syndrome) and toxical epidermal necrolysis [40,82]. Cutaneous drug reactions are more common in patients who are HIV infected [83]. There have been isolated reports of a transient increase in liver enzymes as well as hepatitis occurring after administration of SP; haematological changes, including thrombocytopenia, megaloblastic anaemia and leucopoenia, have also been observed. In very rare cases, agranulocytosis and purpura have occurred. As a rule, these changes regress after withdrawal of the drug. It has a good safety profile in pregnant women. There is a theoretical risk of kernicterus if sulfadoxine is given in the third trimester of pregnancy as sulfonamides compete with bilirrubin for plasma proteins (IPTP) [87]. However, it was reported from a study conducted in western Kenya, that maternal SP exposure or detectable sulfa compounds in maternal urine at delivery were not associated with neonatal kernicterus [85].

Pharmacokinetics: SP pharmacokinetic properties in pregnancy have been studied extensively. Both drugs are highly protein bound, with relatively long mean elimination half-lives of around 180 h for sulfadoxine and 95 h for pyrimethamine. Pyrimethamine is extensively metabolized whereas only a small proportion of sulfadoxine is metabolized to acetyl and glucoronide derivatives. Excretion is mainly in the urine. The two drugs cross the placental barrier and are detected in breast milk [42,86]. Inconsistency of changes in pharmacokinetic parameters between sulfadoxine and pyrimethamine was observed in a recent study where SP was used for intermittent preventive treatment in pregnancy (IPTP) [87]. However, HIV status has little influence on pharmacokinetic parameters of SP in pregnant women [88].

4.3.2 Chloroguanide and proguanil

Recent evidence suggests that mechanisms of action other than antifolate activity may also be involved in the antimalarial activity of chloroguanide and proguanil [38,40]. Unfortunately, effectiveness has been compromised by development of drug-resistant strains of *P. falciparum.* Proguanil is currently used only for profilaxis and in combination with CQ in areas with low prevalence of CQ-resistant *P. falciparum.* The combination of proguanil and CQ can be recommended as prophylaxis in non-immune pregnant women such as travellers to malaria *P. falciparum*-endemic areas [89].

Safety: Proguanil can be given orally, is easily administered and causes few side effects. There are reports indicating that mouth ulcers, hair loss and gastrointestinal discomfort may occur following prophylactic use. The drug should not be used in persons with liver or kidney dysfunction. Gross over dosage gives rise to abdominal pain, vomiting, diarrhoea and haematuria [40]. There is no evidence that proguanil is harmful at prophylactic doses during pregnancy [32].

Pharmacokinetics: Chloroguanide and proguanil are prodrugs that are metabolized to the active compound, cycloguanil, which was the first antifolate developed. Pregnancy reduces the conversion of proguanil to the active metabolite [90]. Pharmacokinetic studies on proguanil are limited. Absorption is rapid, peak plasma concentrations of both proguanil and its active metabolite, cycloguanil, are achieved within 4 h of administration. The elimination half-life is approximately 16 h [40].

4.4 Peroxides: artemisinin derivatives

Artemisinin derivatives are the fastest active antimalarial drugs with a potent and rapidly acting schizontocide, eliciting shorter parasite clearance times than CQ or QN and rapid symptomatic responses. Different compounds have been used; the derivatives are actually more active than artemisinin itself and all of them are readily metabolized to the biologically active metabolite, DHA. Artemisinin is active at nanomolar concentrations *in vitro* on both CQ-sensitive and resistant *P. falciparum* strains. These compounds prevent gametocyte development and, therefore, can reduce transmission [91].

Safety: The artemisinin derivatives are well tolerated when used for acute malaria, despite the fact that neurotoxicity was observed in animals with higher doses than used clinically [91]. Most adverse events are mild and include nausea, vomiting, itching and drug fever. In addition, abnormal bleeding and dark urine have occasionally been documented and minor

cardiac changes, mainly non-specific ST changes and first degree A-V block, have been noted during clinical trials. These returned to normal after improvement of malaria symptoms. Preclinical studies have consistently shown that artemisinin and its derivatives exhibit mutagenic or teratogenic activity, and could cause fetal resorption in rodents at relatively low doses when given after the sixth day of gestation [92]. These drugs are also embryolethal in cynomologus monkeys at doses close to therapeutic range [93]. Safety data in human pregnancy are still limited and more information is urgently needed, especially for the first trimester.

