

# Community-Based Intermittent Preventive Treatment Efficacy in Pregnant Women Across Sub-Saharan African Settings

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## ABSTRACT

Malaria during pregnancy posed substantial risks to maternal and fetal health in sub-Saharan Africa, contributing to maternal anemia, placental parasitemia, low birth weight, and neonatal mortality. Intermittent preventive treatment in pregnancy with sulfadoxine-pyrimethamine represented a cornerstone intervention recommended by the World Health Organization for malaria-endemic regions. Community-based delivery of this intervention extended coverage beyond facility-based antenatal care, potentially reaching underserved populations with limited healthcare access. This review evaluated the efficacy of community-based intermittent preventive treatment compared to facility-based delivery and examined factors influencing effectiveness across diverse sub-Saharan African settings. A comprehensive synthesis of randomized controlled trials, cohort studies, and implementation research conducted across sub-Saharan Africa over the past fifteen years was performed. Community-based delivery substantially increased coverage of intermittent preventive treatment, particularly among rural and marginalized women, resulting in improved maternal hemoglobin concentrations, reduced placental malaria, and higher mean birth weights. Effectiveness varied by transmission intensity, sulfadoxine-pyrimethamine resistance patterns, HIV prevalence, and quality of community health worker training. Operational challenges included drug supply chain reliability, adherence monitoring, and integration with existing antenatal care systems. Community-based intermittent preventive treatment demonstrated significant efficacy for improving pregnancy outcomes in sub-Saharan Africa, but programmatic success required context-specific adaptation, robust pharmaceutical supply systems, and sustained investment in community health infrastructure.

**Keywords:** Intermittent preventive treatment, Pregnancy malaria, Community health workers, Sulfadoxine-pyrimethamine, Sub-Saharan Africa.

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## INTRODUCTION

Malaria infection during pregnancy represents a major public health challenge across sub-Saharan Africa, where an estimated 33 million pregnancies occur annually in malaria-endemic areas [1]. Pregnant women exhibit increased susceptibility to *Plasmodium falciparum* infection due to pregnancy-associated immunological changes and the selective sequestration of infected erythrocytes in the placental intervillous space through binding to chondroitin sulfate A expressed on syncytiotrophoblasts [2, 3]. This placental accumulation triggers local inflammatory responses, impairs maternal-fetal nutrient exchange, and directly damages placental architecture. The clinical consequences are profound, with maternal malaria contributing to an estimated 10,000 maternal deaths and 200,000 neonatal deaths annually across the African continent [4]. Additional morbidities include severe maternal anemia, which compounds existing nutritional deficiencies and increases risk for postpartum hemorrhage, as well as intrauterine growth restriction resulting in low-birth-weight infants with elevated mortality risk and long term

developmental impairments. Primigravidae and secundigravidae demonstrate particular vulnerability due to a lack of acquired immunity to pregnancy-specific parasite variants.

Intermittent preventive treatment in pregnancy with sulfadoxine-pyrimethamine has emerged as the principal chemoprophylactic strategy for malaria control in pregnant women across endemic Africa [5]. This approach involves administration of curative doses of sulfadoxine-pyrimethamine at scheduled intervals during antenatal care visits, regardless of parasitemia status, to clear existing infections and provide post-treatment prophylaxis spanning several weeks. The World Health Organization recommends at least three doses administered from the second trimester onward, with the first dose given as early as possible after quickening and subsequent doses spaced at least one month apart. Despite demonstrated efficacy when delivered through facility-based antenatal care, coverage remains suboptimal across much of sub-Saharan Africa due to limited healthcare infrastructure, geographic barriers, cultural factors, and inadequate antenatal care attendance. Community-based delivery models that utilize trained community health workers to administer intermittent preventive treatment during household visits or community gatherings represent a promising strategy for extending coverage to underserved populations, particularly in rural areas where formal health facilities are geographically distant or operationally constrained [6]. The objective of this review is to critically assess the efficacy of community-based intermittent preventive treatment delivery compared to standard facility-based approaches across diverse sub-Saharan African settings, examining maternal and neonatal outcomes, coverage indicators, implementation challenges, and contextual factors that modify effectiveness.

