Reducing the burden of malaria in pregnancy by preventive strategies

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Malaria is one of the most common and preventable causes of adverse birth outcomes. In Africa, important progress has been made in the past decade with the introduction of a preventive strategy for malaria in pregnancy consisting of intermittent preventive treatment in pregnancy (IPTp) and insecticide-treated nets, yet their coverage is still unacceptably low and malaria continues to demand a huge toll on pregnant women and their newborn babies. Increasing the frequency of dosing of IPTp with sulfadoxine-pyrimethamine might provide temporary respite, but increasing resistance to sulfadoxine-pyrimethamine makes research into safe, efficacious, and affordable alternatives for IPTp one of the highest priorities for the control of malaria in pregnancy. A number of promising alternatives are, or will soon be, available that need to be evaluated as IPTp after their safety and pharmacokinetics in pregnancy have first been assessed in parasitaemic women. Little is known about appropriate control strategies in Asia and Latin America for *Plasmodium falciparum* and *Plasmodium vivax* malaria in pregnancy, which in most countries rely on responsive case management approaches. The role of case management based on proactive screening for malaria infection of women attending antenatal care or preventive approaches with insecticide-treated nets or IPTp are urgently needed. To achieve these objectives, multicentre and multidisciplinary approaches are required across the range of malaria transmission settings that include assessment of immunological effect of successful preventions, the perceptions and acceptability of different preventive approaches, and their cost-effectiveness.

Introduction

In malaria endemic regions, the burden of malaria is mainly in children and pregnant women. Every year, approximately 50 million women living in malaria endemic areas become pregnant; half of them in sub-Saharan Africa, many in areas of intense *Plasmodium falciparum* transmission.[1] In these regions, malaria in pregnancy is predominantly asymptomatic and yet is a major cause of severe maternal anaemia and low birthweight babies. Because of the strong association between low birthweight and child survival, successful control of malaria in pregnancy might prevent 75 000–200 000 infant deaths every year.[2]

In low transmission areas, such as in many parts of Asia and Latin America, women have little acquired immunity to malaria by the time they become pregnant and so infections are often symptomatic and are more likely to become severe and result in maternal and fetal deaths. *Plasmodium vivax*, another important contributor to maternal anaemia and low birthweight, is common and often coexists with *P falciparum*.[3–5]

The burden of malaria in pregnancy has been exacerbated by the advent of HIV, which increases susceptibility to malaria in pregnancy, reduces the efficacy of antimalarial interventions, and complicates the use of antimalarials because of potential drug interactions.[6]

Successful control of malaria in pregnancy thus might save lives of mothers and babies, and is a high public-health priority in all endemic countries, although the optimum methods for achieving this may vary according to local conditions.

Current recommendations for malaria control in pregnancy

For sub-Saharan Africa, WHO has developed guidelines for the control of malaria during pregnancy. These consist of prompt and effective case management of malaria illness (addressed in detail by François Nosten and colleagues)[7] combined with prevention of infection and/or disease by insecticide-treated nets (figure) and intermittent preventive treatment in pregnancy (IPTp).[1]

Figure: Pregnant woman sitting in front of her long-lasting insecticide treated net

Yara Alonso

Generic prevention guidelines are not available for Asia and Latin America, areas that represent half the world's population exposed to some risk of malaria, although this is generally much less intense than in Africa. In these regions, control of malaria in pregnancy relies mainly on case management, although some countries promote chloroquine chemoprophylaxis and insecticide-treated nets.

Vector control

Insecticide-treated nets

In Africa, insecticide-treated nets reduce all-cause mortality for children under 5 years of age by 18% and are one of the main strategies of the Roll Back Malaria Partnership.[8] Although initial studies in pregnant women gave conflicting results,[9–11] a recent systematic review of all published and unpublished randomised trials of treated nets (n=6) shows that insecticide-treated nets are beneficial to both mother and newborn baby in sub-Saharan Africa.[12] Insecticide-treated nets, compared with no nets, substantially reduced the risk of placental malaria (risk ratio [RR] 0·79, 95% CI 0·63–0·98) in all gravidae and reduced the risk of low birthweight (RR 0·77 95% CI 0·61–0·98) and stillbirth/abortion (RR 0·67 95% CI 0·47–0·97) in the first few pregnancies (up to the second or fourth pregnancy, depending on the study design).[12] Two of the trials included in the systematic review were from western Kenya and were done simultaneously in contiguous sites with the same intense malaria transmission, but one randomised entire communities (villages)[13] and the other randomised individuals.[14] The beneficial effects were apparent in both trials, suggesting that insecticide-treated nets work when provided to entire communities or when provided to individuals who benefit from personal protection. Insecticide-treated nets that are provided to pregnant women have the added benefit that they continue to protect the newborn baby during infancy, since most babies sleep with their mothers.