Pharmacokinetics: Oral artesunate is rapidly absorbed; peak levels of both the parent compound and DHA are reached by about 60 min. Levels of both can be detected for 4 – 8 h. Similar pharmacokinetics have been reported following the oral administration of artemether; mean peak plasma concentrations and mean plasma half-lives being 3 h, 3.1 h and 10.6 h for the parent compound and DHA respectively. The plasma concentrations of both artemether and DHA were similar in both healthy subjects and those with acute uncomplicated malaria [91]. The kinetics of DHA are modified by pregnancy. The plasma levels of the active antimalarial metabolite DHA are lower than reported previously in non-pregnant adults [94].

4.5 Other drugs with antimalarial activity

Several antibiotic drugs present antimalarial properties and have been used in combination with antimalarials for malaria treatment [95].

Clindamycin is a semi-synthetic antibiotic derived from lincomycin. It is an efficient blood schizontocide with a relatively slow action [96]. It is usually given in combination with QN for the treatment of *P. falciparum* malaria when decreased susceptibility to quinine has been reported [97]. It has been mainly used in endemic areas of Latin America. Clindamycin use has not been related to adverse events in pregnancy, although it does pass through the placenta and may be accumulated in the fetal liver. The experience of its use during pregnancy is limited.

Azithromycin is a macrolide antibiotic, semi-synthetic derivative of erythromycin with activity against *P. falciparum* [98]. Azithromycin is synergistic with quinine against *P. falciparum* strains. The azithromycin-quinine combination appears safe, well tolerated, and effective in drug-resistant *P. falciparum* malaria [99]. The drug has a slow onset of action and has been proposed to be used in combination with fast-acting substances, such as artemisinin derivatives [98]. Recent studies have demonstrated the safety and efficacy of combinations of azithromycin and SP or artesunate for the treatment of *P. falciparum* malaria in pregnant women [62,100]. The azithromycin–chloroquine combination is active against *P. falciparum* and *P. vivax* infections [101]. Azythromicin combinations are still under clinical evaluation for their use in the prevention or treatment of malaria in pregnant and non-pregnant patients. The interest in using azithromycin for IPTp is not only because of its favourable safety profile in pregnancy but also because of its antibiotic effect on other infections, mainly sexually transmitted infections, which are very prevalent in many malaria-endemic areas [102].

4.6 Combination therapies

The combination of different antimalarial drugs has been suggested because of its potential to rapidly decrease parasitaemia and also because the synergistic effect of the combination could improve the clinical cure, shorten the duration of therapy so as to minimize the risk of recrudescence, provide a way in which resistance can be delayed and might also reduce malaria transmission [103,104]. Sulfadoxine and pyrimethamine is the most widely used combination.

4.6.1 *Chlorproguanil-dapsone*

Chlorproguanil–dapsone (CD) is a fixed-dose antifolate combination similar to SP but with a shorter half life; thus, it could reduce the probability of selecting resistant parasites. Dapsone is effective in combination with other antifolates in preventing *P. falciparum* malaria; it is also effective in clearing *P. falciparum* parasitaemia in children younger than 5 years of age [83]. However, toxicity is a serious concern with this combination [40]. In a recent study for treatment of malaria in pregnancy in Tanzania, CD showed high parasitological failure rates at day 28 (18%) compared with other combinations [105]. Adverse effects reported include hemolytic anaemia, particularly in patients with G6PD deficiency [106]. Due to this unacceptable haematological toxicity, the drug has been withdrawn from clinical use [107].

4.6.2 *Atovaquone–proguanil*

Atovaquone–proguanil is another antimalarial in fixed-dose combination. The efficacy of atovaquone in prevention and treatment of *P. falciparum* malaria is maximized in combination with proguanil. Atovaquone is also effective in treating and preventing *P. vivax, P. malariae* and *P. ovale* infections, although more evidence is desirable for this indication. As atovaquone is structurally unrelated to the 4-aminoquinolines, quinoline–methanols or other arylaminoalcohols, it is also effective against *P. falciparum* strains resistant to these drugs [86]. This combination is well tolerated and more effective than CQ alone, CQ-SP, or MQ, against acute uncomplicated multi-drug-resistant *P. falciparum* [108]. Pregnancy is currently listed as a contraindication to the use of the atovaquone–proguanil combination but studies are in place to evaluate its safety profile [109].

