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A Strategic Framework for Malaria Prevention and Control During Pregnancy in the African Region

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Preface

Africa bears 90% of the world's burden of malaria. Pregnant women and children in Africa are particularly vulnerable to the adverse consequences of malaria caused by the most lethal parasite, *Plasmodium falciparum*. The African Region of the World Health Organization (WHO) experiences the majority of the global burden of malaria-associated maternal illness and low birth weight. Pregnant women in malaria-endemic areas do not always receive the necessary prevention and treatment they need, and this contributes to the extremely high numbers of maternal and infant deaths caused by malaria.

Developing and strengthening national capacity for prevention and control of malaria during pregnancy is a high priority for the Region, and the Malaria Control Programme of the WHO Regional Office for Africa is committed to supporting countries' efforts to decrease the burden of malaria on pregnant women and infants. The Malaria Control Programme works within the context of the Roll Back Malaria initiative, a global partnership committed to halving the malaria burden by 2010.

This publication is a strategic framework intended to provide guidance to policy-makers and National Programmes for the prevention and control of malaria in pregnant women, who remain the main adult target group in the WHO African Region. Strengthened collaboration between malaria control and reproductive health programmes is required for the successful reduction of malaria, and it provides an opportunity for reducing maternal morbidity and mortality as well as improving the health care and well being of all Africans.

The framework describes the burden of malaria in pregnancy, recommends interventions for the prevention and control of malaria during pregnancy, proposes a strategy for delivering interventions and suggests approaches for programme development in highly endemic areas in the African Region. Guidelines for the diagnosis, treatment and prevention of malaria in pregnancy have been developed as a companion document to this framework.

As countries develop national health plans, national malaria control programmes and reproductive health programmes, they are encouraged to adapt and expand this framework according to their epidemiologic and programme realities. With stronger collaboration for effective antenatal services at national and local levels, the Abuja Malaria Summit (2000) target of 60% of pregnant women covered by effective interventions can be achieved by 2005.

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Executive summary

The WHO African Region experiences the highest proportion of malaria-related illnesses and deaths, especially those caused by the most lethal malaria parasite, *Plasmodium falciparum*. Supporting countries to reduce the enormous health impact associated with malaria is therefore of utmost importance.

In Africa, malaria's ill effects on pregnant women and children under 5 differ according to transmission and immunity levels. In areas of low or unstable malaria transmission, women have no significant level of immunity and will develop clinical illness when parasitaemic. They are at risk of dying from severe malarial disease or from experiencing spontaneous abortion, premature delivery or stillbirth. In areas of high or moderate (stable) malaria transmission, women are semi-immune, and most malaria infections, although asymptomatic, can contribute to severe maternal anaemia and thus increased risk of maternal death. Malaria infection of the placenta and malaria-caused maternal anaemia contribute to low birth weight, which results in higher infant mortality and impaired child development.

Despite this extraordinary toll, malaria prevention and control during pregnancy has not received broad programme support until recently. Malaria infection in pregnant women is largely asymptomatic in areas of greatest burden and thus requires a preventive approach. The control approach to date, weekly chloroquine chemoprophylaxis, has been difficult to implement in terms of delivery and compliance and has been affected by increasing antimalarial drug resistance. The limited number of safe and effective antimalarial drugs for use during pregnancy and the weak collaboration between malaria control and reproductive health programmes have also limited the success of efforts to control malaria during pregnancy. In the past decade, however, effective prevention and control approaches have been identified to address these limitations.

This strategic framework for malaria prevention and control during pregnancy in areas of stable malaria transmission recommends three interventions: intermittent preventive treatment (IPT), insecticide-treated nets (ITNs) and case management of malaria illness and anaemia.

In most settings of stable malaria transmission in Africa, most pregnant women attend an antenatal clinic at least once during their pregnancy, making clinic-based prevention feasible. Priority should be placed on developing programmes based in antenatal clinics that support both IPT and ITNs along with other essential elements of the antenatal care package. This will require strengthened collaboration between national malaria control programmes and reproductive health programmes.

Expanding programme coverage will require careful monitoring of programme implementation and evaluation of impact. Research is urgently required to improve implementation efforts, develop new approaches, address issues related to prevention of malaria during pregnancy in areas of low transmission and discover and develop new drugs.

1. Introduction

The African Summit on Roll Back Malaria (RBM) in April 2000 adopted the Abuja Declaration in which regional leaders committed to ensuring that 60% of pregnant women in malaria-endemic communities accessed effective prevention and treatment of malaria by 2005.

The following approaches will be used to meet the Abuja targets of:

- Supporting and promoting access to correct, affordable and appropriate treatment within 24 hours of the onset of symptoms;
- Supporting and promoting access to a suitable combination of personal and community protective measures such as insecticide-treated nets (ITNs);
- Supporting and promoting the use of malaria preventive measures such as chemoprophylaxis or intermittent preventive treatment (IPT) for pregnant women, especially those in their first pregnancies.

This bold commitment can be realized if effective mechanisms for programme interventions are implemented to apply what is known about the impact and the prevention and control of malaria infection during pregnancy.

Each year, approximately 25 million African women become pregnant in malaria-endemic areas and are at risk of *Plasmodium falciparum* malaria infection during pregnancy.[1] Most women in the African Region reside in areas of relatively stable malaria transmission where the principal effects of malaria infection during pregnancy are associated with malaria-related anaemia in the mother and with the presence of parasites in the placenta [1–3]. The resultant impairment of fetal nutrition contributes to low birth weight (LBW), which is a leading cause of poor infant survival and development in Africa [4, 5].

Pregnant women who reside in areas of low or unstable malaria transmission have little or no immunity to malaria, and their risk of developing severe disease as a result of malaria infection is two to three times greater than that of nonpregnant women living in the same area [6]. In these areas, pregnant women may die as a direct result of severe malaria or as an indirect result of malaria-related severe anaemia [6, 7]. In addition, malaria infection of pregnant women may result in a range of adverse outcomes, including spontaneous abortion, neonatal death and LBW [5].

Although the serious impact of malaria infection during pregnancy has been known for a half century, coverage of pregnancies at risk for malaria infection according to World Health Organization (WHO) and national guidelines has been low in most malaria-endemic countries. Control of malaria during pregnancy depends on both preventing infection, since most women in areas of stable transmission will not experience serious clinical illness themselves, and clearing

[1] In the year 2000, an estimated 24.6 million liveborn babies were delivered in malarious areas of Africa. This estimate is based on a model developed by Snow and colleagues using Mapping Malaria Risk in Africa (Snow RW et al., Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population, *Bulletin of the World Health Organization* 1999; 77:624–640) and its application to UNICEF data on live births (UNICEF, State of the world's children, Oxford: Oxford University Press, 1998) adjusted for the year 2000.

parasitaemia when it occurs. The effectiveness of the previous policy of weekly chemoprophylaxis with chloroquine (CQ) was limited by poor compliance outside the clinic setting [5, 8]. The expansion of drug resistance of *P. falciparum* to CQ and other drugs has further eroded the effectiveness of CQ chemoprophylaxis [5, 8, 9].

