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REVIEW

# Impact of Placental *Plasmodium falciparum* Malaria on Pregnancy and Perinatal Outcome in Sub-Saharan Africa

# I: Introduction to Placental Malaria

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Placental malaria is one of the major features of malaria during pregnancy and has been widely used as a standard indicator to characterize malaria infection in epidemiologic investigations. Although pathogenesis of placental malaria is only partially understood, placental sequestration of *Plasmodium falciparum* results in the accumulation of parasitized erythrocytes in the intervillous space, infiltration by inflammatory cells, and release of pro-inflammatory mediators, which cause pathologic alterations that could impair materno-fetal exchanges, often resulting in adverse pregnancy outcome. In this report, the impact of placental malaria on pregnancy and perinatal outcome is reviewed using data from studies conducted in sub-Saharan Africa. Generally, placental malaria was associated with increased risk of maternal anemia, HIV infection, and maternal mortality, with younger women and primigravidae more likely to be affected. A variety of adverse perinatal outcomes, including low birth weight, preterm delivery, intrauterine growth retardation, reduced fetal anthropometric parameters, fetal anemia, congenital malaria, increased mother-to-child HIV transmission, and perinatal mortality, were associated with placental malaria. There were, however, conflicting reports on whether the risk of these adverse perinatal outcomes associated with placental malaria were statistically significant. There is a clear need to strengthen the malaria prevention and intervention measures for pregnant women in sub-Saharan Africa.

## INTRODUCTION

Malaria, which has been described as a disease of poverty and underdevelopment, remains a complex and overwhelming health problem, with 300 to 500 million cases and 2 to 3 million deaths per year [1]. About 90 percent of all deaths attributable to malaria occur in sub-Saharan Africa [1], and two factors are largely responsible. First, the majority of infections in this region are caused by *Plasmodium falciparum*, the most dangerous of the four human malaria parasites; and second, the most effective malaria vector — the mosquito *Anopheles Gambiae* — is the most

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†Abbreviations: RDT, rapid diagnostic test; sVEGFR1, soluble vascular endothelial growth factor receptor 1; VEGF, vascular endothelial growth factor; CSA, chondroitin sulfate A; IPT, intermittent preventive treatment; SP, sulfadoxine-pyrimethamine.

widespread in the region and the most difficult to control [2,3]. In areas where malaria is highly endemic, a protective semi-immunity against *P. falciparum* is acquired during the first 10 to 15 years of life, and the majority of malaria-related morbidity and mortality occur in young children [4]. However, in contrast with low malaria prevalence in adults, pregnant women in endemic areas are highly susceptible to malaria, and both the frequency and the severity of disease are higher in pregnant women [5]. In pregnancy, there is a transient depression of cell-mediated immunity that allows fetal allograft retention but also interferes with resistance to various infectious diseases [6]. Furthermore, cellular immune responses to *P. falciparum* antigens are depressed in pregnant women [7,8].

Malaria during pregnancy is therefore a serious problem in sub-Saharan Africa, affecting an estimated 24 million pregnant women annually [9]. Although *P. falciparum* infection in pregnancy is usually asymptomatic, it often contributes to adverse perinatal outcomes with a high risk for infant death, particularly in areas of lower malaria endemicity [9]. Pregnancies in women living in malaria endemic regions are associated with a high frequency and density of *P. falciparum* parasitemia, with high rates of maternal morbidity, including fever and severe anemia, abortion, and placental malaria [5,9]. Each year, between 75,000 and 200,000 infant deaths are attributed to malaria infection in pregnancy globally [6,10].

Despite the public health importance of placental malaria, its impact on pregnancy outcome in sub-Saharan Africa has not been comprehensively reviewed. In this three-section report, an attempt was made to comprehensively review data from studies conducted in sub-Saharan Africa that investigated association between placental malaria and a variety of adverse perinatal and maternal outcomes. Searches in Medline/PubMed and in bibliographies of relevant articles were used to collect articles for review. In this section of the report, the diagnosis and pathologic features of placental malaria will be reviewed. In the following two sections, the known effects of malaria infection in pregnancy on the fetus and the mother will be comprehensively reviewed.