4.6.3 *Sulfadoxine–pyrimethamine and amodiaquine*

Co-administered sulfadoxine–pyrimethamine and amodiaquine (SP + AQ) was the first antimalarial combination to replace CQ as first-line treatment in many African malaria-endemic countries due to its availability and low cost. The SP + AQ combination has been found to be significantly more effective than CQ in parasite cleaning on day 7 in *P. falciparum*-uncomplicated malaria [110]. Recent studies in

pregnant women have shown that this combination presents low parasitological failure rates at day 28 (1%) than other combinations [105].

4.6.4 *Artemisinin-based combination therapies*

The artemisinin derivatives are strongly recommended to be used in combination with other antimalarial drugs [22]. Several combinations have been used, including artemether–lumefantrine (AL), artesunate + amodiaquine (AS + AQ), artesunate + SP (AS + SP), artesunate + mefloquine (AS + MQ), dihydroartemisinin + piperaquine (DHA + PIP) and artesunate + pyronaridine (AS + PD).

The combination AS + SP was found to be safe and effective for malaria treatment in pregnant women in The Gambia [111]. A recent study in Tanzania has also shown that AS + AQ was safe and efficacious in pregnancy [105]. In Thailand, the combination AS + MQ was more effective than QN in the treatment of acute uncomplicated *P. falciparum* malaria in the second or third trimesters of pregnancy [48].

Studies in Vietnam have assessed the efficacy of DHA–PIP for the treatment of uncomplicated malaria in children and adults [112,113]. However, there is very little information on the use of this drug in pregnancy. A report from Thailand, where 50 pregnant women with recurrent *P. falciparum* infections were treated with DHA–PIP, indicates that the drug was effective and well tolerated [114]. Studies are planned to evaluate the use of this combination for the treatment and prevention of malaria in pregnancy.

Artesunate–pyronaridine was shown to have a good tolerability and safety profile in uncomplicated *P. falciparum* malaria in children [81]. There is no information on the safety and efficacy of this combination in pregnancy.

Fixed-dose combinations for the existing drugs in the market, in particular with artemisinin derivatives, include AS–SP, AS–AQ, DHA–PIP and AS–MQ, and have completed clinical trials in Africa and south-east Asia. AS–MQ and AS–AQ were evaluated in Brazil, Malaysia, Thailand and France and are now available [115].

4.7 Antimalarial drugs contraindicated in pregnancy

Tetracycline and doxycycline are used in combination with quinine or artesunate in areas of multi-drug resistance. In human pregnancy, their use can be associated with disturbances of fetal bone growth and with irreversible teeth coloration in the infant; congenital cataract has also been reported. The hepatotoxicity of tetracycline is increased in pregnancy.

Halofantrine is embryotoxic in animals. No data exist on the use of halofantrine in pregnant women, but the cardiotoxicity of the drug has compromised its role in the treatment of uncomplicated *P. falciparum* malaria.

Primaquine is also contraindicated in pregnancy because of the risk of intravascular hemolysis in the mother and the fetus. This risk is linked to the dose administered and the degree of G6PD deficiency.

4.8 Upcoming drugs

The beginning of the twenty-first century is witnessing a renewed enthusiasm in the malaria research community, and malaria in pregnancy has been considered a priority research area. Different institutions are involved in drug discovery and development to achieve the goal of malaria eradication. Most of them are focused on developing antimalarials for use in combination therapy.

Artemisone, a metabolically stable, semi-synthetic derivative of artemisinin, is being developed. Several tioxanes obtained by total synthesis are now available and are being assessed for further development [116]. Isoquine is an isomeric derivative of amodiaquine that should not generate the toxic quione-imine metabolites that are thought to have a role in the hepatic and neutrophil toxicities [117]. Short-chain chloroquine analogues with better efficacy on chloroquine resistant isolates are also being studied [118,119]. Fosmidomycin has recently been tested in small number of patients and produced modest cure rates; however, it could be used in combination with other antimalarials, this compound inhibits 1-deoxy-D-xylulose 5-phosphate reductoisomerase, an enzyme of the non-mevalonate pathway of isoprenoid biosynthesis, which is absent in humans but present in many pathogens and plants. The combination of fosmidomycin and clindamycin has also been tested in a study involving 70 patients with acute uncomplicated *P. falciparum* malaria. It was well tolerated and a cure rate > 95% was found [120].