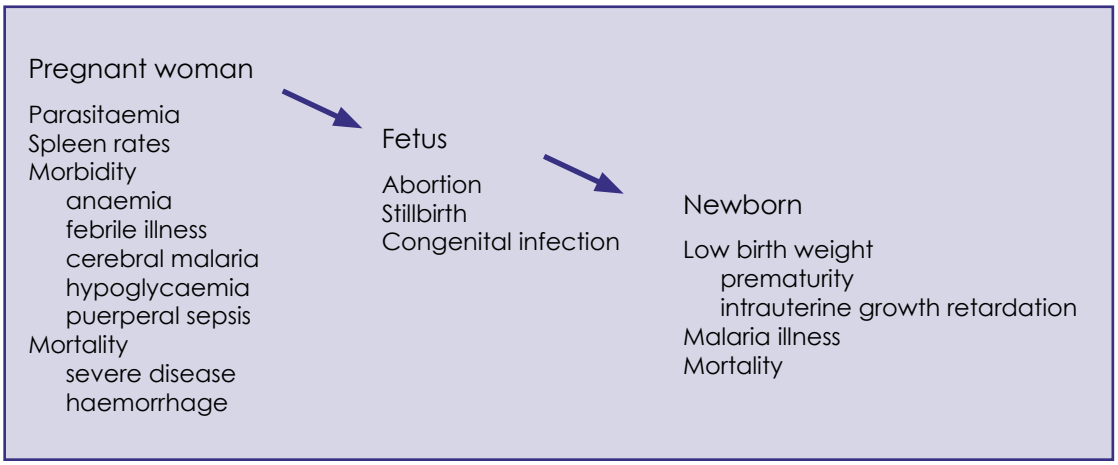
In the past decade, strategies have been developed to more effectively control the adverse effects of malaria during pregnancy, and these can serve as the basis for highly effective programmes in the African Region. The development of the IPT approach constitutes a major advance for achieving high programme coverage and effectiveness [10, 11]. Similarly, the demonstrated success of ITNs used during pregnancy to reduce both maternal and infant morbidity due to malaria infection provides a powerful prevention approach for Africa [12, 13].

2. Malaria infection during pregnancy

2.1 Overview

Malaria infection with *P. falciparum* during pregnancy results in a wide range of adverse consequences for the pregnant woman, the developing fetus and the newborn infant (Figure 1).

Figure 1: Adverse consequences of malaria during pregnancy



Effects on maternal health

The effect of infection on the mother may range from negligible to severe, depending on the level of immunity to malaria infection that the mother has acquired prior to pregnancy and the efficacy of these immune responses during her pregnancy [5]. Acquired antimalarial immunity depends on the intensity of malaria transmission, the number of previous pregnancies and the presence of other conditions such as human immunodeficiency virus (HIV) infection which may further impair the efficacy of immune responses during pregnancy [14–17].

Even asymptomatic infections (those that do not produce fever or clinical illness) frequently worsen maternal anaemia [18]. Anaemia is more common in pregnant women than nonpregnant women for a variety of reasons, including the dilutional effects of increased intravascular volume during the second trimester as well as the increased demand on iron and folate stores [11, 19]. Although anaemia during pregnancy may have multiple causes (HIV infection, inadequate nutrition, haemoglobinopathies and hookworm infection), the contribution of malaria is substantial. Severe maternal anaemia increases the mother's risk of death, and malaria-related anaemia is estimated to cause as many as 10 000 maternal deaths each year in Africa [20].

HIV infection diminishes a pregnant woman's ability to control *P. falciparum* infections [14]. The prevalence and intensity of malaria infection during pregnancy is higher in women who are HIV-infected [14–17]. Women with HIV infection are more likely to have symptomatic infections and to have an increased risk of malaria-associated adverse birth outcomes [16, 21]. Multigravidae with HIV infection are similar to primigravidae without HIV infection in terms of susceptibility to and negative consequences of malaria infection [16]. Therefore, in the presence of HIV infection, the risk associated with placental malaria appears to be independent of the number of pregnancies [16].

Effects on infant health

Malaria infection in the mother, especially in areas of low or unstable transmission, can result in abortion, stillbirth or congenital infection [22–27]. During the second half of pregnancy, malaria infection, in combination with maternal anaemia, can interfere with fetal weight gain and contribute to intrauterine growth retardation or prematurity and thus result in LBW [28–32] (see Figure 1).

Effects of infections with other malaria species

The effects of the other three parasites that cause malaria in humans (*P. vivax, P. malariae* and *P. ovale*) are less clear. Pregnant women in Africa at risk of *P. vivax* infection reside primarily in areas of low or unstable transmission. In these areas, *P. vivax* infections are likely to result in febrile illness. A study among nonimmune pregnant women in Thailand reported that *P. vivax* malaria during pregnancy is associated with maternal anaemia and LBW but to a lesser extent than is *P. falciparum* [33]. Studies are needed to better define the effects of *P. vivax* infection on the health of pregnant African women and newborns.

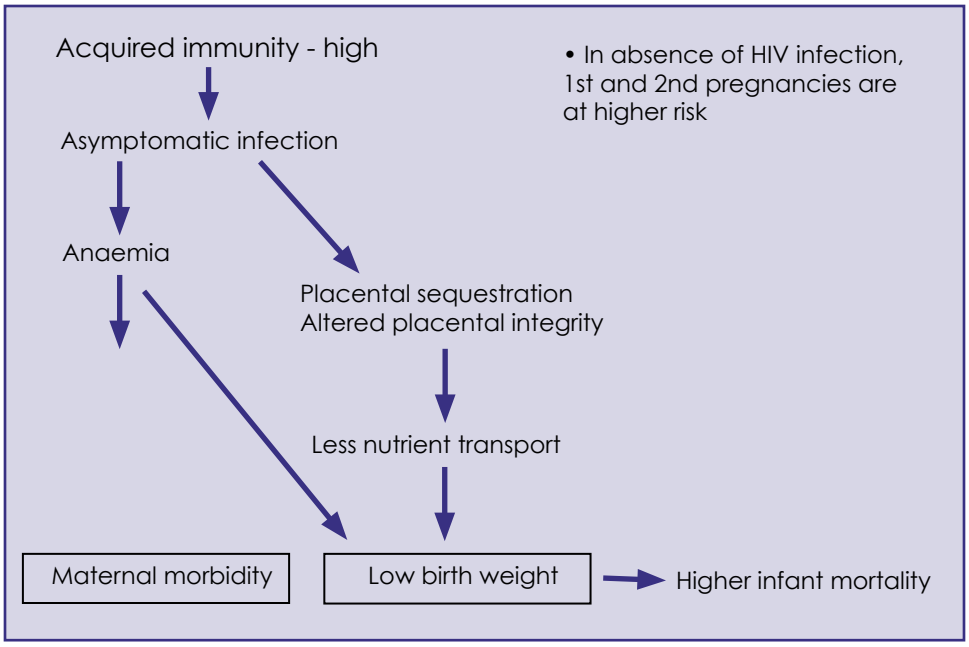
2.2 Effects of intensity of transmission

The symptoms and complications of malaria during pregnancy differ according to the intensity of malaria transmission in a particular setting and thus the pregnant woman's level of immunity. While two distinct epidemiologic settings are recognized, in reality, the intensity of transmission and immunity in pregnant women occur on a continuum, with potentially diverse conditions occurring within a single country.

