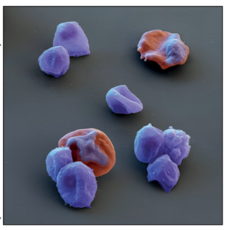
The unanticipated benefits of protecting young children from malaria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Young children in sub-Saharan Africa account for the majority of malaria-associated deaths worldwide. Every time a new intervention is proposed to protect this population, the research and policy communities voice the concern that the burden of severe disease will shift to older children who are no longer protected by the intervention. This situation is referred to as rebound and is not merely a theoretical concern. In the context of scaling up malaria control interventions, over the past two decades large retrospective studies in Kenya and The Gambia showed an epidemiological shift in the distribution of disease—ie, the mean age of clinical malaria increased as transmission declined.[1,2] However, as Mary Muhindo and colleagues highlight in their trial[3] in *The Lancet Infectious Diseases*, results of studies evaluating rebound malaria after targeted interventions in young children have been inconsistent and rebound malaria remains poorly characterised.

The impact of preventing malaria during the first 2 years of life on subsequent malaria infection and disease is a key finding addressed by Muhindo and colleagues. The authors report the results of a double-blind, randomised, controlled phase 2 trial in which they provided intermittent preventive treatment (IPT) with dihydroartemisinin–piperaquine to Ugandan children from age 8 weeks to 24 months either every 4 or 12 weeks. They assessed the incidence of symptomatic malaria during the intervention and up to 1 year after cessation of the intervention to detect rebound. As expected in this high transmission setting, the investigators showed that during the intervention, treatment every 4 weeks reduced the incidence of symptomatic malaria by 96% compared with treatment every 12 weeks (adjusted incidence rate ratio [aIRR] 0·041, 95% CI 0·012–0·150, p<0·0001). Importantly, this protection seemed to continue in the year following treatment: children who had previously received IPT with dihydroartemisinin–piperaquine every 4 weeks had a 38% lower incidence of symptomatic disease than children who had received dihydroartemisinin–piperaquine every 12 weeks (aIRR 0·62, 0·40–0·95, p=0·028). Although the finding of sustained protection is promising, the study has an important limitation with regard to the assessment of rebound. No control group was included in the trial, because of the previously demonstrated benefit of IPT in this age group at this site. Thus, although unlikely, the possibility that the incidence of disease in both treatment groups was higher than in children who had not received the intervention cannot be excluded.

The proposed mechanism of continued protection following more frequent treatment is that dihydro-artemisinin–piperaquine protects children from blood-stage malaria infection, but does not prevent exposure to pre-erythrocytic stage parasites that are important for the development of immunity; children who received IPT with dihydroartemisinin–piperaquine every 4 weeks continued to be bitten by infected mosquitos and develop infections within the liver but were protected from disease-causing blood-stage parasites by continuous chemoprophylaxis with dihydroartemisinin–piperaquine. Active blood-stage infection might also interfere with the acquisition of an effective immune response.[4] An additional benefit of this strategy, not discussed by Muhindo and colleagues, is that these children are also unlikely to have infections that include the gametocyte stage, which is the parasitic stage required for human-to-mosquito parasite transmission and perpetuation of the cycle of infection. Previous studies[5] of monthly dihydroartemisinin–piperaquine treatment in this setting showed marked reductions in gametocyte carriage. Thus, children receiving dihydroartemisinin–piperaquine every 4 weeks are also unlikely to infect mosquitos, which might have further indirect benefit by conferring some protection to others in the surrounding community. Targeted treatment of older children, who are thought to be important asymptomatic reservoirs of infection, can decrease transmission in the surrounding community.[6,7]

The results reported by Muhindo and colleagues illustrate that the complex biology and pathophysiology of malaria continues to challenge efforts to determine whether temporary interventions result in rebound malaria. Although studies should continue to evaluate the potential for rebound, or even protection, following interventions, they should also evaluate the potential community-level benefits of decreased transmission. A complete evaluation of the impact of a targeted prevention effort must compare the risk of rebound with the potential for decreased transmission and the individual-level benefits of malaria prevention.

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Devising a strategy for prevention of malaria in pregnant women in the Asia Pacific

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Malaria in pregnancy is a leading cause of adverse pregnancy outcomes in low-income and middle-income countries.[1] WHO recommends intermittent preventive treatment (IPT) with sulphadoxine–pyrimethamine in areas of Africa where there is moderate to high transmission of *Plasmodium falciparum*, the most prevalent malaria species in the region. However, parasite sensitivity to sulphadoxine–pyrimethamine is compromised, particularly in parts of east Africa, prompting trials of IPT with dihydroartemisinin–piperaquine.[2–4]

WHO does not have an equivalent prevention strategy for the Asia-Pacific region where we estimate (unpublished) that more than 90 million pregnant women are at risk of malaria. The epidemiological context of the region poses unique challenges. *Plasmodium vivax* infection is characterised by unpredictable relapses when hypnozoites emerge from dormancy in the liver, and primaquine—the only effective treatment against liver-stage infection—is contraindicated in pregnancy. *P falciparum* resistance to sulphadoxine–pyrimethamine emerged 40 years ago along the Thai–Cambodia border and quickly saturated the region,[5] two decades before WHO recommended its use for IPT in Africa. Malaria transmission intensity is diverse, and most mosquito vectors in the Asia-Pacific region are exophagic, exophilic, and active in early evening, all behaviours that undermine the effectiveness of insecticide-treated bednets and indoor residual spraying.[6] In 2012, Indonesia was the first country in the region to implement a strategy of screening and treating malaria at the first antenatal visit, with passive case management provided thereafter.[7]

In *The Lancet Infectious Diseases*, Rukhsana Ahmed and colleagues[8] report the results of the first IPT study in the WHO South-East Asia region, a three-arm, open-label, cluster-randomised controlled trial in HIV-negative women from Sumba island (site of low malaria transmission) and southern Papua (site of moderate, year-round, malaria transmission), eastern Indonesia. Participants (of any gravidae between 16 and 30 weeks' gestation) received either single screening with a rapid diagnostic test and treatment with dihydroartemisinin–piperaquine if parasitaemic or passive case detection to delivery, intermittent screening with a rapid diagnostic test at each antenatal visit and treatment with dihydroartemisinin–piperaquine if parasitaemic, or IPT with dihydroartemisinin–piperaquine at monthly visits without screening. The primary endpoint was malaria infection in the mother at delivery.

Malaria prevalence was much lower than expected in Sumba, where only one woman of the first 696 tested