### **Biochemical Rationale and Pharmacological Mechanisms**

Sulfadoxine-pyrimethamine combines two synergistic antifolate compounds that sequentially inhibit the folate synthesis pathway essential for *Plasmodium falciparum* nucleotide biosynthesis and replication [7, 8]. Sulfadoxine competitively inhibits dihydropteroate synthase, blocking the incorporation of para-aminobenzoic acid into dihydropteroic acid, while pyrimethamine inhibits dihydrofolate reductase, preventing the reduction of dihydrofolate to tetrahydrofolate. This dual blockade produces synergistic antiparasitic effects, with combination therapy overcoming resistance mechanisms that might compromise either agent alone. The long elimination half-lives of sulfadoxine (approximately 7 to 9 days) and pyrimethamine (approximately 4 to 6 days) provide extended post-treatment prophylaxis, suppressing new infections for several weeks following a single dose. This pharmacokinetic property makes sulfadoxine-pyrimethamine particularly suitable for intermittent preventive treatment, as infrequent dosing can maintain protective drug concentrations throughout intervals between administrations.

During pregnancy, sulfadoxine-pyrimethamine readily crosses the placental barrier, achieving fetal drug concentrations approximating maternal levels and providing direct antimalarial protection to the fetus [9]. The drug combination exerts its primary therapeutic benefit by clearing maternal peripheral and placental parasitemia, thereby interrupting the pathological inflammatory cascade triggered by infected erythrocyte accumulation in the intervillous space. Elimination of infected erythrocytes reduces local production of inflammatory mediators, including tumor necrosis factor alpha, interferon gamma, and various chemokines that disrupt trophoblast function and impair placental angiogenesis. Additionally, by preventing new infections during the prophylactic period, sulfadoxine-pyrimethamine allows restoration of maternal hemoglobin concentrations through enhanced erythropoiesis and reduced hemolysis. Improved maternal oxygenation and nutrient delivery to the placenta translate directly into enhanced fetal growth velocity and increased birth weight [10]. However, the efficacy of sulfadoxine-pyrimethamine is increasingly compromised by parasite resistance mediated through point mutations in the dhps and dhfr genes encoding the target enzymes. High-level resistance, particularly the combination of dhfr triple mutations with dhps mutations, substantially reduces treatment efficacy and prophylactic duration, necessitating consideration of alternative regimens in areas where resistance prevalence exceeds critical thresholds.

### **Coverage, Acceptability, and Implementation Across Diverse Settings**

Community-based delivery of intermittent preventive treatment fundamentally restructures the healthcare encounter by transferring service provision from facility-based midwives and nurses to trained community health workers who operate within the communities they serve [11, 12]. This decentralization strategy has demonstrated substantial improvements in intervention coverage across diverse sub-Saharan African settings. Studies from rural districts in Tanzania, Uganda, and Burkina Faso report coverage increases of 30 to 50 percentage points when community-based delivery supplements or replaces facility-based approaches, with the greatest gains observed among women residing more than 5 kilometers from health facilities and those in the lowest wealth quintiles [13, 14]. The convenience of receiving treatment during home visits or at nearby community gathering points eliminates transportation costs and time burdens associated with facility attendance, while culturally concordant community health workers can address local beliefs and misconceptions that might otherwise deter women from seeking biomedical interventions.

Acceptability studies employing qualitative methods reveal that pregnant women value the personalized attention and culturally sensitive counseling provided by community health workers, who often share language, ethnicity, and social networks with beneficiaries [15]. However, implementation quality varies substantially based on community health worker training adequacy, supervision intensity, and integration with existing health systems. Programs that

provide comprehensive initial training covering malaria pathophysiology, drug administration protocols, identification of contraindications, and recognition of adverse effects, coupled with regular refresher sessions and supportive supervision, achieve superior adherence to treatment guidelines and better safety outcomes. Conversely, programs characterized by brief training, infrequent supervision, and inadequate logistical support report higher rates of protocol deviations, including administration to women in the first trimester (when sulfadoxine-pyrimethamine is contraindicated) and failure to screen for sulfa drug allergies.

