

An Overview of Malaria in Pregnancy

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Abstract

One hundred twenty-five million pregnant women are at risk for contracting malaria, a preventable cause of maternal and infant morbidity and death. Malaria parasites contribute to adverse pregnancy and birth outcomes due to their preferential accumulation in placental intervillous spaces. Pregnant women are particularly vulnerable to malaria infections, and malaria infections during pregnancy put their fetuses at risk. Malaria in pregnancy is associated with anemia, stillbirth, low birth weight and maternal and fetal death. We review the challenges to diagnosing malaria in pregnancy, as well as strategies to prevent and treat malaria in pregnancy. Finally, we discuss the current gaps in knowledge and potential areas for continued research.

Introduction

Globally, an estimated 125 million pregnant women reside in areas where they are at risk of contracting malaria in pregnancy (MIP), and MIP remains an important preventable cause of adverse birth outcomes.¹ Although there are five species of malaria that infect humans, two main species of *Plasmodium* contribute to adverse maternal and fetal outcomes in pregnancy, *P. falciparum* and *P. vivax*. In sub-Saharan Africa, where the majority of adverse birth outcomes attributable to malaria occur, *P. falciparum* is the dominant species. However, over half of pregnancies that are potentially exposed to malaria occur in Southeast Asia and the Western Pacific where *P. falciparum* and *P. vivax* coexist. Co-existence of *P. falciparum* and *P. vivax* also occurs in South America, where 3% of the global total of women at risk for MIP reside.¹

Over the past decade, there has been significant progress in reducing the global prevalence of *P. falciparum*, particularly in Africa. However, women remain at high risk of MIP, with over 50% of women in high transmission areas having *P. falciparum* detected in peripheral blood at presentation to antenatal care.^{2,3} This high prevalence of disease results from an increased risk of contracting malaria among pregnant compared to non-pregnant women. Women who are younger, malnourished, primigravidae/secundigravidae, lack immunity to pregnancy-associated malaria, or living with HIV are at the highest risk of malaria-associated adverse pregnancy outcomes.^{4,5}

Pathophysiology of Malaria in Pregnancy

MIP contributes to adverse pregnancy outcomes, at least in part, due to the preferential accumulation of parasites in the placental intervillous space. Placental sequestration is common in infections with *P. falciparum* because malaria parasites export a protein, VAR2CSA, to the red blood cell membrane that facilitates adherence to chondroitin-sulfate A (CSA) on syndecan-1, which is anchored in placental tissue.⁶ This interaction is associated with the recruitment, retention and activation of mononuclear cells in the placenta—and is thought to mediate malaria's effect on birth outcomes.⁷ Maternal antibodies against VAR2CSA are protective.⁵ *P.*

vivax can also lead to placental changes, but to date no studies have unequivocally documented the sequestration of *P. vivax* infected erythrocytes in the placenta.⁸

A number of histological changes in *P. falciparum* infected placentae have been described, including the infiltration of mononuclear cells, deposition of malaria pigment, thickening of the trophoblast basement membrane, syncytial knotting, and complement deposition.⁹⁻¹¹ Inflammation in the placenta has been linked to impaired transplacental transport of glucose¹² and amino acids,¹³ and disruption of the insulin-like growth hormone axis.¹⁴ Impaired nutrient transport across the placenta may be further exacerbated by altered placental angiogenesis¹⁵ leading to changes in both the villous architecture¹⁶ and surface area for nutrient exchange, as well as impaired uteroplacental blood flow.^{15, 17} These histologic and functional changes likely contribute to impaired fetal growth. Longitudinal Doppler data support the idea that malaria in the first half of pregnancy can lead to changes in umbilical artery blood flow and fetal growth in pregnancy, and this is affected by both gravidity and nutritional status.¹⁸