Gaps in knowledge of insecticide-treated nets

No further trials of insecticide-treated nets alone in pregnancy are required in sub-Saharan Africa.[12] However, their coverage is still well below the Abuja target of 60% and more operational research is needed to find the best way of achieving increased insecticide-treated net use by pregnant women (addressed in detail in a companion Review).[15]

Despite the evidence of insecticide-treated net efficacy in pregnant women in malaria endemic Africa, very little is known about their effect in Asia and Latin America. The only trial in pregnant women done outside sub-Saharan Africa showed that insecticide-treated nets, compared with untreated nets, reduced maternal anaemia and stillbirths/abortions in all gravidae, but did not reduce clinical malaria or low birthweight.[16] The more complex vector populations with exophagic/exophilic and early biting behaviour might result in lower efficacy

in some settings than observed in Africa. In this context other methods of reducing the human–vector contact should be investigated.

Indoor residual spraying

Indoor residual spraying is recommended in specific situations such as in the context of malaria epidemics. It has been used in the past in some endemic countries. Although the efficacy of indoor residual spraying is good in the short-term, its logistic complexities, cost, and decreasing acceptance by the population have been major limitations for its success as a malaria control strategy. However, indoor residual spraying is now again one of the three main interventions promoted by WHO's Global Malaria Programme to control malaria, including the use of DDT.[17] The role of indoor residual spraying in the prevention of malaria in pregnancy has not been evaluated. Its effect on malaria in pregnancy regarding both efficacy and, especially safety, should be evaluated in the settings where it is used.

Safety of insecticides

Pyrethroids are the only class of insecticides that have been extensively used to treat nets. They appear well tolerated by pregnant women, with no evidence of toxicity to the fetus when used in compliance with their directions.[18] The safety of pyrethroids or other insecticides when used for indoor residual spraying has not been formally evaluated in pregnant women. Resistance of the anophelines vector to pyrethroids is now emerging in some areas. Work is in progress to develop alternative non-pyrethroid and synthetic pyrethroid insecticides for nets and indoor residual spraying and their evaluation must include the demonstration of their safety in pregnant women.

Insect repellents

In pregnant women, DEET (diethyltoluamide) can reduce exposure to mosquito bites.[19] The risk of its accumulation in the fetus is low and DEET is considered safe in pregnancy.[20] A randomised controlled trial of an insect repellent (20% diethylbenzamide) in an area of low malaria transmission at the Thai-Burmese border showed a non-significant reduction of 28% in the incidence of *P falciparum* infection.[21] Similar data from areas of more intense transmission are not available.

Antimalarial drug based prevention

Chemoprophylaxis

In sub-Saharan Africa, until the mid to late 1990s, prevention of malaria in pregnancy relied on weekly chloroquine prophylaxis. Although very effective,[22–24] poor compliance was a problem, even before the emergence and spread of drug resistance.[25] Furthermore, concerns were raised about the long-term effect of regular chemoprophylaxis on the acquisition of pregnancy-specific malaria immunity and the infant's susceptibility

to malaria.[26] However, only one prospective study has investigated this association. This study from The Gambia did not show that pyrimethamine-dapsone (maloprim) prophylaxis during the first pregnancy enhanced susceptibility to malaria infection during the subsequent pregnancy.[27] Currently, chloroquine chemoprophylaxis, though not widely implemented, continues to be policy in India, and in several countries in west Africa and Latin America.