The geographic and epidemiological context significantly influences implementation effectiveness. In areas of high stable transmission where year-round malaria risk persists, community-based delivery achieves consistent coverage throughout the antenatal period, translating into measurable reductions in placental malaria and low birth weight [16]. In regions with seasonal transmission patterns, timing intermittent preventive treatment delivery to coincide with periods of peak transmission intensity optimizes resource utilization and maximizes impact. Urban and peri-urban settings present distinct challenges, as higher population density, greater mobility, and more developed health infrastructure reduce the comparative advantage of community-based approaches, with some studies reporting no coverage benefit over facility-based care in these contexts. The heterogeneity of implementation outcomes underscores the importance of tailoring delivery models to local epidemiological, geographic, and health system contexts rather than applying uniform programmatic approaches across diverse settings.

### **Maternal and Neonatal Health Outcomes**

Randomized controlled trials and large cohort studies from sub-Saharan Africa have consistently demonstrated that community-based intermittent preventive treatment delivery improves key maternal health indicators compared to standard care or facility-based delivery alone [17, 18]. Meta-analyses incorporating data from multiple countries reveal that women receiving community-based intermittent preventive treatment exhibit mean hemoglobin concentrations approximately 0.4 to 0.7 grams per deciliter higher at delivery compared to controls, with corresponding reductions in the prevalence of moderate to severe anemia (hemoglobin below 7 grams per deciliter) of 30 to 50 percent. These hematological improvements reflect both clearance of existing infections and prevention of new infections during the extended prophylactic period following each sulfadoxine-pyrimethamine dose. Enhanced maternal hemoglobin status confers multiple clinical benefits, including improved exercise tolerance, reduced fatigue, and decreased risk of adverse outcomes during delivery and the postpartum period.

Placental malaria, defined by the presence of parasites, pigment, or both in placental tissue upon histological examination, represents a sensitive marker of infection impact and a strong predictor of adverse birth outcomes [19, 20]. Community-based intermittent preventive treatment reduces placental malaria prevalence by approximately 40 to 60 percent compared to no intervention, with effect sizes varying based on baseline transmission intensity and achieved intervention coverage. Studies employing standardized histopathological assessment demonstrate reductions in both acute placental infection (characterized by parasitized erythrocytes and minimal pigment deposition) and chronic infection (characterized by substantial pigment accumulation and inflammatory cell infiltration). The reduction in placental pathology directly translates into improved fetal growth, with community-based programs reporting mean birth weight increases of 50 to 100 grams and reductions in low-birth-weight prevalence (below 2500 grams) of 20 to 35 percent. These seemingly modest increases in mean birth weight correspond to substantial reductions in neonatal mortality risk, as the relationship between birth weight and mortality is nonlinear, with steepest gradients occurring in the low-birth-weight range.

Neonatal and infant outcomes extend beyond birth weight to encompass mortality, morbidity, and developmental trajectories [21]. Several large prospective cohorts have documented reductions in neonatal mortality of 15 to 25 percent associated with maternal receipt of community-based intermittent preventive treatment, with benefits most pronounced among infants born to primigravidae and in high transmission settings. Infant anemia prevalence at 6 months of age is similarly reduced, reflecting both improved iron endowment at birth due to higher birth weight and reduced in utero malaria exposure. However, the magnitude and consistency of benefits vary substantially across studies, with effectiveness strongly modified by drug resistance patterns, HIV coinfection status, insecticide-treated net usage, and nutritional supplementation practices, highlighting the complex interplay between intermittent preventive treatment and other determinants of pregnancy outcomes.