Risk Factors for Malaria in Pregnancy

Environmental, parasite, and maternal factors influence the severity of MIP. In areas where malaria transmission is high, the primary burden of malaria is in primigravidae, whereas, in areas of low transmission, all gravidities are at risk. In areas of high transmission, primigravidae develop antibodies to VAR2CSA protein produced by malaria parasites, and are partially protected during subsequent pregnancies; this tends not to happen in areas of low transmission.¹⁹ Overall, pregnant women living in areas with low or unstable (episodic) transmission have little or no immunity to malaria and are at a two-to-three times higher risk of severe disease compared to non-pregnant controls.²⁰ *P. falciparum* has typically been associated with more severe MIP than *P. vivax*, although *P. vivax* is more likely to occur in a mother with little acquired immunity.²¹ Maternal age and gravidity also play a role in the severity of MIP. Younger mothers are at greater risk for severe malaria infection compared to older mothers, who appear to have some protection from severe disease.⁴ In high transmission areas,

such as sub-Saharan Africa, primigravidae and secundigravidae are at greater risk for severe malaria infection compared to multigravidae, but this is not true in areas of low transmission, where multigravidae have not had prior malaria exposure nor developed immunity.²²

Malnourished pregnant women are at increased risk for adverse birth outcomes with MIP.²³ A meta-analysis using individual patient data from 14,633 pregnancies from Africa and the Western Pacific between 1996-2015 showed that malaria and malnutrition are common exposures, with 35% of women having either of those exposures. Pregnant women with malnutrition and malaria were at an increased risk of LBW compared to women with only 1 of those risk factors.²⁴ Recent data suggests reduced L-arginine intake is one mechanism through which malnutrition contributes to low birth weight with both nutritional survey data²⁵ and preclinical models²⁶ suggesting that L-arginine supplementation may reduce preterm birth²⁵ and increase fetal viability, placental vascularization, and birth weight.²⁶

Burden of Malaria

Maternal Effects

The clinical effects of malaria on pregnant women vary from no symptoms to severe anemia and death. Women living in areas of low malaria transmission who have a lower degree of acquired immunity are more likely to experience complications such as renal failure, pulmonary edema, and cerebral malaria.²⁷ Despite this, the overall maternal mortality rate is similar in low-transmission areas (0.6-12.5%) compared to malaria-endemic areas (0.5-23%).⁴ More research is warranted on the topic of malaria-related mortality during pregnancy, as the current data are limited and inconsistent.

Maternal anemia is one of the most common symptoms of MIP. *Plasmodium* causes anemia through hemolysis, increased splenic clearance of erythrocytes, and reduced red blood cell production. While severe anemia during pregnancy (hemoglobin <7 g/dL) is often multifactorial with significant nutritional components, malaria can play an important role.²⁸ In one estimate in sub-Saharan Africa, the population attributable fraction of malaria to severe anemia

during pregnancy was 26%.⁴ For endemic areas with a 5% baseline prevalence of severe anemia, epidemiological modeling predicts malaria-induced anemia to contribute to nine maternal deaths per 100,000 live births.⁴ However, in a population-based study in the Democratic Republic of the Congo, malaria played little or no role as a driver of anemia during pregnancy.²⁹

Pregnant women are three times more likely to be affected by severe malaria.³⁰ The World Health Organization defines severe malaria as parasitemia with evidence of end organ dysfunction (Table 1). The presenting features of severe malaria can include severe anemia, hypoglycemia, acute respiratory distress syndrome, renal failure and cerebral malaria.³⁰ The median mortality of severe MIP is 39% (range 8-100%).³⁰ Severe malaria must be treated promptly with intensive care and parenteral antimalarial medication to reduce mortality.³¹

Fetal Effects

Malaria is an important cause of stillbirth throughout endemic areas (Figure 1). MIP contributes to 12-20% of stillbirths in endemic regions of sub-Saharan Africa, with lower rates if the mother undergoes treatment.³² *P. falciparum* detection both in peripheral blood samples or placental samples at delivery nearly doubles the odds of stillbirth (odds ratio 1.81 and 1.5, respectively).³² Stillbirth risk is higher in areas with low to intermediate endemicity compared to areas of high endemicity.³³ The risk of stillbirth can be modified with appropriate malaria intervention efforts. For example, the use of insecticide-treated bed nets (ITN) is associated with lower rates of placental malaria and stillbirth (risk ratio 0.67 [95% CI 0.45 to 1.00] for stillbirth).³⁴