## CHARACTERISTICS OF MALARIA-INFECTED PLACENTA

The placenta is a complex, sophisticated organ with several important functions throughout gestation, with the primary purpose of providing sustenance for the developing fetus. The placenta is also a site for *P. falciparum* sequestration. Many hypotheses, based on a systemic or local failure of the immunological response to malaria, have been proposed to explain the "preference" of the parasites for replication in the placenta; some have been reviewed elsewhere [11]. At term, the placenta is usually a circular-shaped structure measuring approximately 20 cm in diameter and 2.5 cm in thickness. The fetal portion of the placenta consists of the chorionic plate and its villi and the peripheral trophoblastic shell that surrounds the intervillous space and covers the maternal tissue. Anchoring villi contact the decidua basalis. The decidua basalis (maternal portion of the placenta) rests on the stratum basalis and is characterized by large, polyhedral pale blue stromal (decidua) cells [12,13].

The placental sequestration of *P. falciparum* (placental malaria) results in the accumulation of parasitized erythrocytes in the intervillous space, infiltration by inflammatory cells, and release of pro-inflammatory mediators [12], which cause pathologic alterations [13-15]. Histologically, placental malaria is characterized by the presence of intervillous parasites and leukocytes, malarial pigment within macrophages, fibrin deposits and trophoblasts, proliferation of cytotrophoblastic cells, and thickening of the trophoblastic basement membrane [11,14]. In a study conducted in Haut-Ogooue, Gabon, malarial brown pigment was observed in all cases of placental malaria examined; it was characterized by ultrastructural features and occurred in perivillous deposits of fibrinoid, in

macrophages, or free in intervillous spaces [13]. Excessive perivillous fibrinoid deposits were a constant histologic finding and were usually associated with syncytiotrophoblastic necrosis or ultrastructural damage, such as partial microvilli loss, filamentous material accumulation in intracytoplasmic vacuoles, and "podocytelike" cytoplasmic projections on the basal surface [13]. It is at these sites that the trophoblastic basal lamina was usually thickened.

In the Gambia study, the deposition of malaria pigment in circulating cells was associated with active infection. Pigment in fibrin and fibrinoid necrosis of chorionic villi were features of active chronic infections; thickening of the trophoblast basement membrane occurred in all infection categories [16]. Despite increased understanding of the placental malaria pathology, the exact mechanisms leading to placental changes impairment of materno-fetal exchange are not completely understood. However, it has been suggested the parasites are unlikely to be directly responsible for the placental pathology. Rather, leucocytes, through the production of non-chemotactic cytokines, might be associated with the thickening of the trophoblastic basement membrane and might cause mechanical blockage of placental oxygen and nutrient transport [11]. The high frequency of adverse perinatal outcomes, including, but not restricted to, premature, hypotrophic neonates, and stillbirths in the malarial population, has been linked to the intervillous macrophages, which decrease the maternal blood output, and perivillous excess of fibrin, which reduces the materno-fetal exchanges [17]. A deeper understanding of pathological mechanisms involved in placental malaria is vital in the design of effective protective interventions among pregnant women in malaria endemic areas.

## DIAGNOSING PLACENTAL MALARIA

The sequestration of malaria parasites in the placenta is one of the major features of malaria infection during pregnancy. In semi-immune women (i.e., those residing in areas of unstable malaria transmission), the proportion of parasitized erythrocytes is often higher in the placenta than in peripheral blood [18]. Additionally, placental infection may be detected in the absence of peripheral blood parasitemia and may persist after initiation of antimalarial treatment [19].

Because not all malaria-exposed pregnant women in areas of malaria endemicity suffer from placental malaria and its serious consequences, a number of studies have assessed the prevalence and risk factors of placental malaria in sub-Saharan Africa, while others have attempted to elucidate protective immune responses against placental infection and/or immune pathogenesis. However, results from the various studies are often discordant, due in part to different techniques of sample collection and analysis in different studies, based on the differences in the definition of placental malaria [20]. Some studies based their definition on the presence of malaria parasite and/or pigments in blood smears from placental blood [21,22,23]. Others based their definition on histological findings [21,24-26], while yet others based their definition on the use of histidine-rich-protein-2 (HRP2) capture test [22,27-29] and polymerase chain reaction (PCR) [22,29-31]. In various parts of sub-Saharan Africa, placental malaria prevalence rates ranging from 9.5 percent to 37.1 percent were obtained by placental blood smear microscopy, 35 percent to 75.5 percent by placental histological examination, 41 percent to 43.1 percent by HRP2, and 51 percent to 59 percent by PCR [21,22,24,29,32].