Intermittent preventive treatment in pregnancy

IPTp was explored and developed to avoid the limitations of daily or weekly chemoprophylaxis.[28–31] It consists of an antimalarial treatment given at regular intervals during pregnancy, regardless of malaria infection or disease. IPTp safety and efficacy data are available only for chloroquine and sulfadoxine-pyrimethamine, the latter being the only drug currently used because of widespread chloroquine resistance. Sulfadoxine-pyrimethamine is cheap, safe in the second and third trimester, and can be given as a single dose. In areas with stable *P falciparum* malaria transmission, WHO recommends that at least two doses are given from the second trimester onwards at least 1 month apart.[1]

Drug resistance

The alarming increase of sulfadoxine-pyrimethamine resistance in Africa has raised concerns about its use as IPTp. Pharmacokinetic modelling suggests that the suppressive prophylactic effect of sulfadoxine-pyrimethamine, assuming similar pharmacokinetic profiles as in non-pregnant adults, may last approximately 2–3 months in areas with sensitive parasites.[32] The period of effective post-treatment prophylaxis then progressively shortens with increasing drug resistance, compromising the efficacy of the two-dose regimen given at 3-month intervals.[32] Sulfadoxine-pyrimethamine resistance is linked to mutations in the dihydrofolate reductase (*dhfr*) and dihydropteroate synthetase (*dhps*) genes. Parasites with four mutations in the *dhfr* gene, including the 164L mutation (highly prevalent in Thailand), are fully resistant. Such parasites have already been observed in Malawi, Uganda, and western Kenya[33–37] though their rate of spread cannot be predicted. It might be slowed if sulfadoxine-pyrimethamine use in the general population is not widespread and is limited to intermittent preventive treatment.

Semi-immune pregnant women respond better to failing antimalarials than symptomatic young children.[38,39] Meta-analysis of two trials in primigravidae and secundigravidae has shown that the protective efficacy of two-dose IPTp-sulfadoxine-pyrimethamine against placental malaria remains high (52%, 95% CI 32–67), even in areas where the treatment failure rate by day 14 in symptomatic children is between 20% and 40% (ter Kuile FO, unpublished).[40] No data on IPTp with sulfadoxine-pyrimethamine efficacy in areas with high sulfadoxine-pyrimethamine resistance (more than 40% treatment failure by day 14 in children) is available.

Gaps in knowledge of IPTp with sulfadoxine-pyrimethamine

Although there is clear evidence that IPTp with sulfadoxine-pyrimethamine is associated with a reduction in maternal anaemia and low bodyweight,[14,29–31,41] it is remarkable how much we do not know about a strategy that is so widely recommended.

Pharmacokinetics and pharmacodynamics

Surprisingly, there are no published studies of the pharmacokinetics of sulfadoxine-pyrimethamine in pregnant women. The pharmacokinetics of many drugs are altered in pregnancy so that the standard dose for non-pregnant adults might not be adequate, resulting in sub-optimal drug levels and shorter duration of the post-treatment prophylaxis.

Almost all countries with an IPTp policy have implemented a two-dose IPTp strategy.[1] Pharmaco-dynamic modelling suggests that increasing the frequency of IPTp to at least three doses for all women (HIV-infected women already require three doses)[29,40] may partly restore IPTp with sulfadoxine-pyrimethamine efficacy in areas where high grade antifolate resistance has not yet been established.[32]

In sub-Saharan Africa, antenatal clinic attendance is high: 68% of women attend at least once, most of them (95%) attend twice, and more than half of women attend four times. The most recent WHO-recommended schedule for antenatal care includes a total of four antenatal clinic visits, including three after quickening. Thus at least three instead of two doses would have the practical advantage that sulfadoxine-pyrimethamine could be given during each scheduled antenatal clinic visit after quickening, regardless of the HIV status of the pregnant woman.

Although increasing the frequency of the dosing to three or more might provide temporary respite in areas with increasing sulfadoxine-pyrimethamine resistance, it needs to be weighed against the major efforts that are required for successful and timely change of existing guidelines. Another concern is the lack of adequate safety information with the more frequent dosing regimen. The available evidence does not suggest that monthly dosing increases the risk of severe cutaneous reactions but the number of women exposed to three or more doses in controlled trials is still limited (850, of whom 346 were known to be HIV infected),[29,40,42] and more data are needed. Three further studies comparing monthly sulfadoxine-pyrimethamine with two-dose sulfadoxine-pyrimethamine are ongoing in Zambia, Malawi, and Tanzania. Finally, the effect of more complete protection from frequent dosing on the development of malaria-specific immune responses both in the pregnant woman and her baby will need to be evaluated.