MIP increases the risk of low birth weight (LBW), and approximately 20% of cases of LBW in malaria-endemic areas are attributed to placental infection with malaria (Figure 1).³⁵ A mother with a malaria-infected placenta is twice as likely to have a baby with LBW.³⁶ LBW in turn is associated with higher infant mortality rates. In Africa, LBW has been associated with a three - to 20-fold increase in the probability of infant mortality.^{36, 37} Parity is an important factor in LBW. Primigravidae with MIP have two to seven higher odds of LBW and mortality than

multigravidae.³⁸ The timing of infection also seems to play a role in infant size. Second-trimester infection is more likely to result in LBW than third-trimester infection; but data on first-trimester infection are limited.³⁹

MIP causes LBW due to both intrauterine growth restriction (IUGR) and prematurity. Up to 70% of IUGR in endemic areas is due to malaria, presumably as a result of impaired oxygen and nutrient delivery to the fetus.^{35, 36} The contribution of malaria to preterm birth is also substantial, with up to 36% of prematurity in malaria-endemic areas attributable to *Plasmodium* infection. Prematurity may result from the host's immune response to malaria parasites triggering early labor.³³ These adverse fetal effects are species specific, as *P. ovale* and *P. malariae* species are not associated with adverse birth outcomes.

Congenital Malaria

Congenital malaria is defined as the identification of asexual *P. falciparum* parasites in the cord blood or peripheral blood of an infant during the first 7 days of life.⁴⁰ The true prevalence of congenital malaria is uncertain. While the prevalence was previously thought to be between <1% and 6%,⁴⁰ more recent studies have demonstrated a prevalence rate up to 33% in high-endemicity areas; but it is not clear how many of these congenital infections persist and cause clinical illness.⁴¹ Most descriptive reports of congenital malaria are from infants who are born in non-endemic areas to mothers with a history of travel to endemic areas. Infant symptoms include fever associated with hepatosplenomegaly, hemolytic anemia, thrombocytopenia, and feeding intolerance.⁴¹ These infants often become symptomatic between 10 and 30 days of life, although they can present later. Their symptoms may progress rapidly and can be fatal.^{27, 42} Because, much of the literature on congenital malaria is derived from case reports, more research is needed to better understand the epidemiology and pathophysiology of congenital malaria.

Effects in Early Childhood

Offspring are affected by placental malaria into childhood, (Figure 1). Prenatal malaria exposure is associated with an increased risk of early malaria infection in children as young as four to six months of age.⁴⁰ Placental parasitemia may increase the risk of malaria infections in infancy and childhood through several mechanisms. For example, MIP might interfere with maternal antibody passage to offspring, compromising the immunity of the fetus and newborn, making the offspring vulnerable to early malaria infections.⁴⁰ In utero exposure to malaria induces the development of T_{reg} cells that lead to fetal immune tolerance to malaria antigens that persists into childhood.⁴³ Placental malaria has been associated with subsequent susceptibility to non-malaria infections, including measles and tetanus, suggesting additional effects on infant immunity that may be due to the obstruction of antibody passage across the placenta.⁴⁴ Acute placental malaria infection has been associated with increased one-year mortality in infants⁴⁵ and decreased length and weight gain in the first year of life.^{46, 47} MIP is also associated with anemia during infancy and the infant's risk for anemia with maternal peripheral parasitemia at delivery is 11.8% and 9.2% with placental malaria infection.⁴⁸