Areas of high or moderate (stable) transmission

Stable transmission predominates in Africa south of the Sahara; consequently, this region bears the greatest burden of malaria infections during pregnancy. In these areas of high or moderate (stable) malaria transmission, the ill health effects are particularly apparent in the first and second malaria-exposed pregnancies (Figure 2).

Figure 2: Adverse consequences of malaria during pregnancy: Areas of high or moderate (stable) transmission



Despite the higher prevalence of parasitaemia and higher parasite density in pregnant women than nonpregnant women, *P. falciparum* infection in pregnant women in these areas is usually asymptomatic. Maternal immunity reduces the risk of severe illness. Thus, clinical malaria is not a prominent feature of the infection during pregnancy, and in settings of stable malaria transmission, maternal mortality due solely to malaria is uncommon. In these settings, the major detrimental effect of infection is LBW and maternal anaemia.

In areas with stable malaria transmission (where prevalence during pregnancy ranges from 10% to 65%), malaria during pregnancy contributes to approximately 2% to 15% of maternal anaemia and 8% to 14% of LBW [1, 34] (Table 1). Malaria contributes to an estimated 8% to 36% of prematurity and to an additional 13% to 70% of intrauterine growth retardation, depending on level of malaria risk [1]. Importantly, maternal malaria infection accounts for almost 30% of all the causes of LBW that can be prevented during pregnancy (that is, by antenatal interventions) [34]. Maternal malaria infection is estimated to account for 3% to 8% of all infant deaths [1, 34].

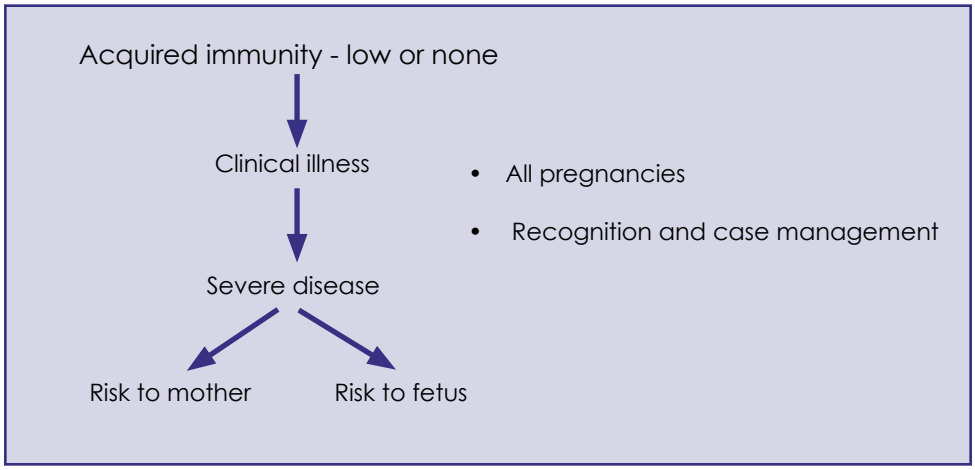
Table 1: Malaria's contribution to anaemia, low birth weight and infant death

Adverse health event	% of total
Maternal anaemia	2–15
Low birth weight	8–14
Preterm	8–36
Intrauterine growth retardation	13–70
Infant death	3–8

Areas of low or unstable transmission

In areas of low or unstable malaria transmission, women of reproductive age have relatively little acquired immunity to malaria, and hence all pregnant women are at similar risk for malaria infection. Consequences in these settings include maternal illness, severe malaria with central nervous system complications, anaemia and adverse reproductive outcomes, including stillbirths, abortions and LBW [5, 6, 22–26] (Figure 3). Malaria infection contributes to pregnancy loss in the first trimester, while malaria infection during the third trimester contributes to premature delivery. Other consequences during pregnancy commonly associated with *P. falciparum* infection include hypoglycaemia, hyperpyrexia, severe haemolytic anaemia and pulmonary oedema [35].

Figure 3: Adverse consequences of malaria during pregnancy: Areas of low or unstable transmission



3. Developing effective prevention and control programmes

3.1 Learning from history

In the past, WHO recommended that pregnant women in malaria-endemic areas receive full antimalarial treatment on their first contact with antenatal service followed by weekly chemoprophylaxis (i.e. frequent, regular use of an antimalarial drug given at less than a therapeutic dose) [8]. The drug most commonly used for chemoprophylaxis has been CQ. The implementation of this policy has been limited by a number of factors, including (i) spread of antimalarial drug resistance, particularly to CQ, (ii) poor compliance with a weekly regimen throughout pregnancy and (iii) adverse effects, especially pruritus associated with CQ.

The spread of CQ resistance across most of Africa has seriously affected the choice of antimalarial drugs available for preventing malaria during pregnancy. In the east, central, southern and western areas of Africa, CQ will no longer eliminate *P. falciparum* infection. Consequently, national policies that continue to advocate CQ use for weekly prophylaxis will have negligible programme effectiveness due to the drug's marginal efficacy in addition to the aforementioned problems with compliance resulting from the need for frequent dosing (Box 1).

Box 1
Chloroquine prophylaxis no longer recommended

Weekly chemoprophylaxis with chloroquine (CQ) during pregnancy has been shown to be of limited effectiveness because of poor compliance with the regimen and increasing drug resistance. Therefore, weekly CQ chemoprophylaxis no longer has a role in national policies for the prevention and control of malaria during pregnancy in stable transmission areas in the African Region.

Even as recently as the late 1980s, few African countries had programmes that provided chemoprophylaxis to most pregnant women. For example, one well-supported community health programme in western Kenya that used village health-care workers to provide chemoprophylaxis to pregnant women was able to provide weekly CQ chemoprophylaxis to only 29% of primigravidae [36]. One problem limiting coverage of pregnant women was acceptability of the CQ chemoprophylaxis regimen.

In Malawi, where more than 90% of pregnant women attend antenatal clinics, local taboos against ingesting bitter substances, such as CQ, during pregnancy limited women's acceptance of chemoprophylaxis [37, 38]. A survey of seven regions in four countries found that although 34% to 68% of pregnant women reported using an antimalarial drug during their pregnancy, only 1% to 18% reported using an antimalarial drug on a weekly basis at a dosage close to the WHO recommendation [5].

3.2 Programme collaboration

The African Region experiences the highest proportion of the global burden of malaria-associated maternal illness and LBW. Consequently, this region requires an accelerated effort to implement comprehensive programmes to prevent and control malaria during pregnancy.