Integrated approaches

Most studies of IPTp were done before the introduction of insecticide-treated nets to prevention policy in pregnancy. The absence of apparent risks associated with insecticide-treated net use and the additional benefits provided to the mothers and their infants dictate that future IPTp trials should be conducted in the context of insecticide-treated nets in Africa. However, the limited information does not suggest a synergistic or even additive effect between the combined effects of IPTp and insecticide-treated nets. One randomised controlled trial in Kenyan primigravidae and secundigravidae showed that the combination of insecticide-treated nets and (two-dose) IPTp with sulfadoxine-pyrimethamine was associated with only a slightly greater reduction of anaemia than either intervention alone, and only in primigravidae.[14] Three ongoing studies are assessing the interaction between these two interventions in Mozambique (Menéndez C and colleagues, unpublished), Uganda (Clark S and colleagues, London School of Hygiene and Tropical Medicine, London, UK, personal communication), and Rwanda (D'Alessandro U, and colleagues, unpublished).

Concomitant insecticide-treated net use might reduce the need or frequency of IPTp dosing, which may be an important advantage with new antimalarials and antimalarial combinations that are less well tolerated, involve more complex dosing regimens, and are more expensive than sulfadoxine-pyrimethamine. Although this may be attractive, insecticide-treated nets provide only partial protection against malaria, and the operational effectiveness might be compromised by incorrect or irregular use of nets and failure to re-impregnate the net. The operational benefits of single versus multipronged preventive approaches to malaria control in pregnancy deserve further investigation.

Coverage

It was initially thought that a drug regimen based on a few supervised doses would overcome the compliance limitations of chemoprophylaxis. However, studies in countries where IPTp has been implemented for several years show that the uptake of a second dose is surprisingly poor.[1,43] More operational research is needed to develop strategies to improve the uptake and effectiveness of this promising strategy, which is discussed in more depth in the companion Review by Jane Crawley and colleagues.[15]

Low or seasonal transmission areas

Many studies have been done in highly endemic areas. It is still unclear whether IPTp is effective in low transmission areas, mainly outside Africa, and at what level of transmission it would no longer be cost effective compared with case management alone.

A study in The Gambia, where malaria transmission is moderate and highly seasonal, showed that malaria chemoprophylaxis with pyrimethamine-dapsone in pregnancy was also effective during the low transmission season.[44] The efficacy and effectiveness of seasonal IPTp—ie, given at specific times of the year—has not yet been explored.

Alternative antimalarials for IPTp

During the past 10 years, the prospects for new antimalarial drugs have considerably improved. Several new antimalarials have or will soon become available. However, little is known about their safety, pharmacokinetic properties, and efficacy in pregnant women because of the systematic exclusion of pregnant women from drug trials for fear of toxicity to the fetus, the lack of a drug development programme specifically targeted at pregnant women, and the difficulties of extrapolating in vitro and animal studies to human beings.

Considerations for alternative antimalarials

Defining the ideal properties for a drug to be used for IPTp will help the choice of alternatives to sulfadoxine-pyrimethamine. Understanding the mechanism of action of IPTp is a crucial first step that establishes what pharmacokinetic or pharmacodynamic properties are required of alternatives to sulfadoxine-pyrimethamine.[32] IPTp might provide intermittent clearance of existing asymptomatic placental infections (treatment effect) and, with a slowly eliminated drug, might also prevent new infections by maintaining suppressive drug levels for several weeks after each treatment (post-treatment prophylactic effect). Although the precise mechanism of how falciparum malaria produces intrauterine growth retardation (IUGR) is not yet defined, IUGR tends to be greater with high placental parasite burden and high accumulation of monocytes and macrophages.[45] Thus, IPTp might also act by the suppression of parasitaemia to levels too low to cause adverse effects. If the duration of post-treatment prophylaxis is an important determinant of IPTp efficacy, drugs with long-half lives are likely to be more effective.[32] This should be verified by comparing drugs with different pharmacokinetic profiles. Similar trials are ongoing in infants and might provide useful information.