Diagnosis

The diagnosis of MIP can be challenging due to placental sequestration of parasitized erythrocytes, low circulating levels of parasites and limited resources in malaria endemic areas for advanced diagnostic techniques. Microscopic identification of malaria from the blood by an experienced and well-equipped technician remains the gold standard for malaria diagnosis.⁴⁹ However, rapid diagnostic tests (RDTs) that test for malaria antigens, like histidine-rich protein-1 (PfHRP2), are another option for malaria diagnosis.⁴⁹⁻⁵¹ RDTs are easier than microscopy to perform in low-resource settings, because they are not dependent on highly trained technicians in well-equipped laboratories. Therefore, RDTs might be the most appropriate point of care testing among symptomatic mothers in low-resource settings.^{31, 50} However, the use of RDTs might be insufficient in diagnosing MIP among mothers with asymptomatic infection, because RDTs require a higher circulating parasite burden than microscopy for detection.⁵² RDTs are

also insufficient to detect low amounts of circulating parasites because of placental sequestration. In research studies, the gold standard for malaria diagnosis has been placental histopathology, but it is not practical in many field sites.^{53, 54} Using microscopy of placental blood as the referent, the sensitivity of RDTs is 81% (95% CI 55-93) and the specificity is 94% (95% CI 76-99).³¹ Molecular techniques, such as polymerase chain reaction (PCR) diagnosis, have increased sensitivity of diagnosis when compared to microscopy of placental blood to 94% (95% CI 86-98), but specificity of 94% (95% CI 86-98).³¹ A new generation of ultrasensitive RDT's is now being developed and might mitigate these diagnostic problems.⁵⁵

Prevention and Treatment

Prevention Strategies in Africa

In malaria-endemic areas in Africa, a combination of vector control (preventing exposure to mosquitos) and chemoprevention (preventive medication-based treatment) strategies are used to prevent MIP. The World Health Organization (WHO) recommends a combined approach using insecticide treated bed nets (ITNs) to reduce exposure to mosquitoes carrying malaria and chemoprevention.⁵⁶ ITNs work by providing a physical barrier from mosquitoes, and repelling or killing susceptible mosquitoes, which reduces mosquito density and maintains the nets' effectiveness even after the integrity of the barrier is compromised.⁵⁷ The use of ITNs in Africa have been shown to reduce LBW by 23%, miscarriages and stillbirths by 33%, and placental parasitemia by 23%.⁵⁸ Despite the proven efficacy of ITNs, uptake was estimated at only 39% in Africa between 2009 and 2011.⁵⁹ Since that time, ITN use has steadily increased, and an estimated 61% of pregnant women at risk for malaria slept under an ITN in 2017⁵⁶, (Figure 2). Malarial resistance to pyrethroids, the most commonly used insecticide in ITNs has been reported across sub-Saharan Africa and might impair future efficacy.⁵⁷

Spraying the walls of households with insecticide to reduce human exposure to mosquitos, a procedure known as indoor residual spraying (IRS) is part of a comprehensive vector control program. Globally, IRS usage has declined and only 3% of the population at risk

was protected by IRS in 2017, which might be related to a switch in insecticide from pyrethroids to more expensive chemicals.⁵⁶ IRS has been shown to improve outcomes of MIP, with women protected by IRS having lower incidence of MIP and lower risk of placental malaria.^{60, 61} When women were protected during greater than 90% of the time of their pregnancies, women had lower risk of preterm birth (risk ratio 0.35, 95% CI, 0.15-0.84).⁶⁰ IRS is an important part of a comprehensive vector control program and might contribute to improved birth outcomes in malaria-endemic regions.

Chemoprevention strategies have been successfully used to prevent adverse health outcomes associated with MIP. The most efficacious of these strategies uses a technique of intermittent preventive treatment in pregnancy (IPTp). IPTp consists of providing monthly doses of anti-malarial medication to all pregnant women starting in the second trimester. Women who receive at least 2 courses of IPTp have a relative risk reduction of 40% for moderate to severe anemia, 61% for antenatal parasitemia, 55% for placental parasitemia and 27% for low birthweight.⁶² Since 2012, the WHO has recommended monthly IPTp to reduce the incidence of these complications of pregnancy.⁶³ However, despite WHO recommendations, in 2017, only 22% of pregnant women received three or more doses of IPTp in Sub-Saharan Africa (Figure 3).⁶⁴