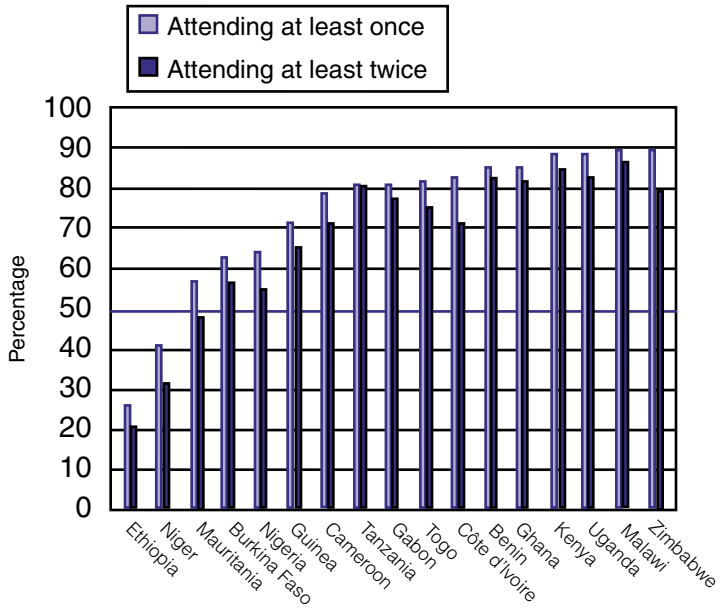
It has been documented that across Africa an average of more than 70% of women attend antenatal clinics at least once during pregnancy, and many attend at least twice [39] (Figure 4).

This represents a unique opportunity for prevention of malaria, along with other priority diseases affecting pregnant women.

For this reason, the Malaria Programme of the Regional Office for Africa of WHO has targeted the antenatal clinic as the site for accelerating programme implementation of malaria prevention and control during pregnancy in those areas with stable malaria transmission and high antenatal clinic attendance. In areas with low antenatal coverage, the development and strengthening of community-based programmes is important. In areas with adequate antenatal coverage, community-based programmes can enhance coverage.

The Malaria Programme works in close collaboration with the Safe Motherhood Programme, which is similarly committed to strengthening reproductive health services. Together, these programmes can focus on prevention and case management capacity building in primary care facilities and on the progressive expansion of trained community-based health care workers.

Figure 4: Percentages of pregnant women attending antenatal clinics, selected countries



WHO/UNICEF, The Africa Malaria Report 2003, p 40.

4. Strategic framework for malaria prevention and control during pregnancy

Pregnant women in malaria-endemic areas of Africa often do not receive adequate preventive and curative care. Health care for these women should be delivered in a comprehensive package based on the extent of defined health burden and opportunities for intervention.

Box 2

Recommended interventions for malaria prevention and control during pregnancy (in areas of stable transmission)

The policy for malaria prevention and control during pregnancy in areas of stable transmission should emphasize a package of intermittent preventive treatment (IPT) and insecticide-treated nets (ITNs) and ensure effective case management of malaria illness and anaemia.

Intermittent Preventive Treatment

All pregnant women in areas of stable malaria transmission should receive at least two doses of IPT after quickening. The World Health Organization recommends a schedule of four antenatal clinic visits, with three visits after quickening. The delivery of IPT with each scheduled visit after quickening will assure that a high proportion of women receive at least two doses. IPT-SP doses should not be given more frequently than monthly.

Currently, the most effective drug for IPT is sulfadoxine-pyrimethamine (SP) because of its safety for use during pregnancy, efficacy in reproductive-age women and feasibility for use in programmes as it can be delivered as a single-dose treatment under observation by the health worker.*

Insecticide-Treated Nets

ITNs should be provided to pregnant women as early in pregnancy as possible. Their use should be encouraged for women throughout pregnancy and during the postpartum period. ITNs can be provided either through the antenatal clinic or other sources in the private and public sectors.

Effective Case Management of Malaria Illness and Anaemia

Effective case management of malaria illness for all pregnant women in malarious areas must be assured. Iron supplementation for anaemia should be given to pregnant women as part of routine antenatal care. Pregnant women should also be screened for anaemia, and those with moderate to severe anaemia should be managed according to national reproductive health guidelines.

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*Current scientific evidence suggests the following:
1) At least two IPT doses are required to achieve optimal benefit in most women;
2) One study of IPT in HIV-infected pregnant women has demonstrated that monthly dosing of IPT (with most women getting three to four doses) was necessary to achieve optimal benefit;
3) In settings with HIV prevalence in pregnant women greater than 10%, it is more cost effective to treat all women with a three-dose regimen than to screen for HIV and provide this regimen only to HIV-infected women;
4) There is no evidence that a third dose of IPT causes any additional risk, that more than three IPT doses during pregnancy offers additional benefit or that receiving three or more doses of IPT with sulfadoxine-pyrimethamine will result in an increased risk of adverse drug reactions. Research to assess the safety, efficacy and programme feasibility of other antimalarial drugs for use in IPT is ongoing.

A policy that addresses the control of malaria during pregnancy in the African Region must be responsive to the range of malaria epidemiologic settings and antenatal care conditions encountered (Box 2). The goal of a regional policy is to attain high levels of antenatal coverage for pregnant women with prompt and effective treatment for malaria illness and an effective range of preventive measures (ITNs and IPT). The policy is based on common approaches that will serve most countries or could be adapted to local realities. This policy will provide guidance to individual countries on how to tailor national guidelines according to the local epidemiology of malaria and antenatal care conditions.

This regional approach for the control of malaria during pregnancy is designed to address most ranges of malaria transmission and health care settings encountered in the African Region. The high utilization of antenatal and reproductive health clinics by African women provides an opportunity for national programmes to initially strengthen malaria prevention and treatment services in the clinic setting. This will be accomplished by working with programmes which are responsible for and invest in strengthening clinic services for women of reproductive age.

Programmes are urged to adopt several approaches that include ITNs, IPT and prevention and treatment of anaemia, along with appropriate case management services. Linking with community-based maternal and reproductive health services is important to serve the greatest number of women at risk. In those areas where antenatal clinic services are not well developed, malaria control programmes should explore partnerships with community health care workers, such as traditional and skilled birth attendants.

Countries will be assisted to accelerate programme development; they can then build on established programmes and partnerships in individual countries and communities.

4.1 Management of malaria and anaemia cases during pregnancy

Malaria

Case management of malaria illness is an essential component of malaria prevention and control during pregnancy in all areas where pregnant women are at risk of malaria. Pregnant women with symptomatic malaria are at higher risk of fetal loss, premature delivery and death, and thus urgently need to be treated. Treatment of malaria during pregnancy aims at completely eliminating the infection because any level of parasitaemia is of consequence to the mother and fetus.

Each malaria endemic country in the African Region requires a policy that guides effective case management for malaria illness in pregnant women. These guidelines need to address the unique clinical features of malaria infection in pregnant women as well as specific indications, contraindications and potential complications associated with antimalarial drugs during pregnancy.

The recommended antimalarial drugs for treatment of uncomplicated malaria are CQ in CQ-sensitive areas and sulfadoxine-pyrimethamine (SP) in areas with CQ resistance. Quinine is another alternative in areas where both CQ and SP are not effective, and it is the drug of choice for treatment of uncomplicated malaria in the first trimester of pregnancy and severe malaria. WHO recommends that the following drugs not be used during pregnancy: halofantrine, tetracycline, doxycycline and primaquine.

Health care workers particularly in primary care facilities should be trained in the recognition and management of malaria illness. Collaboration with staff responsible for Integrated Management of Pregnancy and Childbirth as well as responsible for Integrated Management of Childhood Illnesses will be particularly effective in developing systematic management protocols and drug supply logistics.