It is pertinent to state that most studies in sub-Saharan Africa relied on the results of the placental smear, the sensitivity of which is low compared with placental histopathology. Using a more reliable method of assessing placental infection, such as the histopathologic examination, might have changed the results [33,34]. Although microscopy with placental blood is less sensitive than placental histology, it is considerably more sensitive in the diagnosis of maternal malaria than peripheral blood smears [35]. For instance, in southern

Ghana, the vast majority of *P. falciparum* infected delivering women were asymptomatic, and microscopy of thick films from peripheral blood missed more current infections than it detected, with roughly half of the women with microscopically proven placental parasitemia having a *P. falciparum* negative peripheral blood film [22]. In Blantyre, Malawi, blood smear microscopically detectable *P. falciparum* peripheral and placental infection was more common in women with their first and second pregnancies than in multigravid women, but neither infection detected by histology only nor incidences of past infection differed with gravidity, and similar numbers of women were uninfected [35].

Placental histology is therefore considered the "gold standard" of malaria diagnosis in pregnancy for epidemiological or biological study purposes, because it can show signs of active infection (presence of infected erythrocytes in the intervillous space), past or chronic infection (malarial pigment), or both [33]. However, due to limited technical expertise, such testing is rarely available in endemic areas; examination of thick films of blood samples obtained by placental incision is comparatively easier [22]. As compared to histology, sensitivity and specificity of this method have been reported to be 76 percent and 99 percent, respectively, and thus is in the range of blood film microscopy produced by scraping the wall of placental incisions or by spinning down erythrocyte pellets from biopsy washings [35]. Although placental hemozoin is described as the clinically most relevant marker of infection, detection of hemozoin on placental thick blood films is likely influenced by this difference in sensitivity and also neglects pigment deposition in placental structures [22]. It has been argued that staging placental infection based on placental thick blood films findings — although deduced from the histological classification [36] is not fully comparable to histology and needs further evaluation [22].

The comparisons of microscopy, HRP2 (or other rapid diagnostic tests (RDTs†)), and PCR in placental malaria diagnosis are challenging to interpret because they detect infection in different ways: microscopy detects viable whole parasites in red blood cells, HRP2 detects specific parasite proteins, and PCR detects parasite DNA [29]. Although the HRP2 and PCR are able to detect parasite debris present in the blood when viable parasites may be sequestered in the placenta or persist at very low densities, both parasite proteins and DNA can be detected after successful treatment, making the results of HRP2 and PCR potentially confusing in a clinical setting [29]. PCR assays also detect low-level infections that produce no major fetal impairment; however, some studies have shown that submicroscopic infections detected by PCR are associated with mild maternal anemia and inflammation, and submicroscopic infections detected by rapid diagnostic test are associated with maternal anemia and low birth weight [22,37,38]. A better understanding of the clinical and epidemiological relevance of detection techniques is imperative for proper interpretation.

## PLACENTAL MALARIA, MATERNAL HEALTH, AND PUBLIC HEALTH

*Plasmodium falciparum* infections of the placenta remain a major medical challenge among pregnant women in sub-Saharan Africa. A number of factors influence the prevalence of placental malaria in pregnant women, including maternal age, gravidity, use of prophylaxis, nutrition, host genetics, and level of antiparasite immunity, as well as parasite genetics and transmission rates [23]. Maternal anemia has been shown to be one of the major complications of placental malaria in sub-Saharan Africa. The mechanisms by which malaria causes anemia are fairly well understood. The pathophysiology of malaria-associated anemia is multifactorial. The most likely mechanisms include (1) hemolysis or the direct destruction of parasitized red blood cells that occurs both intravascularly and by sequestration in the microcirculation, mainly in the spleen; (2) specific/nonspecific immune responses, whereby red cell survival is shortened; (3)

nonspecific, defective red cell production, which depresses erythropoiesis, inhibits reticulocyte release, and prematurely destructs red cells during maturation in the bone marrow; and (4) hypersplenism associated with a reduction in all three blood cell series, that is, causing not only anemia but also thrombocytopenia and leucopenia [39,40].

The relationship between maternal anemia with obstetric factors however, is not fully understood, and thus, evaluating the link between malaria, obstetric disorders, and maternal death has been recommended [41]. There have been efforts to quantify the contribution of malaria to maternal morbidity and mortality with the expectation this would provide the evidence necessary to improve the effectiveness of advocacy to incorporate malaria prevention strategies in Safe Motherhood Programs [42,43]. The effects of placental malaria on maternal health can better be understood when considered in relation with various maternal parameters, including maternal age, parity, peripheral malaria infection, anemia, and HIV infection.