The safety profile of any drug to be used for IPTp needs to be excellent because it will be used in all women, regardless of malaria infection (the safety in pregnancy should be established first by treating parasitaemic women). It needs to be well tolerated to avoid low compliance, easy to use (ideally as a single dose), and affordable. None of the existing candidates fulfil this profile. It is clear that the days of very cheap, single dose therapies are over and that any alternative to sulfadoxine-pyrimethamine will require more complicated regimens and will cost substantially more. There are several promising candidates that are already available and some of which are, or have been, used for prophylaxis in pregnant women and for which sufficient safety data exists to warrant their evaluation for IPTp.

Alternative candidates

Mefloquine, currently recommended for chemoprophylaxis in all travellers, is worth considering.[46] It has a long half-life, can be given as a single or split dose, and is effective against both *P falciparum* and *P vivax*.[47] Mefloquine is relatively expensive, although its cost has recently declined. Resistance is rare in Africa but common in Latin America and southeast Asia. A retrospective study of 208 Karen women treated with mefloquine found an increased risk of stillbirths.[48] However, this finding was not confirmed in a large prospective trial of mefloquine prophylaxis in Malawian pregnant women[49] and remains unexplained. It needs to be further evaluated in larger trials. Mefloquine is well tolerated at prophylactic dosages (5 mg/kg per week),[49,50] but dose-dependent side-effects—dizziness in particular—are very common when used for treatment (15 to 25 mg/kg).[51,52] Low tolerability and the rare but more serious neuropsychiatric adverse effects might limit the acceptance of mefloquine for use as IPTp.

Amodiaquine in combination with sulfadoxine-pyrimethamine or artesunate is increasingly used in Africa as first-line treatment for uncomplicated malaria. There are, however, limited data on its safety in pregnancy.[53] A clinical trial from Ghana showed that the combination of amodiaquine with sulfadoxine-pyrimethamine was more effective in clearing peripheral parasitaemia by day 28 than sulfadoxine-pyrimethamine alone.[39] No serious side-effects were registered, although minor side-effects were more frequent in women treated with amodiaquine alone or in combination with sulfadoxine-pyrimethamine. Ongoing IPTp trials with the combination of amodiaquine with sulfadoxine-pyrimethamine in Ghana are expected to provide useful information on the combination's safety, tolerability, and efficacy in 2007.[39]

Chlorproguanil-dapsone is cheap but like most other combination therapies requires a 3-day treatment course. There is currently no information on its pharmacokinetics, safety, and efficacy in pregnancy (treatment studies in pregnant women are ongoing in Tanzania and Mali). The individual components have a good safety profile in pregnancy but severe haemolysis in women and offspring with glucose-6-phosphate dehydrogenase deficiency is of concern. Its major limitation for use as IPTp might be its short half-life.

Although chloroquine is virtually useless against falciparum malaria in most of Africa, southern Malawi has recently seen a complete reversal of chloroquine resistance several years after it withdrew chloroquine from the market.[54] In view of its excellent safety profile in pregnancy, including during the first trimester, perhaps there is a new role for this drug in the prevention of falciparum malaria in pregnant women in certain settings that have seen a return of chloroquine sensitivity. There is some experience with use of chloroquine for IPTp from a study in Mali, which showed IPTp with chloroquine was well tolerated and as effective as weekly chloroquine in preventing placental infection, although less effective than IPTp with sulfadoxine-pyrimethamine.[55]

Although the effects of *P vivax* infection in pregnancy are now recognised,[4] no policy exists for its prevention. With the exception of Indonesia and Papua New Guinea, chloroquine remains effective against *P vivax* malaria. One published trial with weekly chloroquine prophylaxis (300 mg base) from the Thai-Burmese border showed complete protection against *P vivax*.[56]

Azithromycin—the most potent antimalarial macrolide antibiotic—has been extensively used in pregnancy. It has low efficacy against falciparum malaria when used alone, but has in vitro synergistic properties with quinine and chloroquine against *P falciparum*. Azithromycin is used as prophylaxis for opportunistic infections against sexually transmitted diseases such as syphilis, chlamydia, gonorrhoea, and chancroid. Sulfadoxine-pyrimethamine combined with 2 days of azithromycin at a total dose of 2 g was well tolerated and more effective than sulfadoxine-pyrimethamine alone for treatment of malaria in Malawian pregnant women (Kalilani L and colleagues, University of North Carolina, USA, personal communication). Higher doses (3–6 g) over 2 or 3 days may be required to achieve 95% cure.