### **Drug Resistance, HIV Coinfection, and Evolving Treatment Paradigms**

The emergence and spread of *Plasmodium falciparum* resistance to sulfadoxine-pyrimethamine represents a critical threat to intermittent preventive treatment effectiveness across sub-Saharan Africa [22, 23]. Molecular surveillance studies tracking the prevalence of resistance-associated mutations in *dhfr* and *dhps* genes reveal heterogeneous geographic patterns, with East Africa exhibiting substantially higher resistance frequencies compared to West Africa [24–26]. In regions where quintuple mutant parasites (harboring *dhfr* N51I, C59R, S108N mutations plus *dhps* A437G and K540E mutations) exceed 50 percent prevalence, intermittent preventive treatment efficacy for preventing placental malaria declines by approximately 50 percent compared to areas with predominantly wild-type parasites. The emergence of sextuple mutants carrying additional *dhps* A581G or A613S mutations, particularly

prevalent in parts of Tanzania and Mozambique, further compromises treatment effectiveness, prompting urgent evaluation of alternative drug regimens.

Several candidate replacement regimens have undergone clinical evaluation, including dihydroartemisinin-piperazine, mefloquine, and azithromycin-based combinations. Dihydroartemisinin-piperazine demonstrates superior efficacy compared to sulfadoxine-pyrimethamine in areas of high drug resistance, with pooled analyses showing greater reductions in placental malaria and improved birth weight outcomes [27]. However, the requirement for three-day dosing regimens complicates community-based delivery, as ensuring adherence to multi-day treatment courses presents substantially greater operational challenges than single-dose sulfadoxine-pyrimethamine administration. Programmatic experience with community health worker-supervised multi-day regimens remains limited, and concerns regarding incomplete treatment courses and potential for resistance development to artemisinin-based combinations have tempered enthusiasm for widespread replacement of sulfadoxine-pyrimethamine in community-based programs. The optimal transition strategy likely involves geographically targeted approaches, maintaining sulfadoxine-pyrimethamine in areas where efficacy remains acceptable while transitioning to alternative regimens in high-resistance settings, coupled with continued molecular surveillance to guide policy updates.

HIV coinfection substantially modifies malaria susceptibility during pregnancy and complicates intermittent preventive treatment delivery [28, 29]. HIV-infected pregnant women experience higher malaria infection rates, increased parasite densities, and a greater risk of clinical malaria compared to HIV-uninfected women. Furthermore, potential drug interactions between sulfadoxine-pyrimethamine and antiretroviral medications, particularly those metabolized through folate pathways, raise safety concerns. World Health Organization guidelines recommend that HIV-infected pregnant women receiving daily cotrimoxazole prophylaxis for opportunistic infection prevention should not receive sulfadoxine-pyrimethamine due to overlapping mechanisms of action and increased risk of severe cutaneous reactions. This exclusion necessitates screening for HIV status before intermittent preventive treatment administration, adding programmatic complexity to community-based delivery. Alternative preventive strategies for HIV-infected pregnant women, including daily cotrimoxazole alone or mefloquine-based intermittent preventive treatment, have shown variable effectiveness, and optimal approaches for this vulnerable population remain incompletely defined. The high HIV prevalence in many malaria-endemic regions of southern and eastern Africa, where up to 30 percent of pregnant women may be HIV infected, substantially reduces the population-level impact of sulfadoxine-pyrimethamine-based intermittent preventive treatment programs and underscores the need for integrated service delivery models addressing both infections.

#### **Operational Challenges, Health System Integration, and Sustainability**

Successful scaling of community-based intermittent preventive treatment across sub-Saharan Africa confronts multiple operational challenges that extend beyond clinical efficacy to encompass health system capacity, supply chain reliability, and financial sustainability. Ensuring the uninterrupted availability of sulfadoxine-pyrimethamine at the community level requires robust pharmaceutical supply chains capable of forecasting demand, procuring quality-assured commodities, and distributing them through complex networks to remote and resource-limited settings [30]. Stock-outs represent a persistent challenge, with surveys from multiple countries documenting intermittent preventive treatment drug unavailability at 20 to 40 percent of community distribution points at any given time. These supply disruptions interrupt service continuity, erode community trust, and necessitate referral to distant health facilities, thereby negating the primary advantage of community-based delivery. Strengthening pharmaceutical supply systems through improved quantification methods, decentralized warehousing, and community health worker inventory management training represents an essential prerequisite for program sustainability.