## MATERNAL HEALTH AND MALARIA

### *Increased Morbidity and Mortality*

Although pregnant women in malaria endemic areas have higher rates of parasitemia and parasite density compared with non-pregnant women, infection is largely asymptomatic because some degree of preexisting immunity is retained during pregnancy [44]. However, even malaria-immune women (i.e., those who have evolved some level of immunity against severe infection as a result of long residence in areas of stable malaria transmission) are susceptible to placental malaria [23,24]. Because so many parasites become sequestered within the placenta, peripheral blood smears often fail to detect evidence of infection. The resulting lack of appropriate or timely treatment may lead to adverse pregnancy outcome, including severe anemia, which is the main maternal consequence of malaria and can be deadly [44]. Apart from anemia, malaria may contribute to maternal mortality by increasing the risk and severity of obstetric conditions such as pre-eclampsia/eclampsia and postpartum hemorrhage by as much as 50 percent [45,46].

### *Maternal anemia*

Anemia is the most common consequence of *P. falciparum* malaria infection. In sub-Saharan Africa, it is estimated that between 200,000 and 500,000 pregnant women develop severe anemia as a result of malaria [9], and *P. falciparum* malaria in pregnancy is the primary cause of up to 10,000 maternal anemia-related deaths in sub-Saharan Africa annually [43,47]. However, there have been conflicting reports from parts of sub-Saharan Africa on the relationship between placental malaria and maternal anemia. An earlier report from the Ubangi district of Zaire noted that malarious placentas had no consistent relationship to maternal anemia [48]. In other studies, maternal anemia and placental malaria were associated in all gravidity and age groups, with maternal anemia higher among women with placental malaria than those without placental malaria (by gravidity, prevalence ranged from 28.8 percent to 31.6 percent for positive cases and 15.3 percent to 16.7 percent for negative cases; by age, prevalence ranged from 26.5 percent to 31.8 percent for positive cases and 15.3 percent to 17.7 percent for negative cases) [23]. The reason for this variation is not clear, but it may be connected to the complex and multifactorial etiology of anemia in pregnancy in sub-Saharan Africa [39].

In most areas of malaria endemicity, many other causes of anemia have been identified, including both nutritional (iron, folate and protein deficiency) and non-nutritional (hookworm or HIV infection, hemoglobinopathy) factors, [40,49]. Since many of these causes of anemia occur concurrently in pregnancy and no unique hallmarks of malaria-driven anemia have been identified, it is difficult to evaluate the contribution made to anemia in pregnancy by placental malaria infection [50]. Apart from its significant contribution to maternal mor-

tality and both maternal and fetal morbidity, anemia in pregnancy is a risk factor for infant iron deficiency anemia [51] that, if left uncorrected, can be associated with adverse behavioral and cognitive development [52]. Severe anemia in pregnancy is an important direct and indirect cause of maternal death. During pregnancy, severe anemia may result in circulatory changes associated with an increased risk of heart failure and acute onset of anemia due to rapid cardiac decompensation and decreases in hemoglobin (Hb) concentration to < 80g/L. Such changes can result in the failure of compensatory mechanisms, accumulation of lactic acid and breathlessness at rest [53]. Furthermore, during labor, women with severe anemia are less able to endure even moderate blood loss and, as a consequence, are at a higher risk of requiring a blood transfusion during delivery [40]. For the fetus, severe maternal anemia may result in intrauterine growth retardation, still birth, and low birth weight [54-57]. The mechanism of malaria-driven anemia can be described in association with iron status in pregnancy. The iron status in pregnancy is affected by malaria parasites, which influence the anemia observed in pregnancy. *P. falciparum* may affect iron status through (1) reducing intestinal iron absorption, (2) sequestrating iron within the malarial pigment hemeozoin, (3) consuming iron for its own metabolism, (4) promoting/stimulating the mobilization of iron to body stores, and (5) releasing iron into the circulation during intravascular hemolysis [39,40].

### *Maternal Age and Malaria Infection*

A number of studies conducted in sub-Saharan Africa have reported a significant association between maternal age and malaria infection during pregnancy [58-61]. In a study conducted in Blantyre, Malawi, after stratifying by gravidity, associations between age and parasite prevalence were stronger than those between gravidity and prevalence after stratifying by age [59]. Under conditions of low-to-moderate transmission, pregnancy-specific immunity is slow to develop, and age-related immunity may influence malaria prevalence in child-bearing years [59].