Sulfadoxine-pyrimethamine (SP) has been the drug of choice for IPTp in women who are HIV-negative.⁶⁵ *Plasmodium* resistance to SP has emerged through multiple mutations in the *P. falciparum* dihydrofolate reductase (Pfdhfr) and dihydropteroate synthetase (Pfdhps), with penetrance of this haplotype in some areas of greater than 90%.⁶⁶ Due to increasingly more resistant organisms, IPTp with SP is less effective at inhibiting parasite growth and preventing fetal growth restriction.⁶⁶ In light of increasing resistance, alternative strategies for chemoprevention are being tested, including IPTp with alternative medications and strategies of intermittent screening and treatment in pregnancy (ISTp). ISTp strategies use RDTs to diagnosis MIP at multiple time points and treat only when RDTs are positive. However, these

strategies depend on accurate diagnosis of MIP and have not been proven to be effective alternatives to IPTp-SP even in highly resistant areas.⁶⁶ IPTp with dihydroartemisinin-piperazine (DP) might be a promising alternative to IPTp-SP, but more research is needed in this area.⁶⁶

Prevention Strategies Outside of Africa

In South America and Asia, where malaria transmission is typically lower than in Africa, data on traditional chemoprophylaxis is limited. Prophylaxis with mefloquine or chloroquine has been efficacious for preventing MIP in pregnant women in Thailand.^{67, 68} Other chemoprophylactic strategies employed outside of Africa have included monthly IPTp-SP with azithromycin and ISTp-SP and artesunate. These strategies show promise in the reduction of low birth weight or maternal parasitemia.

Treatment of uncomplicated malaria

All MIP infections should be treated promptly to avoid complications to the mother and fetus.³¹ To ensure safety of treatment in pregnancy, the WHO recommends trimester-specific and species-specific treatment strategies for uncomplicated malaria (Table 1). For first trimester treatment of *P. falciparum*, the WHO recommends a 7-day treatment course of quinine with clindamycin, and second line treatment includes artemisinin-based combination therapy (ACT) or oral artesunate with clindamycin.⁶⁵ First trimester treatment of uncomplicated non-*falciparum* malaria consists of chloroquine or quinine for chloroquine-resistant infections.

Second and third trimester treatment of uncomplicated malaria follows the same guidelines as treatment for malaria in non-pregnant adults.³¹ Therefore, first line treatments with ACTs can be used in MIP. ACTs include a short-acting artemisinin component and a longer acting partner drug, such as SP.⁶⁹ The potent artemisinin reduces the number of parasites quickly and the longer acting partner drug acts on the remaining parasites and provides a post-treatment prophylactic effect, preventing new infections.⁶⁹ ACTs have achieved cure rates as high as 99.2% for uncomplicated MIP without demonstrating significant safety concerns.⁷⁰

Treatment of Severe Malaria

Severe malaria has historically been attributed to infections with *P. falciparum*, but more recent evidence has included *P. vivax* as a significant contributor to severe malaria.³⁰ For pregnant patients with severe malaria, the WHO recommends the same treatments for both *P. falciparum* and *P. vivax* infections. The WHO also recommends treatment with primaquine after delivery to achieve cure and prevent relapses by eradicating *P. vivax* sequestered in the liver, (Table 1).³⁰

Artemisinins are the most efficacious drugs for severe MIP after the first trimester. Because they are embryotoxic and teratogenic in animal studies, the WHO does not recommend their use in the first trimester for uncomplicated malaria. However, their use is recommended even in the first trimester in cases of severe malaria because of the high risk of maternal mortality.³⁰ Data on the use of artemisinins in the first trimester in humans show no associated increased risk of adverse pregnancy outcomes.³⁰ Long-term neurodevelopmental studies are needed to evaluate the safety of different drug combinations on child development.