5. Guidelines for treatment and prophylaxis of malaria in preganancy

Chemotherapy and prophylaxis of different forms of malaria have become progressively more complex and less satisfactory, primarily due to selection of drug-resistant strains of *P. falciparum* in areas of extensive antimalarial use. Any guideline should be reviewed appropriately, according to the status and habitat of the patient, the geographic origin, species and drug-resistance profile of the likely infecting parasites, and the antimalarials locally available.

5.1 Preventive treatment

Chemoprophylaxis is recommended for travellers to endemic areas, and CQ, CQ + proguanil, MQ, proguanil–atovaquone or doxycycline are examples of drugs that are widely used according to the patient and to the specific endemic area [121].

Various strategies using antimalarial drugs for the prevention of malaria in endemic areas have been recommended in pregnancy. Studies in pregnant women have shown significant effects increasing birth weight and reducing maternal anaemia and parasitaemia in women who received regular chemoprophylaxis [122,123]. Because of concerns on the sustainability and compliance with the regular prophylaxis regimen and the emergence of resistant parasites to CQ, chemoprophylaxis was abandoned in most African countries [122].

More recent studies have shown that intermittent preventive treatment might maintain the benefits of regular chemoprophylaxis regimens without some of their drawbacks [17,124]. This strategy consists on the administration of a therapeutic dose of an antimalarial drug at predetermined time points to pregnant women regardless of the presence of parasitaemia, and coinciding with the women attendance to the routine antinatal clinics. The current recommendation is to administer at least two doses of SP. from the second trimester of gestation [3].

Although the level of resistance at which SP IPTp becomes ineffective is still unknown [125], the increase in SP resistance is a challenge to the sustainability of the implementation of this strategy. A recent study in Tanzania showed that SP IPTp was associated with an increase in the number of parasites carrying the resistance allele at DHPS codon 581 [126]. With the increasing emergence of *P. falciparum* parasites resistant to SP, other alternative drugs need to be explored for their use as IPTp. In an IPTp study in Ghana, AQ and SP–AQ were comparable to SP in reducing maternal anaemia and low birth weight; but the lower tolerability of the AQ-containing arms was a concern [127]. Combinations of azithromycin with other antimalarials, such as CQ or PIP, have been proposed for IPTp; however, studies are still needed to evaluate this option through regulatory trials for their use in pregnancy [101]. MQ has also been found to be more efficacious than SP for IPTp in Benin but, again, tolerability was lower in the MQ arm [128]. The pharmacokinetic characteristics and ease of administration of MQ make this drug the most promising available candidate to replace SP. Studies are on-going to explore the full potential of MQ as an alternative to SP for IPTp (C Menéndez, personal communication).

5.2 Treatment

Prompt and effective treatment of confirmed or suspected malaria cases continues to be the cornerstone of malaria control in pregnancy [22].

CQ is the safest antimalarial drug to treat malaria in pregnant women. With the emergence of CQ-resistant *P. falciparum* parasites, the treatment of malaria in pregnancy has become a very complex issue. There is little information on the efficacy and safety profile of the alternative drugs for pregnancy. The decision on the selection of the appropriate antimalarial drug is based on a risk–benefit assessment taking into account: (1) the severity of the clinical manifestations; (2) the gestational age; (3) the type of *Plasmodium* spp. causing the infection; and (4) the pattern of the parasite drug resistance in the area.

Artemisinin-based combination therapies (ACTs) are the first-line treatment recommended by the WHO in *P. falciparum* endemic areas including in pregnancy [22]. For uncomplicated malaria, the WHO recommends ACTs in the second and third trimesters; the ACT to be used should be the one used as first-line treatment in the area. Based on the safety concerns from preclinical studies, artemisinins are not recommended in the first trimester of pregnancy and can therefore only be considered in the absence of effective alternatives after a risk–benefit assessment has been made [22,129]. Thus, oral QN is still the recommended drug for the treatment of uncomplicated malaria in the first trimester of gestation (clindamycin is rarely available and not used in Africa due to its high cost). Oral QN for uncomplicated malaria has inherent problems of compliance due to the duration (7 days) and low tolerability of this therapeutic regimen. With regard to complicated malaria in the second and third trimesters of pregnancy, the WHO guidelines recommend parenteral AS as the first choice, and parenteral artemether (AM) as the second option, depending on the local availability of these drugs [22]. This recommendation of replacing QN for the treatment of complicated malaria is based on a study showing lower mortality among non-pregnant Asian patients treated with parenteral AS than in those treated with QN [130]. Although these are very important results, they should be confirmed among pregnant African women with complicated malaria, since resistance to QN is still negligible in the African region.