Studies have shown that young women of child-bearing age may be more susceptible than older women to malaria because they are still in the process of acquiring natural immunity to malaria [62-64]. In Cameroon, age was a major risk factor for placental malaria, with younger first-time mothers more likely to have placental malaria [23]. Similarly, in Zaire, mothers with malarious placentas were younger (mean age 24) than mothers with non-malarious placentas (mean age 29) [48]. It was suggested that development of pregnancy-associated immunity, i.e., production of antibodies that inhibit the adherence of placental parasites to chondroitin sulfate A (CSA), may be very important in women less than 25 years of age who have lower levels of acquired immunity (through less frequency of exposure to the bites of *P. falciparum* infected mosquitoes) than in older women who may have obtained adequate immunity following repeated exposures and thus are less dependent on anticytoadherent antibodies [23]. However, it is important to state that in malarious areas, pregnancy-associated and age-dependent immunity to placental malaria may be influenced by host or environmental factors.

## PARITY AND HEALTH

The relationship between placental malaria and parity is well established. Many recent studies have found the prevalence to be higher in primigravidae than multigravidae, and in these studies, results are controlled for age [21,23,65,66]. These observations are consistent with the findings of earlier studies in malaria-endemic regions, where, among several factors, parity independently influenced the placental malaria prevalence rate, with primigravidae having a two- to four-fold increased risk of placental malaria compared to multigravidae [5,67,68]. In Gambia, it was observed that the severest form of placental parasitization occurred in a higher proportion of the primigravidae than in the multigravidae [21].

In the Tanga region of Tanzania, placental malaria was associated with hypertension in young first-time mothers with histologic features of chronic disease but not related to hypertension in older or multigravid women. Similarly, placental malaria was associated with elevated levels of placentally derived soluble vascular endothelial growth factor receptor 1 (sVEGFR1) in first-time mothers but not in multigravid mothers with age being controlled [69]. sVEGFR1 may cause systemic endothelial dysfunction by binding to and sequestering free serum vascular endothelial growth factor (VEGF) and placental growth factor [70,71], which is associated with higher risk adverse perinatal outcome among primigravidae with as much risk as up to 25 percent [70]. The exact reason why primigravidae are more susceptible to placental malaria and suffer from its consequences more than multigravidae is yet to be fully elucidated. However, a common explanation is that pregnancy is associated with a decrease in immunity, which is more pronounced in primigravidae than in multigravidae and may be associated with age [72]. Immunological studies have shown that this increase in susceptibility could be related to the property of parasitized erythrocytes to adhere to chondroitin sulfate A (CSA) expressed by the syncytiotrophoblast of the placenta [73,74]. Thus, the placenta may select for the CSA-binding *P. falciparum* phenotype, putting primigravidae with no previous exposure to this parasite form at increased risk for developing placental malaria. The decreasing susceptibility to pregnancy-associated malaria with increasing parity is reflected in the acquisition of antibodies specific to parasites' variant antigens expressed on the surface of infected erythrocytes [75]. Another possible explanation for this parity-related susceptibility is given by the findings of Duffy and Fried [76], who showed that multigravid mothers develop malaria antibodies that block adhesion of parasites to CSA receptors in the placentae in subsequent pregnancies. More studies using both immunological and molecular biological tools are urgently needed to properly elucidate this parity-related susceptibility to placental malaria. However, since pregnant women in malarious areas produce antibodies that specifically recognize CSA-binding *P. falciparum*, this could form a basis for the development of a vaccine to protect pregnant women against placental malaria.

## PERIPHERAL MALARIA INFECTION

The relationship between maternal peripheral parasitemia and placental malaria has been evaluated in some parts of sub-Saharan Africa. There are no rigorous studies on whether placental infection reflects the existence of peripheral infection over a short period preceding the delivery or whether it is related to infection during pregnancy. Two studies have shown some relation between a late infection (i.e., infection acquired late in pregnancy) and positivity of placental smears or presence of pigment [77,78], but it has been argued that a single measure can hardly reflect the entire history of infection during pregnancy. In one study, the occurrence of peripheral parasitemia at the beginning and at the end of pregnancy was significantly related to placental infection, whereas peripheral parasitemia in the middle of pregnancy was not [72]. This suggests that a peripheral parasitemia at the beginning of pregnancy may persist within the placenta throughout gestation, with possibly more severe consequences for the placenta and the newborn than an infection acquired later in pregnancy.