Quinine is an alternative to artemisinin that has been used for centuries for the treatment of malaria. Although it is not considered embryotoxic or teratogenic in animal studies, it is less well-tolerated in humans.³⁰ Quinine can prolong the cardiac QT interval and is associated with tinnitus, headache, blurred vision, altered auditory acuity, nausea, diarrhea, and, rarely, massive hemolysis.⁶⁵ These side effects reduce compliance with treatment regimens and lead to higher levels of treatment failure.³⁰

Vaccines

An efficacious vaccine against malaria could be of particular benefit for pregnant women. One vaccine, RTS,S, is now approved by the European Medicines Agency, but is only modestly effective.⁷¹ Efforts are also underway to develop a vaccine targeting the VAR2CSA antigen to protect women against pregnancy-associated malaria.⁷²

Co-Infection with HIV

Co-infections with malaria and HIV worsen morbidity and mortality for each disease, possibly due to alterations in the balance between the immune response to malaria and stimulation of viral replication.⁷³ MIP is associated with a two-fold higher HIV viral load. Conversely, women living with HIV experience more placental and peripheral malaria, higher parasite densities, more frequent febrile illnesses, more severe anemia and worse birth outcomes compared to non-HIV infected mothers with MIP.⁷³ Chemoprevention for women living with HIV in malaria-endemic areas includes daily co-trimoxazole. SP is discouraged for chemoprevention due to potential adverse drug reactions between SP and co-trimoxazole.⁷⁴ Although pregnant women living with HIV have the greatest risk of severe MIP, treatment strategies for severe malaria in conjunction with HIV treatments have not been well studied.^{30, 73} The WHO recommends against the use of zidovudine or efavirenz and the use of artesunate amodiaquine due to neutropenia and hepatotoxicity respectively.⁶⁵ Pregnant women receiving highly active antiretroviral therapy regimens should receive quinine when cardiac monitoring is available.

Conclusions

Malaria is among the most common and easily preventable causes of poor birth outcomes in the world. IPTp and ITNs distribution programs have helped decrease malaria risk among pregnant women in many parts of the world. However, greater efforts are needed especially in light of increasing drug and insecticide resistance. A better understanding of the pathogenesis of malaria during pregnancy could lead to the development of new interventions to prevent its health consequences.

Gaps in Knowledge (sidebar)

- What are the mechanisms by which malaria during pregnancy affects fetal growth?
- What is the natural history of congenital malaria?
- How can we increase uptake of IPTp and ITN's by pregnant women?
- When is the optimal gestational age to start IPTp?
- How can we enable women to begin IPTp earlier during pregnancy?

- When malaria prevalence drops, when is it appropriate to stop IPTp?
- When high levels of resistance to SP develop, what should be done to protect pregnant women from malaria?
- Will it be possible to vaccinate primigravidae against pregnancy-associated malaria?