Artemisinin derivatives are given in combination with other antimalarials to prevent the selection of resistant parasites. Potential partner drugs are sulfadoxine-pyrimethamine, mefloquine, amodiaquine, and chlorproguanil-dapsone. A coformulated artemisinin-based combination therapy (ACT) containing artemether and lumefantrine (Coartem) is already available, whereas dihydroartemisinin with piperaquine, and artesunate with either mefloquine or amodiaquine, will be registered soon.

Treatment with artemisinins in second and third trimesters has shown no maternal or fetal toxicity in over 1000 pregnancies.[7,57] However, fetal resorption and cardiovascular and skeletal abnormalities occur when rats and rabbits are exposed to relatively low doses of artemisinins in the first trimester.[58] Studies in primates have confirmed these findings (addressed in more detail by Stephen Ward and colleagues)[59] and suggest that careful evaluation of accidental exposure in the first trimester in human beings is warranted.

Should there be a role for artemisinin-based combinations for IPTp? It has been argued that the main mechanism of action of IPTp is the prevention of new infections.[32] If this is confirmed in mechanistic studies, a rapidly eliminated artemisinin component might provide very little direct benefit. Even if the use of an ACT would accelerate parasite clearance, prevent gametocyte production, and reduce the risk of de novo emergence of resistance, its benefits in asymptomatic pregnant women with low density parasitaemia or no infection are unclear.[32] Another limitation for the use of ACTs is that all of them need to be given over 3 days. The risk–benefit ratio is different in the case

management of malaria in pregnancy. Thus, the main benefit of adding an artemisinin derivative for IPTp might be the prevention of abuse of monotherapies and the further development of resistance in the population. This benefit needs to be weighed carefully against the safety concerns about their accidental use in the first trimester in women attending antenatal care. Clearly, further debate is warranted as more information will become available on the safety of artemisinin derivatives in pregnancy from treatment studies and on the mechanism of action of IPTp.

Effect of HIV infection on malaria in pregnancy prevention

Malaria prevention is particularly challenging in HIV-infected women, who might constitute up to 40% of the antenatal population in southern Africa. HIV-infected pregnant women are more likely to fail antimalarial treatment and require three or more doses of IPTp with sulfadoxine-pyrimethamine to obtain the same effect achieved with two doses in HIV-uninfected women.[29,40,60] At more than 10% HIV seroprevalence a strategy that would provide three or more doses to all women would be more cost effective than differential dosing by HIV-status of the woman.[61] Currently, Zambia is the only country that has implemented a three-dose policy for all pregnant women, and Mozambique is in the process of implementing this policy.

Although not widely implemented, co-trimoxazole prophylaxis against opportunistic infections is recommended for HIV-positive individuals with CD4 counts more than 350 cells per μL, or with WHO clinical stage three or four infection and any CD4 level. In areas with limited health resources and high HIV prevalence, universal co-trimoxazole for all HIV-positive individuals has been proposed, including pregnant women.[62] Co-trimoxazole and sulfadoxine-pyrimethamine share the same mechanisms of action and resistance patterns, and the risk of severe cutaneous reactions might be increased in HIV-infected individuals.[63] Although sulfadoxine-pyrimethamine may not be very effective against bacterial pathogens,[64,65] daily or thrice-weekly co-trimoxazole prophylaxis has been shown to be highly effective in preventing malaria infection and morbidity in children[66,67] and in HIV-infected adults.[68–70] Current WHO guidelines therefore do not recommend IPTp with sulfadoxine-pyrimethamine in pregnant women receiving co-trimoxazole prophylaxis, but the preventive antimalarial efficacy of co-trimoxazole has not been formally evaluated in pregnant women. The role of IPTp with alternative antimalarials in women receiving co-trimoxazole prophylaxis might need to be evaluated, particularly in areas with high antifolate resistance.