Other studies have shown that peripheral infection confers a five-fold increased risk for placental malaria, thus confirming the importance of late maternal infections [79]. Although maternal peripheral infection toward the end of pregnancy (post seven months) predisposes the woman to placental malaria, risk of placental infection is greater if peripheral infection occurs at the beginning of pregnancy [5]. In Malawi, placental infection was more frequent in women who were infected at enrollment (i.e., during the first trimester of pregnancy) in the study than those who were not infected at enrollment [79]. Early peripheral infection during

pregnancy may be a particularly important risk factor for placental infection, due to lower immune protection at the beginning of pregnancy. Nevertheless, susceptibility may be correlated to high exposure to malaria, and repeated episodes of parasitemia, as well as the interplay between several other factors, should form the basis for further investigations.

## PUBLIC HEALTH CONSIDERATIONS

Despite considerable improvement in healthcare delivery services in the African continent, the control of malaria in pregnant African women, one of several child survival strategies applied through antenatal care, continues to be particularly challenging. Prevention and control recommendations for typical areas of high *P. falciparum* transmission have promoted the use of antimalarial chemoprophylaxis to prevent placental infection and its associated adverse perinatal outcome. This confirms prior findings [80]. Other randomized trials show a protective effect of prophylaxis on placental infection or peripheral parasitemia [79,81,82]. However, persistently low program coverage coupled with diminishing intervention effectiveness has forced a re-evaluation of the relative importance of malaria in pregnancy [83]. The prophylactic medicines include sulfadoxine pyremethamine, proguanil, and pyremethamine, while the curative ones include artesunate, chloroquine, and amodiaquine. These drugs are relatively safe in pregnancy and are widely used in malariouos areas of sub-Saharan Africa [84].

In the face of the mounting evidence of the relative failure of many traditional antimalarial drugs, particularly chloroquine, the WHO has put forward new guidelines for combating and preventing malaria during pregnancy [58,84]. The guidelines recommend that women living in high transmission areas of Africa receive intermittent preventive treatment (IPT) with an effective antimalarial agent such as sulfadoxine-pyrimethamine (SP) at scheduled antenatal visits, and all pregnant women in targeted areas should undergo at least two sessions of IPT after first fetal movements (i.e., between 20 to 35 weeks) [84]. Unfortunately, the implementation of the WHO guidelines has been burdened by the notorious problems complicating health service delivery in the developing world, particularly in the African continent, namely, the logistical challenges of reaching remote regions, resource scarcity, lack of infrastructure, inadequate treatment, continuing poverty, and armed conflict.

It is well established that women in Africa use prenatal care extensively when it is available and accessible. This opportunity must be used to implement evidence-based actions with appropriate and realistic goals. There is an urgent need to improve access of rural women to antenatal clinic services in sub-Saharan Africa, either through increasing the number of rural health centers or by establishing functioning outreach services. The distribution of insecticide-treated bed nets needs to become implemented on a large scale.

Since pregnant women have increased specific risks of complications from both malaria and HIV infection, the financial and human resource constraints of health systems in countries most affected by malaria and HIV and the shared determinants of vulnerability for both diseases indicate the need for integration of preventive and curative services for malaria and HIV. The health systems that deliver these services must be strengthened [55]. Reproductive health services offer a critical opportunity for routine provider-initiated HIV testing and counseling. They can provide follow-up care with prevention of MTCT interventions according to national policy for those who test positive, coupled with entry to antiretroviral therapy programs for those sick and in need of immediate therapy. These services need to be strengthened to ensure the delivery of the WHO-recommended antenatal care schedule of four visits (focused antenatal care), which includes a minimum package of interventions for the prevention of both malaria and HIV [85].

Studies in malarious regions have demonstrated that substantial reductions in maternal malaria, anemia, and low birth

weight have been achieved by intervention programs, including the use of preventive intermittent treatment, chemoprophylaxis, and the use of insecticide-treated nets. In fact, studies suggest that between 25 percent and 90 percent of these adverse events might be prevented by full implementation of existing interventions [9]. Interventions, therefore, should also exist for maternal anemia (e.g., good nutrition, iron and folate supplementation, and hookworm treatment) and for reduction of mother-to-infant HIV transmission (e.g., short-course zidovudine or nevirapine), and such can be provided through antenatal care programs [56,86-89]. Better application of these malaria, anemia, and HIV interventions could markedly reduce the infant mortality burden of these diseases.

Finally, collaboration between scientists, policy makers, and control programs should be strengthened and community-level research encouraged in order to guide programs and monitor and evaluate markers of success.

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