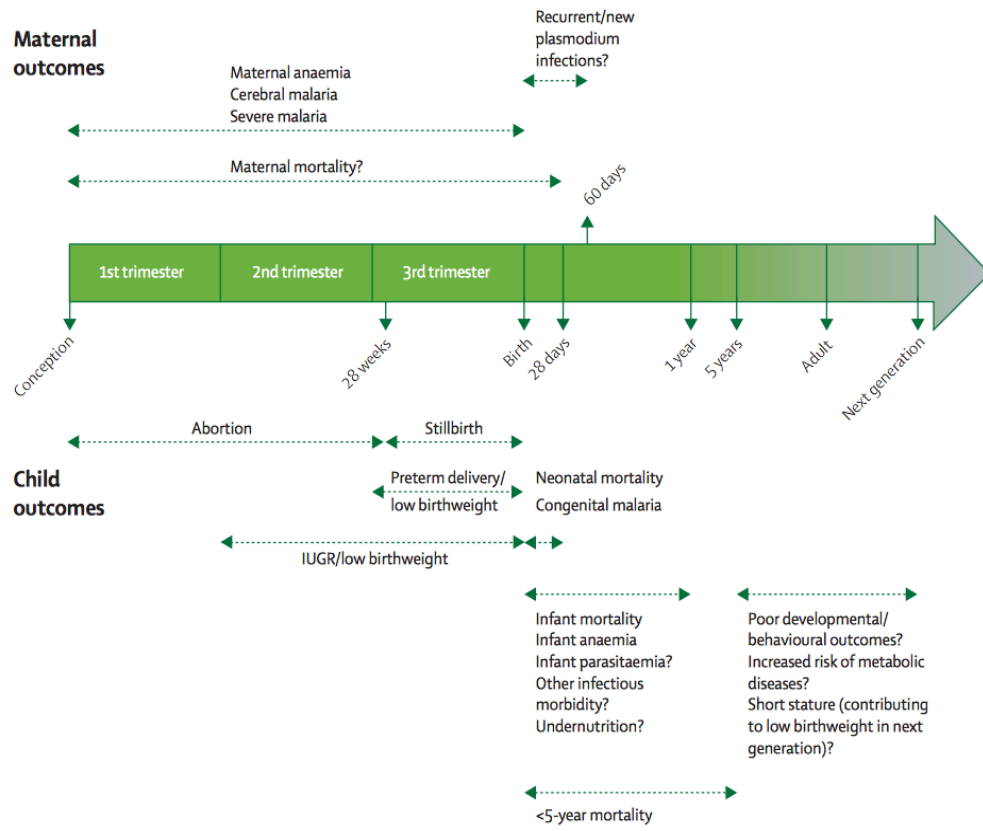
DISCLOSURES

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Table 1: Treatment Strategies for MIP

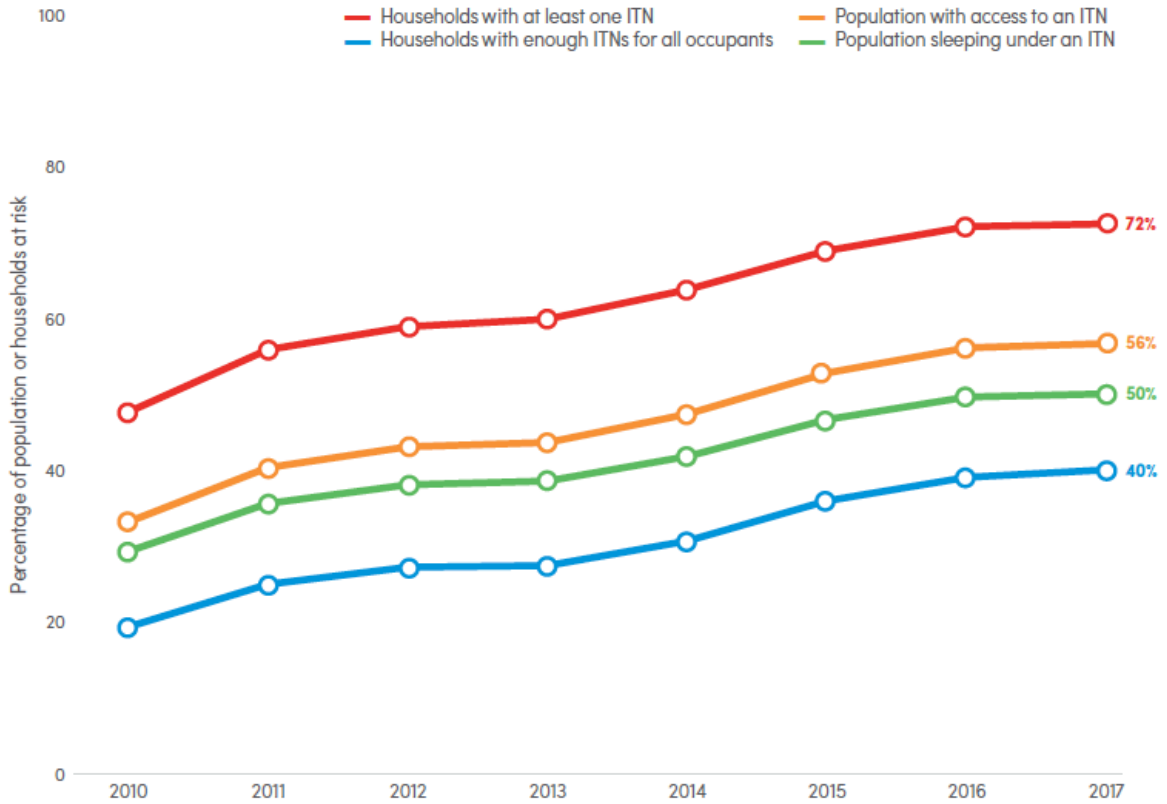
Severity	Uncomplicated Malaria		Severe Malaria
Definition	Symptoms of malaria and positive parasitological test (microscopy or RDT) but no features of severe malaria		Parasitemia and one of the following (not caused by another etiology): 1) Impaired consciousness 2) Prostration 3) Multiple convulsions 4) Acidosis 5) Hypoglycemia 6) Severe malarial anemia (Hemoglobin <7 g/dL) 7) Renal Impairment 8) Jaundice 9) Pulmonary Edema 10) Significant bleeding 11) Shock 12) (<i>P. falciparum</i> only) Hyperparasitemia >10%
Treatment	First Trimester	Second and Third Trimester	All Trimesters
<i>P. falciparum</i>	Quinine and clindamycin x 7 days	Artemisinin-based combination therapy (ACT) for 3 days, Options include 1) artemether + lumefantrine 2) artesunate + amodiaquine 3) artesunate + mefloquine 4) artesunate + SP 5) dihydroartemisinin + piperaquine	<i>Treatment for all Plasmodium species</i> IV or IM artesunate at least 24 hours then ACT for 3 days Add primaquine in areas of low-transmission
Non-<i>falciparum</i>	Chloroquine or <i>If chloroquine-resistant:</i> quinine Add weekly chemoprophylaxis with chloroquine through pregnancy and breastfeeding Add Post-delivery/lactating: treatment with primaquine x 14 days	ACT or Chloroquine <i>If chloroquine-resistant:</i> ACT Add weekly chemoprophylaxis with chloroquine through pregnancy and breastfeeding Add Post-delivery/lactating: treatment with primaquine x 14 days	