Integration with existing antenatal care systems and broader maternal child health platforms offers opportunities to enhance efficiency and reduce duplication, while introducing coordination challenges [31]. Optimal models balance community-based intermittent preventive treatment delivery with facility-based antenatal care, leveraging the strengths of each platform. Community health workers provide convenient access to intermittent preventive treatment and basic antenatal counseling while facilitating referrals for complications and ensuring linkage to facility-based services, including HIV testing, syphilis screening, tetanus vaccination, and skilled delivery. However, poorly coordinated parallel systems risk fragmentation, with women receiving redundant services or falling through gaps between platforms. Electronic health information systems that track individual women across community and facility encounters can improve continuity but require substantial investment in digital infrastructure and training. The lack of such systems in most rural African settings necessitates paper-based tracking mechanisms that are labor-intensive and prone to incompleteness.

Financial sustainability remains a critical concern, as most community-based intermittent preventive treatment programs depend on external donor funding, primarily from the Global Fund and the President's Malaria Initiative [32, 33]. Transition to domestic financing has proven challenging in low-income countries where competing health priorities strain limited government budgets. Cost-effectiveness analyses consistently demonstrate favorable

economic profiles for community-based intermittent preventive treatment, with incremental cost-effectiveness ratios well below commonly cited willingness-to-pay thresholds. However, these analyses typically exclude health system strengthening costs, including community health worker training, supervision, and supply chain infrastructure, which constitute substantial initial investments. Programmatic experience suggests that integration with existing community health platforms addressing multiple health needs (vaccination, nutrition, family planning) rather than vertical malaria-specific programs offers greater financial efficiency and sustainability. Moving forward, demonstrating value for money and building domestic political commitment will be essential for transitioning successful pilot programs to a national scale and ensuring long term program viability.

### CONCLUSION

Community-based intermittent preventive treatment in pregnancy represents a highly effective intervention for improving maternal and neonatal health outcomes across malaria-endemic regions of sub-Saharan Africa. By extending service coverage beyond facility-based antenatal care to reach geographically isolated and socioeconomically marginalized populations, community health worker delivery substantially increases the proportion of pregnant women receiving recommended intermittent preventive treatment doses. This expanded coverage translates into measurable improvements in maternal hemoglobin concentrations, reductions in placental malaria prevalence, and increased mean birth weights with corresponding decreases in neonatal mortality. The magnitude of benefit varies substantially across settings, influenced by baseline malaria transmission intensity, sulfadoxine-pyrimethamine resistance patterns, HIV coinfection prevalence, quality of program implementation, and contextual factors including insecticide-treated net coverage and nutritional status. Emerging parasite resistance to sulfadoxine-pyrimethamine threatens long term effectiveness in parts of East and southern Africa, necessitating ongoing molecular surveillance and potential transition to alternative drug regimens in high-resistance settings. Operational challenges, including pharmaceutical supply chain reliability, health system integration, community health worker training and supervision quality, and financial sustainability, require sustained attention and investment. Despite these challenges, the substantial body of evidence from diverse African settings demonstrates that well-implemented community-based intermittent preventive treatment programs achieve meaningful reductions in the devastating burden of pregnancy-associated malaria. Continued programmatic innovation, particularly regarding drug resistance monitoring, service integration, and sustainable financing models, will be essential for maintaining and expanding impact as epidemiological and health system contexts evolve. National malaria control programs should prioritize investment in community health worker training, supervision systems, and pharmaceutical supply chain strengthening to ensure sustainable, high-quality community-based intermittent preventive treatment delivery, while implementing molecular surveillance to guide timely transitions to alternative antimalarial regimens in areas where sulfadoxine-pyrimethamine resistance compromises efficacy.

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