The increasing implementation of antiretroviral treatment in HIV-infected individuals is also relevant to malaria control. Very little is known of the potential interactions between antiretroviral and antimalarial drugs in terms of safety, pharmacokinetics, and efficacy.[71]

Although not yet widely used in Africa, protease inhibitors may impair CD36 mediated cytoadherence and non-opsonic phagocytosis of parasitised erythrocytes, and may have antimalarial properties.[72–76]

Primigravidae versus all parities prevention

An important epidemiological feature of malaria in pregnancy is that the adverse effects tend to decrease with increasing parity, particularly where malaria transmission is high. In the early trials among semi-immune women, the substantial impact of malaria chemoprophylaxis was limited to primigravidae. It was then suggested that malaria control should target primigravidae and secundigravidae.[77] This is no longer recommended for several reasons: (1) an accurate assessment of parity is problematic in busy antenatal clinics; (2) HIV has altered the parity-linked pattern of malaria risk;[6] (3) young maternal age is a risk factor for malaria in pregnancy independent of parity;[78–80] (4) placental malaria per se might be associated with an increased risk of malaria infection and morbidity during infancy;[81–84] (5) all newborn babies, regardless of parity, can benefit from insecticide-treated nets; and (6) prevention of malaria in the earlier pregnancies, by preventing the development of the pregnancy-dependent protective immune responses, might increase the risk of malaria in subsequent pregnancies. Therefore, even in high transmission areas, interventions should target all pregnant women.

Gestational age at initiation of prevention

Further studies are required to determine the feasibility, risk, and benefits of prevention strategies that include the first trimester. Although the prevalence of peripheral parasitaemia is highest during the second trimester,[79,85] malaria infection occurs frequently during the first trimester, as has been observed in rural Mozambique (Bardaji A and colleagues, Centre for International Health, Hospital Clinic, Univeristy of Barcelona, Spain, personal communication) and Burkina Faso (D'Alessandro U and colleagues, unpublished). Pharmacological prevention of malaria in the first trimester is a major challenge because of the risk of harming the developing fetus and because of the low antenatal clinic attendance. Community (rather than antenatal clinic) distribution of insecticide-treated nets targeting young women before their first pregnancy, such as through adolescent friendly programmes, could ensure that women are protected as early as possible during pregnancy.

Micronutrients and prevention of malaria in pregnancy

Pregnancy increases nutritional requirements and micronutrient deficiencies are very common in developing countries where many women are already compromised before pregnancy. In most malaria endemic countries folic acid, iron, and vitamin A are routinely given to pregnant and lactating women. It is

important to understand whether the interactions between these micronutrients, the antimalarial drugs, and the parasite itself affect the risk of malaria.

There are complex interactions between folic acid, antimalarial folate-antagonists, and malarial parasitaemia. An earlier report in children showed that sulfadoxine-pyrimethamine antimalarial activity could be compromised by the co-administration of folic acid.[86] However, in this study children received a much higher dosage of folic acid than recommended. Results from two studies that addressed this interaction in pregnant women showed lack of a negative interaction between an antimalarial with antifolate activity (sulfadoxine-pyrimethamine) and folate supplements on the risk of malaria when folate was given in the recommended preventive doses (0·4–0·5 mg per day), but high-dose folate (5 mg per day) compromised sulfadoxine-pyrimethamine treatment efficacy.[87,88]

Iron deficiency and acute malaria commonly coincide. There is a long-standing controversy on the benefits or adverse effects of iron supplementation to individuals exposed to malaria.[89–92] The only two randomised placebo-controlled trials of oral iron supplementation in semi-immune pregnant women found clear benefits of iron supplementation without any increased risk of malaria, with the exception of women with sickle cell trait.[93–95] In view of the high frequency of iron deficiency in pregnant women, the recommendation of routine iron supplementation should not be changed but should be accompanied by adequate protection against malaria. Evaluation of its effect in certain specific groups, such as HIV-infected women, needs to be considered.