Figure 1: Effects of malaria in pregnancy through the life course



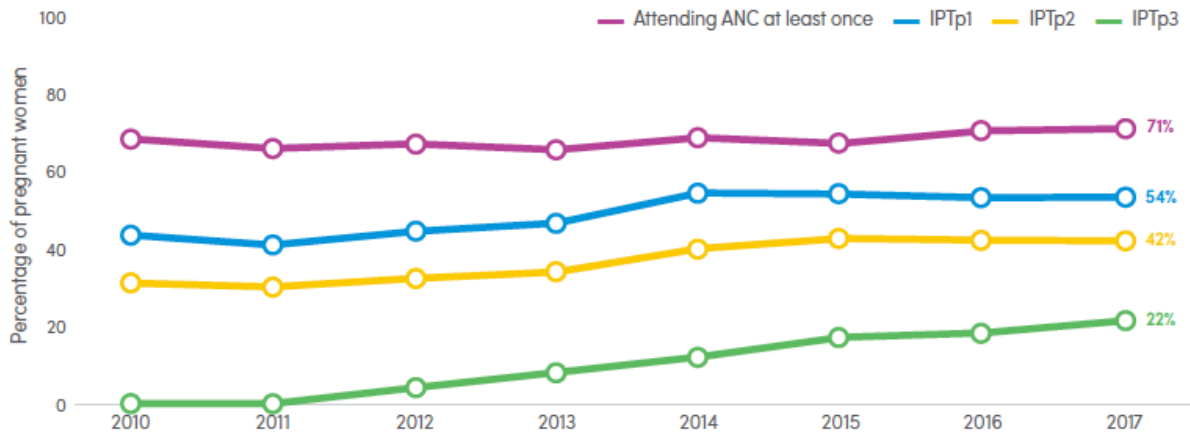
IUGR = Intrauterine growth retardation. Reprinted with permission (4).

Figure 2: Uptake of ITN: Percentage of the population in Sub-Saharan Africa at risk for malaria with access to ITN and using ITNs.



ITN: insecticide-treated bed nets Sources: World Health Organization and Malaria Atlas Project. Reprinted with permission (56).

Figure 3: Uptake of IPTp: Percentage of pregnant women receiving IPTp, by dose in Sub-Saharan Africa, 2010-2017.



ANC: antenatal care, IPTp: intermittent preventive treatment in pregnancy, listed by dose. Sources: National Malaria Programme, World Health Organization, US Centers for Disease Control and Prevention. Reprinted with permission (56).

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