

Declining Malaria Transmission and Pregnancy Outcomes in Southern Mozambique

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Malaria is declining in many parts of the tropical world as a result of increased provision of effective control interventions (mainly insecticide-treated bed nets and artemisinin-based combination therapies).¹ The effects on the clinical epidemiology of malaria differ depending on the level of transmission intensity. Where the transmission intensity was previously low, mortality and case numbers have declined even more, making elimination of malaria at the local and regional levels increasingly possible. Where the transmission intensity was high, the consequences are more complex, reflecting the interplay between malaria transmission and an imperfect acquired immunity. There are places in Africa where a person could be infected with malaria parasites up to three times each day. In these conditions of intense malaria transmission, the rates of disease and death are highest among young children. Profound anemia is the main clinical manifestation of severe *Plasmodium falciparum* infection. If children who are infected at a young age survive, then malaria later in childhood or in adulthood is largely asymptomatic.² Lowering transmission intensity reduces childhood mortality but also results in a slower acquisition of immunity — extending the age range for symptomatic malaria. Cerebral malaria and metabolic acidosis become the predominant lethal manifestations of severe *P. falciparum* malaria. As transmission declines further, and the population becomes correspondingly less immune, older children and adults become susceptible to severe malaria, with acute renal failure as an important cause of death.² Among pregnant women with severe *P. falciparum* malaria, mortality approaches 50%.^{2,3} The incidence of malaria may also become increasingly unstable, with greater fluctuations from year to year and occasional epidemics.

Malaria is particularly hazardous to the developing fetus.^{3,4} In areas where rates of *P. falciparum* transmission are high, an increased risk of anemia may be the only maternal manifestation of repeated malaria infections during preg-

nancy, but enormous numbers of parasitized erythrocytes are sequestered in the placenta (which at delivery may appear black from the accumulated malaria pigment). This results in structural damage and interference with placental transfer, causing intrauterine growth retardation, particularly in the first pregnancy, and a low-birth-weight baby is at increased risk for death in the first few months after delivery.⁴ In contrast, where transmission of malaria is low, malaria is dangerous for both the mother and the fetus, causing abortion, stillbirth, and reduced birth weight.³ Low birth weight resulting from malaria during pregnancy is estimated to result in approximately 100,000 infant deaths each year in Africa.⁴

A study by Mayor et al., now reported in the *Journal*, shows how improvements in malaria control in the south of Mozambique, and the consequent declines in malaria transmission and immunity, have reduced the incidence of malaria but have adversely affected the outcome of pregnancy in women who were infected.⁵ In recent years, the main strategy used to protect women in Africa from the adverse effects of malaria during pregnancy has been to provide insecticide-treated mosquito nets and to give two spaced treatment doses of sulfadoxine-pyrimethamine. Each dose provides protection from malaria for approximately 4 to 6 weeks, depending on the prevailing levels of resistance. This is called intermittent preventive treatment in pregnancy. In studies of such treatment that were conducted from 2003 to 2005 and from 2010 to 2012, which used similar methods, Mayor et al. found that the overall risk of *P. falciparum* malaria during pregnancy decreased substantially from the earlier to the later period, but for the offspring of infected women, as compared with the offspring of uninfected women, the reduction in birth weight was greater in 2010–2012.⁵ Ten years ago, the mean reduction in birth weight associated with maternal malaria infection was 45 g, whereas more recently, it was 165 g — a difference closer to that observed elsewhere in

low-transmission areas and in areas where preventive treatments were not provided.^{3,4} This change was attributed mainly to loss of protective immunity, worsening the clinical consequences of malaria and extending the adverse effects to the fetuses of multigravid women, as well as to those of primigravid women.

The prevention of malaria during pregnancy is increasingly compromised by drug resistance. In southern Mozambique, resistance to antifolates and sulfonamides resulting from mutations in the genes encoding dihydrofolate reductase (*Pf dhfr*) and dihydropteroate synthase (*Pf dhps*), respectively, has increased steadily over the past 10 years.⁶ Parasites with “quintuple” mutations (*Pf dhfr* mutations in codons 108, 51, and 59 and *Pf dhps* mutations in codons 437 and 540) now predominate. Studies from areas of higher transmission (where maternal immunity is correspondingly greater) suggest that the efficacy of intermittent preventive treatment with sulfadoxine–pyrimethamine during pregnancy starts to decline with *Pf dhps* 437G (i.e., quintuple mutations), is further reduced with *Pf dhps* 581G (sextuple mutations), and is presumed to be lost completely with *Pf dhfr* 164L (mutations that are prevalent in parts of East and Central Africa, South and East Asia, and South America).⁷ The recent recommendation to increase the number of preventive doses of sulfadoxine–pyrimethamine to three or more in later pregnancy⁸ will provide only temporary respite if resistance increases further. The clinical implication of the study by Mayor et al. and other studies is that although reducing the transmission of malaria is clearly good, the concomitant reduction in immunity to malaria increases the risk of adverse consequences for women who become infected during pregnancy. From a public health perspective, there can be no letup in malaria-control

activities; otherwise, malaria will return with a vengeance. This is what happened from the 1970s to the 1990s, when malaria-control activities declined in the aftermath of the failed global eradication effort and resistance spread to antimalarial agents (chloroquine) and insecticides (dichlorodiphenyltrichloroethane [DDT]). An increase in resistance to pyrethroid insecticides in Africa and uncontained artemisinin resistance in Asia do not bode well for the future. Preventing malaria during pregnancy in areas where drug resistance is increasing and where transmission rates are low and unstable remains a serious challenge.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMe1511278

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