Since 2006, new studies have evaluated the efficacy of antimalarial drugs as monotherapy or in combination for treatment of uncomplicated malaria in pregnancy. [78,100,105,131]. **Table 2** summarizes the currently WHO recommendations for the treatment of malaria in pregnancy.

5.3 Malaria treatment in HIV-infected women

The global spread of the HIV/AIDS epidemic has contributed to increase the burden of MiP, especially in sub-Saharan Africa, where almost 76% of AIDS deaths occurred in 2007 [132]. **Figure 3** shows the global HIV/AIDS global distribution. The WHO estimates that 61% of adults living with HIV in sub-Saharan Africa are women. HIV infection increases the risk and severity of malaria in pregnant women and alters the malaria parity-related pattern [133-135]. Antimalarial treatment failure is more common among HIV-infected pregnant women, and more doses of antimalarial preventive treatment are required for an effective prevention [85,136,137].

Co-infection with malaria and HIV is associated with increased maternal anaemia, low birth weight and infant mortality to a greater extent than infection with either disease alone [138]. HIV-infected pregnant women are more likely to be malaria parasitaemic, to have higher parasite densities and to be febrile when parasitaemic than HIV-seronegative pregnant women [139]. Given this increased susceptibility, malaria control among pregnant HIV-infected women is a priority in endemic areas. However, both prevention and treatment of malaria becomes a challenge in this particular group due to potential drug interactions between antimalarial and antiretroviral drugs [140].

WHO guidelines recommend prophylaxis of opportunistic infections with cotrimoxazole (CTX, trimethoprim–sulfamethoxazole) in HIV-infected individuals in developing countries [141]. They also mention that SP should not be given

Table 2. Currently recommended drugs for treatment and prevention of malaria in pregnancy by WHO region.

Region	*P. falciparum*					*P. vivax*
	Treatment				Prevention	Treatment
	Uncomplicated		Severe			
	1st T	2 – 3rd T	1st T	2 – 3rd T		
Africa	QN + clindamycin*	ACT[‡]	QN/AS	AS	IPTp–SP[¶]	CQ[#]
Americas	QN + clindamycin* (or CQ**)	ACT or MQ		or	NA	CQ[‡‡]
Eastern Mediterranean	QN + clindamycin*	ACT[§§]		AM	NA[¶¶]	
Europe	-			or	NA	
South-east Asia	QN + clindamycin* (or CQ**)	ACT		QN[§]	NA	
Western Pacific	QN + clindamycin*	ACT			CQ weekly[##]	

WHO World Malaria report 2008 and WHO Malaria treatment guidelines 2006.

*If clindamycin is unavailable or unaffordable, then QN monotherapy should be given.

[‡]ACTs being adopted in the African region are artemether–lumefantrine (Angola, Benin, Bostwana, Burkina Faso, Central African Republic, Comoros, Ethiopia, Gambia, Guinea-Bissau, Kenya, Malawi, Mozambique, Namibia, Niger, Nigeria, Rwanda, South Africa, Tanzania, Togo, Uganda, Zambia, Zimbabwe) and artesunate + amodiaquine (Burundi, Cameroon, Chad, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Ghana, Guinea, Liberia, Madagascar, Mauritania, Sao Tome and Principe, Senegal, Sierra Leone). CQ is used in Cape Verde and Swaziland, CQ + SP in Eritrea. Some of these countries have not yet implemented these current policies.

[§]Parenteral administration. Where available, AS is the first, and AM the second option for treating severe malaria during pregnancy in the second and third trimesters.

[¶]Chloroquine + proguanil is given in Bostwana, South Africa and Swaziland instead of IPTp with SP. In Cape Verde, CQ weekly is policy for preventing malaria in pregnancy.

