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**Title:** Prevention of malaria in pregnancy: a fork in the road?

**Authors: \***R. Matthew Chico1 and William J. Moss2

\*Corresponding author

1London School of Hygiene & Tropical Medicine, London, UK, matthew.chico@lshtm.ac.uk

2Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

In efforts to improve protection against the adverse consequences of malaria in pregnancy, several trials1-3 have investigated alternative drug regimens and strategies to replace sulfadoxine–pyrimethamine for intermittent preventive treatment of malaria in pregnancy. Even before WHO first recommended inclusion of intermittent preventive treatment with sulfadoxine–pyrimethamine in the focused antenatal care package in 2004,4 malaria parasites expressed mutations in the dihydrofolate reductase (*Pfdhfr*) and dihydropteroate synthetase (*Pfdhps*) genes, compromising the protective effect of the intervention.5 The protection conferred by intermittent preventive treatment with sulfadoxine–pyrimethamine against low birthweight has since been shown to decrease as the population prevalence of the *Pfdhps* K540E mutation increases—a proxy for the resistant quintuple *Pfdhfr* and *Pfdhps* mutants.6 In regions where the *Pfdhps* A581G mutation has emerged alongside the *Pfdhfr* and *Pfdhps* quintuple mutant, producing sextuple mutant parasites, the intervention fails to inhibit the growth of parasites.7 Consequently, alternative drug regimens or strategies that are safe, well-tolerated, and efficacious are needed in areas where parasites express this mutation.

In *The Lancet*, Meghna Desai and colleagues8 report the outcomes of the first investigation into use of an artemisinin combination treatment, dihydroartemisinin–piperaquine, for intermittent preventive treatment. The three-group, open-label, randomised controlled trial was done in a region of western Kenya where 96% of parasites had the quintuple mutation and 5.8% carried the A581G mutation. HIV-negative pregnant women were allocated to receive intermittent preventive treatment with either sulfadoxine–pyrimethamine (n=515) or dihydroartemisinin–piperaquine (n=516), or underwent intermittent screening and treatment with dihydroartemisinin–piperaquine if rapid diagnostic tests showed the presence of peripheral parasitaemia (n=515). The primary outcome was malaria infection at delivery, defined as a composite of peripheral or placental parasitaemia that was detected by placental histology, microscopy, or rapid diagnostic test.

In Desai and colleagues’ study,8 prevalence of malaria infection at delivery was lower in the intermittent preventive treatment with dihydroartemisinin–piperaquine group than in the sulfadoxine–pyrimethamine group (15 [3%] of 457 women vs 47 [10%] of 459 women; relative risk 0.32, 95% CI 0.18–0.56), but not in the intermittent screening and treatment group (57 [13%] of 452 women vs 47 [10%] of 459 women; 1.23, 0.86–1.77). Compared with sulfadoxine–pyrimethamine, intermittent preventive treatment using dihydroartemisinin–piperaquine reduced the incidence of clinical malaria during pregnancy by 84% (37.9 vs 6.1 episodes) and the risk of maternal anaemia by 22% at delivery (crude prevalence ratio 0.78, 95% CI 0.64–0.96). Secondary analysis showed that women given intermittent screening and treatment had the highest prevalence of peripheral or placental malaria at delivery (199 [44%] of 452 women vs 140 [31%] of 457 women in the intermittent preventive treatment with dihydroartemisinin–piperaquine group and 166 [36%] of 459 women in the sulfadoxine–pyrimethamine group). This finding suggests that the intermittent screening and treatment strategy is not suitable for settings with intense transmission. Intermittent preventive treatment with dihydroartemisinin–piperaquine decreased the incidence of stillbirths by three-quarters compared with sulfadoxine–pyrimethamine (four [1%] of 452 births vs 16 [4%] of 453 births), and the number of perinatal deaths by 70% (eight vs 27).