Anaemia

During the past decade, the burden of malaria-associated anaemia for the pregnant woman (risk of death) and the fetus (LBW) has been increasingly recognized [19, 40–44]. Anaemia need not be symptomatic to pose appreciable risk during pregnancy. *P. falciparum* parasites may be present in the placenta and contribute to maternal anaemia even in the absence of documented peripheral parasitaemia. Therefore, a pregnant woman with severe anaemia from a malaria-endemic area must be treated presumptively with an effective antimalarial drug, whether or not peripheral parasitaemia is present or whether or not she has a history of fever.

4.2 Prevention of malaria during pregnancy

Controlling the effects of malaria infection on the pregnant woman and her fetus requires a balanced programme of effective case management of malaria illness and anaemia and prevention of the consequences of asymptomatic infection. In most areas of malaria transmission, highly effective prevention interventions are required. These interventions consist of intermittent preventive treatment and insecticide-treated nets.

4.2.1 Intermittent preventive treatment (IPT)

The most promising preventive approach using antimalarial drugs for pregnant women is intermittent preventive treatment (IPT). IPT is based on the use of antimalarial drugs given in treatment doses at predefined intervals after quickening. WHO recommends that in areas of stable transmission, IPT with an effective, preferably one-dose, antimalarial drug be provided as part of antenatal care, starting after quickening.

Box 3
Successful intermittent preventive treatment in east and southern Africa

Studies in Kenya and Malawi have shown that intermittent preventive treatment (IPT) with sulfadoxine-pyrimethamine (SP) has a beneficial impact on maternal and infant health. IPT with SP, when delivered as part of antenatal care, significantly reduces the prevalence of maternal anaemia and placental parasitaemia and the incidence of low birth weight [2, 45–47]. No significant adverse reactions to SP in either mother or infant have been detected.

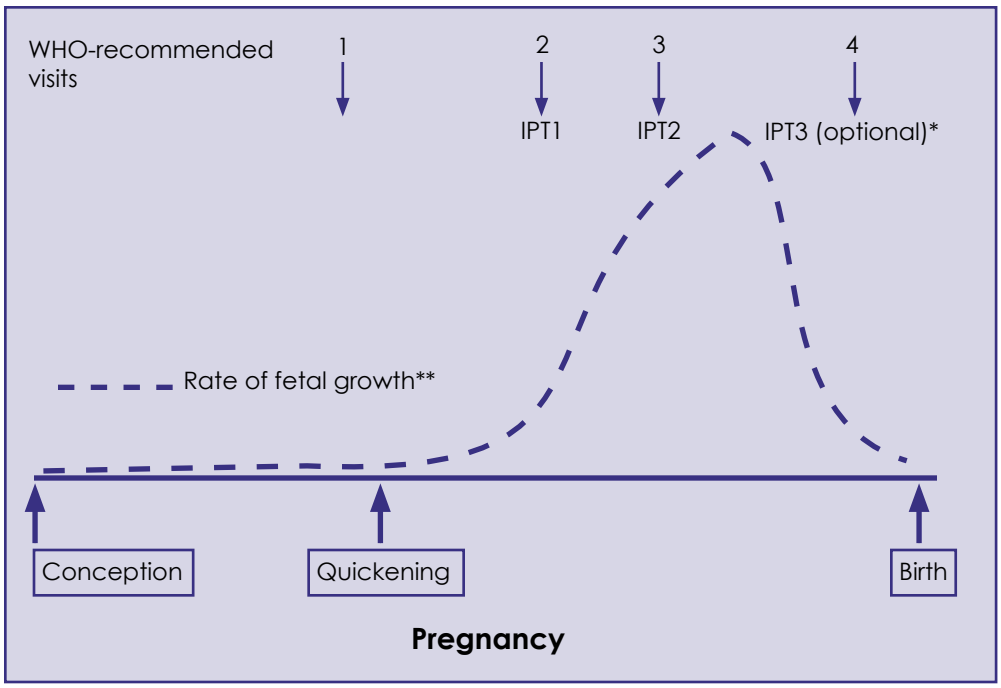
With sulfadoxine-pyrimethamine

Sulfadoxine-pyrimethamine (SP) is currently the most effective single-dose antimalarial drug for prevention of malaria during pregnancy in areas of Africa where transmission of *P. falciparum* malaria is stable and where resistance to SP is low (Box 3). SP is safe in pregnancy, efficacious in reproductive-age women in most areas and feasible for use by control programmes because it can be given as a single-dose treatment under observation by a health worker. Monitoring of antenatal programmes that are using IPT with SP has demonstrated high levels of IPT acceptance by pregnant women. Malawi, which has experience with wide-scale IPT programming, has found strong acceptance with the IPT regimen distributed in antenatal clinics and has consistently achieved coverage levels greater than 80% for the first dose.

Dosing schedule

All pregnant women in stable malaria transmission areas should receive at least two doses of the recommended antimalarial drug, currently SP, at the first and second regularly scheduled antenatal clinic visit after quickening (first noted movement of the fetus) (Figure 5). Studies conducted in Malawi and Kenya showed that the maximum benefit of IPT can be gained by receiving two or more (in HIV-infected pregnant women) doses of SP. However, even a single dose of SP is beneficial.

Figure 5: IPT doses given at antenatal clinics after quickening



* In areas where HIV prevalence among pregnant women >10%, a third dose should be administered at the last scheduled visit.

**The rate of fetal growth is low within the first trimester of pregnancy; the rate increases rapidly in the second trimester and then declines in the last month of pregnancy.

To ensure that women receive at least two doses, delivery of IPT doses should best be linked to routinely scheduled antenatal clinic visits. WHO presently recommends an optimal schedule of four antenatal clinic visits, with three visits after quickening [55, 56] (Box 4). The delivery of IPT during scheduled visits after quickening will ensure that a high proportion of women receives at least two doses. If the pregnant woman had received only one dose at the time of the third visit, a second dose should be administered at the fourth visit. For women first presenting in late pregnancy, even a single dose of SP is beneficial. Also, in HIV-infected pregnant women, the full effect of IPT may require three doses of IPT after quickening.

Box 4

Recommended antenatal visits

The World Health Organization recommends that each pregnant woman should make four antenatal clinic visits during her pregnancy, one within the first trimester and three after quickening. Each pregnant woman should receive at least two doses of IPT after quickening.

There is no evidence that receiving more than three IPT doses of SP during pregnancy offers additional benefit; however, there is similarly no evidence that receiving three or more IPT doses of SP will result in increased risk of adverse drug reactions. IPT doses should not be given more frequently than monthly. For pregnant women who have four or more antenatal visits after quickening, it is advisable to deliver no more than three doses of IPT.

Both sulfonamides and pyrimethamine are generally considered safe in the second and third trimesters of pregnancy [48]. Although there are concerns that sulfa drugs may be associated with kernicterus when given to premature neonates, this problem has not been noted in studies of IPT where SP has been administered to the mother [2, 45, 46]. Studies examining the risk to the fetus from *in utero* exposure to SP combinations have generally not found any increased risk of spontaneous abortions or congenital defects [2, 45, 46].

One retrospective study of antifolate drugs given before and during pregnancy found that there was an increased risk of birth defects when such drugs were taken during the first trimester but not during the second or third trimester [49, 50]. When given weekly as prophylaxis, SP has been associated with rare severe cutaneous reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome [51]. However, there is no evidence that the risk of severe cutaneous reactions is any greater in pregnant women or in treatment doses (Dr John Gimnig, personal communication).