[#]CQ is recommended in Algeria, Ethiopia and Mauritius, where the malaria parasite is CQ sensitive.

**CQ is indicated for the treatment of *P. falciparum* infections in areas where the parasite is CQ sensitive (eg. Guatemala, Myanmar).

[‡‡]CQ is given for treatment and then weekly until delivery; primaquine is contraindicated in pregnancy and is administered only after delivery.

[§§]AS + SP is given in Dijibouti, Pakistan, Somalia, Sudan and Yemen; CQ + SP is indicated in Afghanistan.

[¶¶]IPTp with SP is the policy in Somalia and Sudan.

[##]Weekly prophylaxis with CQ is recommended drug policy for prevention of malaria in pregnancy in Malaysia, Papua New Guinea, Philippines, Vanuatu and Vietnam.

ACT: Artemisinin-based combination therapy; AM: Artemether; AS: Artesunate; CQ: Chloroquine; IPTp: Intermittent preventive treatment in pregnancy; MQ: Mefloquine; NA: Not adopted; QN: Quinine; SP: Sulfadoxine–pyrimethamine; T: Trimester.

to patients on CTX to avoid the risk of sulfa-related adverse effects. Thus, this implies that IPTp with SP for malaria prevention is not recommended for HIV-infected pregnant women. Although CTX also has antimalarial activity, it is unclear whether CTX prophylaxis would be effective in preventing the harmful effects of malaria in pregnancy in HIV-infected women. A multicentre study involving pregnant African women evaluating CTX is currently ongoing (C Menendez, personal communication).

6. Conclusions

The treatment of malaria in pregnancy has been hampered since the appearance of CQ resistance. New antimalarial drugs and combinations are being studied. However, due to the systematic exclusion of pregnant women from clinical drug trials, decisions are being taken on the basis of limited safety and efficacy data for their use in pregnancy.

The prevention of malaria in pregnancy in endemic areas of Africa is also faced with the problem of drug resistance and alternative antimalarials are urgently needed. To further complicate the issue, in some of the areas with the highest malaria transmission, the incidence of HIV is also highest, making the treatment of both infections a new and yet unresolved challenge especially in pregnancy.

7. Expert opinion

Malaria poses an enormous burden to public health services of endemic countries as well as a challenge to manage it in the context of limited resources. One of the reasons for this challenge is the need to use adequate antimalarial drugs that are not only safe and effective but that are also affordable for the weak economies of endemic countries. Because of changes in the development of drug resistance and of epidemiological situations, like interactions with other infections such as HIV, there is a need to regularly revisit the list of available antimalarial drugs and their recommendation in different populations at risk. This has been possible because in the last years an unprecedented effort from public and private international health agencies has been made. One of these organizations is the Medicines for Malaria Venture (MMV), which has a focus on the development of new antimalarial drugs with specific target product profiles. This new perspective of the research on drugs against malaria is certainly very positive and should be encouraged if the goal is to eradicate malaria in a not too