In resource-poor countries, between 2% and 31% of pregnant women have been reported to have low vitamin A levels, contributing to the development of vitamin A deficiency in the newborn baby during the first months of life.[96] WHO recommends daily or weekly vitamin A supplementation during pregnancy plus a single dose shortly after delivery.[96] One study in children showed that vitamin A reduced the risk of malaria.[97] More recently, a non-significant reduction in placental malaria was observed in women under vitamin A supplementation.[98] These observations deserve further investigation.[98]

Vaccines to prevent malaria in pregnancy

Pregnancy-specific vaccines that block cytoadherence of infected red-blood cells from binding to chondroitin sulphate A in the placental syncytiotrophoblast could prevent placental sequestration of *P falciparum* and a number of research groups are currently working on this. The success of such a vaccine would depend on whether placental sequestration is either the only or the main pathophysiological mechanism responsible for the harmful effects of malaria in pregnancy. A pre-erythrocytic vaccine that effectively prevents blood stage infections and is not strain specific could also protect pregnant women. Of all the malaria vaccines under

Panel: High priority general research questions for malaria in pregnancy prevention strategies

- What new/alternative drugs can be used for IPTp?
- What is the the optimum dosing pattern for IPTp in all areas, including highly seasonal transmission, and in low-transmission settings in the context of insecticide-treated net coverage?
- What is the effect of co-trimoxazole prophylaxis on malaria prevention in HIV-positive women?
- What is the need for, and approach to, the prevention of malaria in pregnancy in settings of lower transmission and settings where both *P falciparum* and *P vivax* are prevalent?

development, the pre-erythrocytic vaccine RTS,S/AS02A is in the most advanced stage of development.[99] If trials in children continue to show promise, tests of RTS,S/AS02A in pregnant women will be justified.

Discussion and research priorities

In the past decade important progress has been made in the development of key control strategies for malaria in pregnancy in Africa, such as the introduction of IPTp and insecticide-treated nets. However, the rate at which sufficient evidence became available, the process that led to policy changes, and their subsequent implementation has taken more than 15 years. Widespread resistance to sulfadoxine-pyrimethamine and chloroquine, the most commonly used antimalarials in pregnancy, has caught up with us. In Africa, concomitant insecticide-treated net use and increasing the frequency of dosing of IPTp with sulfadoxine-pyrimethamine might partly restore efficacy and provide temporary respite, but careful documentation of the effect and safety of more frequent dosing is required.

From the range of research questions regarding the prevention of malaria in pregnancy that are discussed in this manuscript, we have summarised the key research questions that we consider of highest priority in the panel.

The identification of safe and affordable alternatives to sulfadoxine-pyrimethamine is one of the highest priorities for the control of malaria in pregnancy. A number of promising alternatives are available and need to be urgently evaluated with a series of sequential studies that will generate pharmacokinetic, safety (mother and baby), and efficacy data. For some of the newer antimalarials, safety in pregnancy needs to be assessed in parasitaemic women first before they can be considered as candidates for IPTp. In malaria endemic Africa, these studies should be done within the context of insecticide-treated net use so that the benefits of integrated approaches are better understood.

Despite the increased recognition of the importance of the burden of falciparum and vivax malaria in Asia and Latin America, where at least half of all malaria-exposed

pregnancies occur, almost nothing is known of the true effect of malaria in pregnancy in these regions nor of appropriate prevention, and studies on the efficacy and cost-effectiveness of IPTp, or seasonal IPTp, are urgently required in these settings.

Enhanced coordination (between research groups, the private sector, donors, and policymakers) is necessary for a rapid evaluation of promising interventions and their transfer into practice. This evaluation will require a series of randomised controlled trials using a multicentre approach to allow for variations in cultural and political factors, parasite species, drug resistance, host-genetic polymorphisms, and HIV prevalence. These studies would need to include careful follow-up of the infant to establish the effect of malaria in pregnancy prevention strategies on the development of malaria-specific immunity in both the woman and her offspring,[100] and will require multidisciplinary approaches to allow evaluation of the perceptions and acceptability of different preventive interventions,[15] and their cost-effectiveness.[101] The low insecticide-treated net coverage and poor implementation and compliance with IPTp with sulfadoxine-pyrimethamine in most countries where both preventive strategies are currently implemented reflect the failure of translating scientific findings into effective programmes.[15] Involvement of policymakers from the outset together with operational research to answer questions raised by implementers should be key components of a research strategy.

A malaria in pregnancy consortium of interested scientists, industrial partners, funding agents, and policymakers, which coordinates the agreed overall programme of research and ensures comprehensive and appropriate coverage of research priorities, has been proposed to work in a complementary way to address these issues. Bringing together key stakeholders will ensure that new ways of preventing and treating malaria in pregnancy are found and implemented as rapidly and effectively as possible.

Conflicts of interest
We declare that we have no conflicts of interest.

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