Pyrimethamine is usually given in combination with sulfadoxine. However, studies in which pyrimethamine has been given alone have also found no increase in adverse pregnancy outcomes [52]. In addition, pyrimethamine is considered to be compatible with breastfeeding [53].

Several studies have been conducted to detect adverse reactions to SP, including cutaneous reactions and other potentially serious conditions that would either pose risks to the pregnant woman or infant or limit programme effectiveness. No evidence has been found of increased risk for serious cutaneous side effects or for increased jaundice in the newborn when SP has been delivered in the second and third trimesters [2, 45, 46]. Although the data on safety of SP are reassuring, there remains an ongoing need for monitoring the safety of all antimalarial drugs used for treatment and prevention in pregnancy, including SP.

With other antimalarial drugs

In areas of Africa where resistance to SP is intensifying, alternatives to SP—either alone or in combination with artemisinin compounds—require urgent evaluation for use in pregnancy. A WHO meeting to review the preclinical (animal) and limited human data on use of artemisinin compounds in pregnancy concluded that these drugs are safe for use in the second and third trimesters of pregnancy and during lactation [54]. Although formal trials of the safety of these drugs in pregnancy are needed, these may be difficult to conduct. It is, then, essential that postmarketing surveillance of pregnant women who are exposed to new drugs be as vigilant and complete as possible.

4.2.2 Insecticide-treated nets

The second prevention intervention is the use of insecticide-treated nets (ITNs). ITNs reduce human-vector contact by physically excluding vector mosquitoes, killing them if they land on ITNs or repelling them, thereby driving them from the vicinity of sleepers. Because of their documented effect in several studies on reducing malaria-related illness and death [13, 55–61], ITNs are being promoted for use through public and private sector outlets in African countries.

The use of an ITN by a pregnant woman benefits the woman as well as her family (Box 5). The demonstrated impact of ITNs on lessening the risk for LBW and maternal anaemia is important. Further, the infant who sleeps under the net with the mother will also have marked benefits: reduced malaria exposure, decreased incidence of anaemia, decreased risk of death and enhanced development.

Box 5
ITNs reduce LBW and prematurity in Kenya

In highly malarious western Kenya, studies indicate that women who were protected by insecticide-treated bed nets every night in their first four pregnancies delivered approximately 25% fewer babies who were either small for gestational age or born prematurely than women who were not protected by ITNs [62].

The distribution of ITNs and the development of effective community-based infrastructure to achieve high levels of coverage is a major challenge; locally defined and applied strategies will be most successful. Incorporation of messages about the benefits of ITNs will be important in achieving high levels of use; such messages can be posted in antenatal clinics, well-baby clinics and other health care facilities.

4.3 Opportunities for community-based programming

In areas where most women attend an antenatal clinic at least once during pregnancy, country programmes should focus initially on the antenatal clinic for malaria prevention and control during pregnancy. The antenatal clinic will be the logical point of service for IPT. Strong collaboration between malaria and reproductive health programmes will be necessary for success; cooperation should include the full range of implementation steps—training, procurement of drugs and supplies, service delivery, supervision, monitoring and evaluation. The antenatal clinic can also provide valuable ITN distribution, advocacy and education among pregnant women. In some communities, ITNs may be distributed and supported through public and private sector programmes.

In some malaria-endemic areas, antenatal clinic programmes may not be well developed, and thus attendance will be low. Programmes will need to assess the most cost-effective strategies for controlling malaria during pregnancy.

To accelerate the delivery of services to pregnant women, national programmes should explore partnerships with nongovernmental organizations and community-based health providers to deliver some components of the proposed malaria prevention and control package. Community health workers may be effective at promoting the use of antenatal clinic services and ITNs and, with appropriate training and logistic support, could deliver IPT.

Table 2: Intervention strategies for malaria during pregnancy, by transmission intensity

	Case Management	Intermittent Preventive Treatment (IPT)	Insecticide-Treated Nets (ITNs)
High/medium transmission—perennial (stable)*	Risk for febrile illness and severe malaria limited Screen and treat anaemia with recommended antimalarial drug and iron supplement Promptly recognize and treat all potential malaria illness with an effective drug	Provide pregnant women a standard IPT[1] dose at the first regularly scheduled antenatal clinic visit after quickening. At the next routine visit,[2] provide an IPT dose, with a minimum of two doses given at not less than a one-month interval.[3]	Begin use early in pregnancy and continue postpartum Emphasize young children sleeping under ITNs
High/medium transmission—seasonal (stable)*	Risk for febrile illness and severe malaria limited Screen and treat anaemia with recommended antimalarial drug and iron supplement Promptly recognize and treat all potential malaria illness with an effective drug Risk for febrile illness and anaemia high	Provide pregnant women a standard IPT[1] dose at the first regularly scheduled antenatal clinic visit after quickening. At the next routine visit[2] provide an IPT dose, with a minimum of two doses given at not less than a one-month interval.[3]	Begin use early in pregnancy and continue postpartum Emphasize young children sleeping under ITNs
Low transmission (unstable)**	Risk for severe malaria illness high Promptly recognize[2] and treat all potential malaria illness with an effective drug Screen and treat anaemia with recommended antimalarial drug and iron supplement Consider *P. vivax* infection in east Africa[4]	Based on present evidence, IPT cannot be recommended in these areas.	Begin use early in pregnancy and continue postpartum Emphasize young children sleeping under ITNs

* Adult women have a high level of acquired antimalarial immunity; first and second pregnancies are at higher risk of adverse consequences of malaria.

** Adult women have no or very low level of acquired antimalarial immunity; all pregnancies are at risk of adverse consequences of malaria.

1 Presently the most effective drug for IPT is sulfadoxine-pyrimethamine.

2 WHO recommends an ideal schedule of three antenatal clinic visits after quickening.

3 In areas where HIV prevalence among pregnant women is > 10%, a third dose should be administered at the last scheduled visit. If the pregnant woman had received only one dose at the time of the third visit, a second dose should be administered at the fourth visit.

4 CQ chemoprophylaxis to decrease the burden of *P. vivax* in pregnancy may be considered, but no evidence on effectiveness of this strategy is presently available.

Programmes are encouraged to explore innovative opportunities in the community for programme delivery both to extend antenatal clinic-based programmes and to serve women where clinic-based programming is underdeveloped. Within the community, the woman's partner and family (e.g. mother or mother-in-law) as well as other local groups may be resources for developing capacity to make healthy choices. These resources should be fully tapped in order to take complete advantage of the range of opportunities to develop effective and sustainable approaches for prevention and control of malaria during pregnancy, as well as for other diseases posing an undue burden for the pregnant woman and her infant.

4.4 Estimated cost-effectiveness of malaria prevention during pregnancy

Malaria prevention during pregnancy using a package consisting of IPT and ITNs can be highly cost-effective. IPT with either SP or CQ has been estimated to cost in the range of US $12 to US $21 per disability-adjusted life year prevented, a very favourable cost [63].