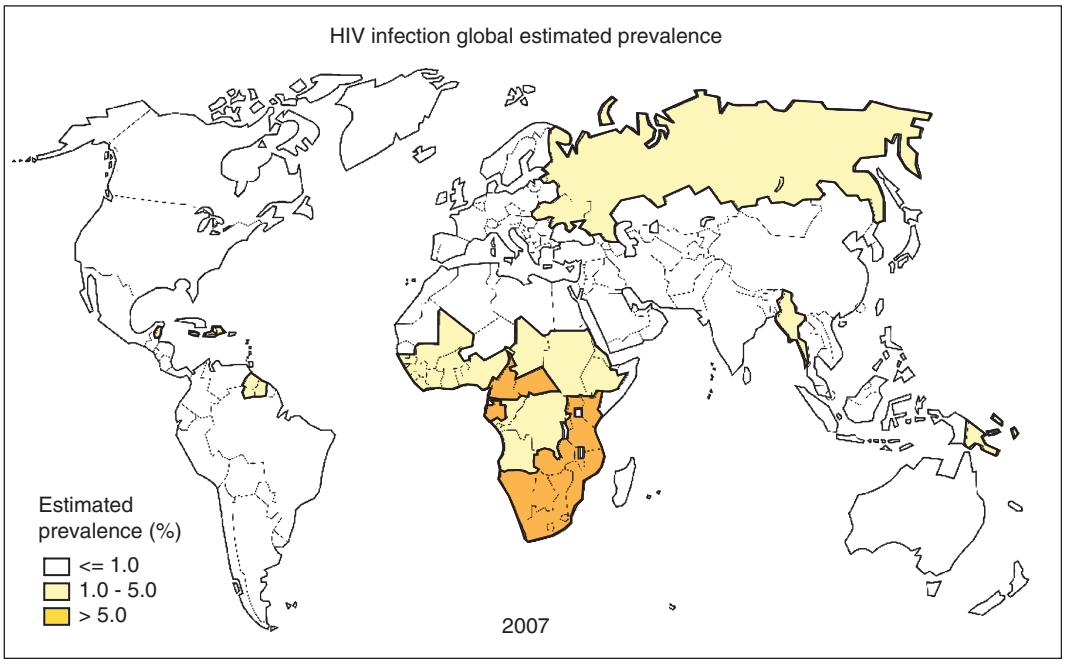

Figure 3. Global HIV/AIDS prevalence distribution 2007.
Adapted from WHO.

distance future, and because the parasite, with more or less efficiency and speed, will continue developing resistance against the drugs used to destroy it.

New antimalarial drugs also represent new challenges; their efficacy and safety have to be proved also in special populations such as very small babies and pregnant women, none of whom are part of clinical trials for the drug registration process. This issue is especially complex in the case of pregnant women not only because they are systematically excluded from drug trials for ethical, legal, sociological concerns and for fear of toxicity to the fetus, but also – and mainly – for matters concerning the liability of pharmaceutical companies. The pressure of having to resolve the need to treat and prevent malaria in pregnancy has led to the use of antimalarial drugs with very limited information on their safety profile and efficacy in pregnant women. The WHO recommendation of ACTs as first-line treatment for individuals living in endemic areas has improved malaria case management in these areas. However, it has also raised concerns about having to treat pregnant women in the same way as the rest of the population, without any evidence that ACTs are safe in pregnancy. This is especially relevant because artermisinins have been found to be embryotoxic in several animal species. The recommendation of the use of ACTs in pregnancy constitutes an example of how when it comes to treatment in pregnant women the decision is mainly based on a risk-benefit assessment rather than on the balance of safety and efficacy as well.

The choice of antimalarial drug has increased in recent years, although it is still limited and many drugs are still under development. As discussed above, this choice is even more limited in pregnancy. Given that pregnancy is a special physiological situation, pregnant women should be considered specifically and not necessarily included in the recommendations made for the rest of the population with regard to malaria control, both case management and prevention. The decision on which drug should be given has to be based not only on general tolerability and safety but also on reprotoxic safety. It also has to be based on drug resistance in the area; for example, a non-artemisinin combination therapy might be as effective as an ACT in a particular area and may have a better safety profile for pregnancy than the ACT compound, and should thus be preferable. Finally, the decision should also be based on the acquired immunity of the woman, which will depend on the malaria endemicity of the area. Thus, recommendations should not be extrapolated and generalized on the basis from findings from a particular endemic area to another very different one without having carried out the appropriate evaluation.

In conclusion, in recent years malaria in pregnancy has received more attention than ever before from the international malaria community, as exemplified by the Malaria in Pregnancy (MiP) Consortium, among other international initiatives. This interest is clearly very positive and should serve to contribute to establish rational policies for the use of antimalarial drugs in pregnancy, as well as to find more efficacious and safer

alternatives for this vulnerable group at risk of malaria. In the renewed effort for malaria eradication pregnant women should not be neglected but being one of the main focuses.

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Affiliation

Esperança Sevene[†1,2], Raquel González[2,3] & Clara Menéndez[2,3]
[†]Author for correspondence
[1]Eduardo Mondlane University,
Faculty of Medicine, CIMed,
P.O. Box 257,
Maputo, Mozambique
Tel: +258 21 428076/325227;
Fax: +258 21 325255;
E-mail: esevene68@gmail.com
[2]Manhiça Health Research Centre (CISM),
P.O. Box 08036, Manhiça, Mozambique
[3]Barcelona Centre for International Heath Research (CRESIB),
Hospital Clínic,
Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS),
Universitat de Barcelona,
P.O. Box 08036,
Barcelona, Spain