ITN use by children in several settings has been shown to be very cost-effective [64–66]. More pregnant women are using ITNs, and the cost-effectiveness of ITN use by pregnant women is likely to be similar to that for children. The antenatal prevention package (of IPT and ITNs) is expected to produce comparable enhanced cost-effectiveness. As regional coverage attains the 60% target, the estimated annual infant deaths (75 000–200 000) attributable to maternal malaria infection should be significantly reduced.

5. Programme implementation

Developing and strengthening national capacity for control of malaria during pregnancy is a high priority for the African Region. Implementation of programmes requires a systematic approach to development of national policy and programmes, as well as advocacy for prevention and control approaches. The Malaria Programme places a high priority on effective collaboration with reproductive health programmes.

In each country, the roles of the national, district and local levels of the malaria control programme and reproductive health programmes in the implementation process must be clearly defined. Proposed steps in programme implementation are discussed below.

- **Establish a technical advisory group with national and partner stakeholders to advise on policy and national implementation planning**

The planning and implementation of interventions for malaria prevention and control during pregnancy will require new partnerships among malaria and obstetric, maternal and child health experts. As a country commits to strengthening capacity in malaria prevention and control, a representative technical advisory group that includes malaria, maternal and reproductive health experts and human resource units (both from public and private sectors), key bilateral and multilateral partners, nongovernmental organizations and religious organizations involved in health care delivery should be constituted. The technical advisory group should be charged with providing technical advice for policy and planning issues as well as mobilizing support and resources. This technical advisory group should also have an active role in coordinating and monitoring programme implementation. Most countries have already set up technical advisory

committees for malaria prevention and control; their terms of reference may need to be revised to include issues related to malaria prevention and control during pregnancy.

- **Conduct needs assessment and situation analysis to define the epidemiology of malaria during pregnancy and the capability of the reproductive health and antenatal programmes**

Before a country begins to develop or strengthen its capacity to prevent and control malaria during pregnancy, key programme determinants and needs should be assessed to serve as a baseline [67]. Determination of the intensity of malaria transmission and the effects of malaria during pregnancy (e.g. LBW, anaemia) can in most settings be inferred from available malaria infection prevalence and maternal morbidity data. Some settings, such as urban areas, highland areas and areas at the fringe of stable malaria transmission (e.g. in the Sahel region), may require special studies.

The critical determinant is the capacity of reproductive health services to collaborate, incorporate and efficiently deliver malaria prevention and control interventions for pregnant women. The entry point will be clinic-based services, but outreach and community-based programmes, such as those that have trained and supplied community health workers, should also be assessed.

- **Develop or review the national malaria control policy and policy and guidelines for malaria prevention and control during pregnancy**

Each country will need to develop or review the policy and guidelines for control of malaria during pregnancy. This policy should be an integral part of the national malaria prevention and control policy and should also be reflected in the reproductive health policy. Involvement of all interested parties and contributors is crucial. The policy should address critical issues identified during the situation analysis and needs assessment, clearly define strategies and approaches for malaria prevention and control during pregnancy and be consistent with the goals defined by the national malaria control programme and reproductive health programme. The previous section provides guidance that can assist in the development of the policy.

- **Develop or update a comprehensive strategy and implementation plans for malaria prevention and control during pregnancy**

During the Roll Back Malaria inception process, most malaria-endemic countries in the African Region carried out situation analyses to identify strengths, opportunities, threats and weaknesses related to malaria control and health systems during the last five to ten years. These countries are at various stages of developing strategic and implementation plans for malaria prevention and control. The goal, objectives, strategic options and implementation approaches, as well as indicators for monitoring and evaluation, for malaria prevention and control during pregnancy should be defined in the context of a national five-to-ten-year strategic plan for malaria prevention and control. All stakeholders should be involved in the planning process.

The one-to-two-year implementation plans for the national and district level should be derived from the national strategic plan. The implementation plans should state the expected results within a specific time frame, activities to be implemented, responsible person, indicators to monitor, cost and source of funds for each activity.

- **Develop advocacy and communication strategies for malaria prevention and control**

Appropriate information, education and communication (IEC) strategies and programmes need to be developed to create messages for women and the general public to educate them about the burden of malaria infection during pregnancy and the appropriate prevention and control measures that pregnant women should expect to receive under care. Emphasis should be given to effective communication between service delivery staff and pregnant women in order to enhance compliance with control measures among women and families at risk of malaria.

IEC messages should also target health care providers, particularly in settings that are introducing a change in policy. Compliance of pregnant women and the general public with the new policy will depend on the changes in behaviour of health personnel.

Advocacy tools should be developed to enhance and sustain political commitment, influence key decision makers about the effectiveness and cost benefits of the defined strategies and mobilize resources for programme implementation.

- **Assist to strengthen support systems for antenatal services, including interventions for malaria prevention and control during pregnancy**

The implementation of malaria prevention and control interventions during pregnancy to achieve the Abuja 2000 targets and reproductive health goals requires a favourable environment (e.g. political commitment, provision of facilities and resources) and strengthened human resource capabilities and institutional capacity at the country level. Effective procurement and supply systems, as well as referral, communication, supervision and surveillance systems, need to be established to ensure adequate access to essential services and commodities such as drugs, ITNs and other supplies required for quality care. This will require well-planned logistics and financing. Collaboration with other clinic-based procurement, supply and referral systems, such as those that have been developed for the Integrated Management of Pregnancy and Childbirth, the Integrated Management of Childhood Illnesses and the Expanded Programme on Immunization, will be particularly important.

The aim of these systems is to increase access to and compliance with prevention and control measures by pregnant women and the general population. Adequate geographic coverage should be ensured, as should coverage of marginalized and the poorest populations. Assurance of equitable access to services must be a priority for national programmes.

- **Build personnel capacity for malaria control and prevention during pregnancy**

In most countries, plans to strengthen efforts to prevent and control malaria during pregnancy will initially focus on the capacity of health facilities to deliver effective malaria prevention interventions and case management. The investments in building health system capacity should be made in a coordinated manner involving all programme partners.

Well-trained and well-equipped health care workers are required to support implementation and provide quality care. Intensification of training and retraining of health personnel is a priority. In-service training regarding policy and guidelines for malaria prevention and control during pregnancy should be conducted at all levels of the health system. Adequate training manuals may need to be developed or reviewed. Preservice education through the incorporation of a malaria

prevention and control syllabus into the curriculum of schools of medicine, nursing and public health and related health training institutions is a medium-term strategy to improve health care workers' skills for malaria prevention and control. Nonformal providers should be engaged, and their links with the formal health sector should be ensured. Specific approaches to ensure the involvement of private medical practitioners, who treat a substantial proportion of malaria cases, may be required.

Regular supervision of trained health personnel is important to motivate staff and ensure quality of care. The issue of an overall strategy for human resources development should be addressed within the context of national health systems.

- **Define a research agenda for malaria and its control during pregnancy**

National programmes and research partners may at times find it necessary to conduct operational research to assess both basic issues regarding the biology and control of malaria during pregnancy as well as operational issues relevant to national programme implementation. National programme leaders should participate and have prompt access to results of such investigations to inform national programme planning and implementation. Documenting and sharing best practices is essential for improving programme implementation.

6. Monitoring and evaluation of programmes

An effective system for monitoring progress and evaluating outcomes and impact will be critical to measure a country's success in controlling malaria during pregnancy. *Monitoring* is needed to measure the progress of the health programme at all levels. Monitoring can help verify that activities are being implemented as planned, ensure accountability and detect problems and constraints to provide local feedback to the relevant authorities and support them in promoting better planning. *Evaluation* of outcomes and impact is needed to document periodically whether defined strategies and implemented activities are leading to expected results. Monitoring is a continuous process, while evaluation will need to be conducted intermittently.

Five critical areas for monitoring and evaluation have been identified that relate directly to malaria control objectives:

- impact of malaria, i.e. morbidity, mortality and economic losses
- improvements in malaria prevention and disease management, prevention and control of epidemics
- related health sector development
- intersectora1 linkages that need to be created or reinforced
- support and partnerships.

Each of the interventions for malaria prevention and control during pregnancy (IPT, ITNs, case management) has a key implementation partner; monitoring and evaluation procedures must be developed and shared among these partners. Strong partnerships are needed to conduct

monitoring and evaluation of malaria during pregnancy; from the start, the monitoring and evaluation framework should be a cooperative effort between malaria and reproductive health experts. Therefore, both malaria control and reproductive health programme staff need to work closely to develop and implement this strategy.

The approach to monitoring and evaluation of control programmes for malaria during pregnancy should focus on a limited number of indicators that can be used at minimal cost to track implementation progress and alert programme managers of obstacles. Thus, it will be important that these indicators and approaches to data collection also be integrated into the indicators for the reproductive health programmes at the country level.

The most important indicators for monitoring programmes to control the adverse consequences of malaria during pregnancy are process indicators, i.e. those that measure whether or not interventions known to be effective in reducing the adverse consequences of malaria during pregnancy are being implemented. It is also important to measure the potential impact of prevention programmes in reducing the burden of maternal anaemia and LBW, even though other factors, especially HIV and malnutrition, may affect anaemia and LBW.

The following indicators have been proposed:

Process indicators

- Percentage of antenatal clinic staff trained (in-service training or through supervisory visits) in malaria during pregnancy in the last 24 months (including IPT and counselling for ITNs for pregnant women)
- Percentage of pregnant women given voucher/ITN or who purchase ITN during antenatal clinic visit
- Number of days in the last month with stock-out of SP per health facility and/or percentage of facilities that have reported stock-out of SP in the determined period.

Outcome indicators

- Percentage of pregnant women receiving IPT under direct observation (first dose, second dose, third dose)
- Percentage of pregnant women who report that they slept under an ITN the previous night at second antenatal clinic visit (first visit, delivery).

Impact indicators

- Percentage of screened pregnant women with severe anaemia (haemoglobin ≤ 7 gm/dL) in third trimester by parity
- Percentage of LBW newborns, singleton < 2500 grammes, by parity.

7. Research priorities

Programmes focused on malaria prevention and control during pregnancy will be improved through research on both the biology and control of malaria during pregnancy and on operational issues related to programme implementation. National programme leaders will need the results of this research to assist programme planning and implementation efforts. Four priority areas are the following:

- **Effective drug regimens for IPT**

Alternative antimalarial drugs for use for IPT during pregnancy must have acceptable safety, even when used in the latter half of pregnancy. Among the currently available antimalarial drugs, only SP, mefloquine, proguanil, quinine, amodiaquine and a combination of pyrimethamine and dapsone (in the form of Maloprim®) are available for use during pregnancy. Mefloquine is expensive for most ministries of health in developing countries and is not widely available in Africa. Proguanil, in addition to problems of compliance, has altered pharmacokinetics during pregnancy, and higher maintenance doses are required. Maloprim® has been used in some situations, but has similar problems of compliance as CQ; in addition, resistance to pyrimethamine develops very rapidly. Presently, the best available alternative to CQ, therefore, is SP. With the emergence of SP resistance in east and southern Africa, there is a need to evaluate other antimalarial drugs, either alone or in combination, with priority based on the possible safety and efficacy profile in pregnancy, as well as affordability.

- **Programme options for achieving sustainable high levels of coverage of ITN use by women of reproductive age**

Studies have been conducted to determine the efficacy of ITNs in reducing the burden of malaria illness among pregnant women under study conditions. As programmes are scaled up to provide broad access to ITNs, similar efforts should be directed to documenting the beneficial impact of ITNs on maternal and newborn health under programmatic conditions. Evidence already exists that ITN use by pregnant women will significantly reduce the number of LBW infants. Many options exist for ITN financing and distribution in Africa, including distribution through the public and private sector with or without subsidization. Alternative approaches emphasize the direct provision of ITNs at no cost to highly vulnerable populations such as young children and pregnant women. In addition to assuring high levels of use of ITNs, it is also critical to develop distribution systems that will be sustainable and in which re-dipping of nets as required will be assured. Operational research at the national and community levels is required to define effective models to assure sustainable and effective ITN use.

- **Efficacy of alternative IPT regimens combined with ITNs to control maternal anaemia and LBW**

A central element of the control approach for areas of stable malaria transmission is the use of IPT and ITNs by pregnant women. Operational research is needed to determine if long-acting antimalarial drugs are required for IPT if ITN use is continuous. Some of the next generation of potentially efficacious and safe drugs for IPT have short half-lives; it is a priority to assess whether use of these drugs is programmatically acceptable in an IPT regimen.

- **Analysis of social and cultural determinants of women using services to control malaria during pregnancy**

The reduction of malaria burden among pregnant women and their offspring depends on women having access to and using quality antenatal care services. Many important cultural factors determine how women perceive drug use and other components of the proposed control strategy. Emphasis needs to be placed on a careful assessment and review of such factors as national implementation plans have developed.

8. Conclusion

Effective interventions that are safe for use during pregnancy exist and are ready to be incorporated into national policies to prevent and control malaria during pregnancy. Each country is encouraged to adapt the recommended regional policy to its own epidemiologic and programmatic environment and adopt and implement a policy tailored to its needs. Most countries in the African Region experience stable transmission of malaria, and thus intervention with IPT and ITNs is recommended, in addition to case management of any symptomatic illness and screening and treatment of anaemia, which is often caused by malaria infection.

Antenatal clinics offer an excellent venue for delivering these interventions, as many women visit antenatal clinics during their pregnancy. Delivery of malaria interventions as part of an antenatal package requires strong collaboration of both malaria and reproductive health programmes in order to ensure that pregnant women receive the prevention and care they need, and thus to reach the Abuja Malaria Summit target of 60% of pregnant women covered with appropriate interventions. ■

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Web Resources

Johns Hopkins Program for International Education in Gynecology and Obstetrics (JHPIEGO) http://www.jhpiego.jhu.edu/maternal

Making Pregnancy Safer http://www.who.int/reproductive-health/mps/

PREMA–EU http://www.prema-eu.org/

Roll Back Malaria http://mosquito.who.int

Roll Back Malaria Partnership http://www.rbm.who.int/partnership

United Kingdom Department for International Development (DFID) http://www.dfid.gov.uk

United Nations Children's Fund (UNICEF) http:/ /www.unicef.org/

United States Centers for Disease Control and Prevention (CDC) www.cdc.gov

World Health Organization Regional Office for Africa http://www.afro.who.int/malaria/index/html