The tolerability of intermittent preventive treatment with dihydroartemisinin–piperaquine was good, compliance was greater than 95%, and serious adverse events were least frequent among women in that group. However, the strategy was not superior to sulfadoxine–pyrimethamine for reducing the incidence of low birthweight, small-for-gestational age, or preterm birth. Although the study8 was not powered to detect differences in these three secondary endpoints, birthweight for gestational age was highest in the intermittent preventive treatment with sulfadoxine–pyrimethamine group as calculated by Z scores. How might this finding be explained? Sulfadoxine could provide additional protection against infections other than malaria, resulting in a protective effect against low birthweight that is more apparent in areas where parasite sensitivity to sulfadoxine–pyrimethamine has been lost. Sulfadoxine–pyrimethamine can be used as an efficacious chemoprophylactic drug against *Pneumocystis carinii* pneumonia and *Toxoplasma gondii* infection.9 Moreover, sulfadoxine is related to sulfamethoxazole, the partner compound used with trimethoprim to form cotrimoxazole, a treatment often provided to cure urinary tract infections and to prevent Pneumocystis jiroveci in HIV-infected patients.10 Sulfonamides have also been used to treat *Gardnerella vaginalis*,11 a bacterium found in women with bacterial vaginosis that can double the odds of having a low birthweight baby compared with pregnant women without bacterial vaginosis.12 A meta-analysis of intermittent preventive treatment with sulfadoxine–pyrimethamine showed that the intervention continues to protect against low birthweight until very low levels of malaria transmission,13 which might be attributable to an effect of sulfadoxine–pyrimethamine on infections other than malaria.

So, are we at a fork in the road for prevention of malaria in pregnancy? Possibly. However, before changing direction, several questions need to be answered in clinical trials that compare intermittent preventive treatment with dihydroartemisinin–piperaquine versus sulfadoxine–pyrimethamine that have sufficient power to detect differences in adverse birth outcomes, including the incidence of low birthweight, preterm birth, and small-for-gestational-age newborns. Robust microbiological investigations should be included so that policy makers have a better understanding of the effect of maternal infections other than malaria on adverse birth outcomes and the potential effect of different antimicrobial regimens. There is a clear rationale for assessment of the protective effect of intermittent preventive treatment with dihydroartemisinin–piperaquine plus a broad-spectrum antibiotic to mitigate the dual burden of maternal malaria and bacterial infections. The acceptability of such regimens by health-care providers and pregnant women will require investigation. Additionally, the cardiac safety of dihydroartemisinin–piperaquine use in pregnant women, with and without asymptomatic infection, needs to be confirmed. HIV-infected pregnant women are in particular need of attention; intermittent preventive treatment with sulfadoxine–pyrimethamine is withheld because HIV-infected patients are routinely given co-trimoxazole to prevent opportunistic infections, and simultaneous dosing with sulfadoxine–pyrimethamine could expose these patients to toxic concentrations of the sulfa component. This contraindication would not apply to intermittent preventive treatment with dihydroartemisinin–piperaquine. Nevertheless, drug interaction studies between dihydroartemisinin–piperaquine and antiretroviral regimens are needed, and should be extended to broad-spectrum antibiotics that can be combined with dihydroartemisinin–piperaquine.

Desai and colleagues’ findings8 provide strong evidence of the efficacy of intermittent preventive treatment with dihydroartemisinin–piperaquine in a setting with high sulfadoxine–pyrimethamine resistance, including the A581G mutation, and lay a foundation to translate research into policy for the prevention of malaria in pregnancy. The road ahead is clear.

**References**

1. Clerk CA, Bruce J, Affipunguh PK, et al. A randomized, controlled trial of intermittent preventive treatment with sulfadoxine-pyrimethamine, amodiaquine, or the combination in pregnant women in Ghana. *J Infect Dis* 2008; **198**(8): 1202-11.

2. Tagbor H, Bruce J, Agbo M, Greenwood B, Chandramohan D. Intermittent Screening and Treatment versus Intermittent Preventive Treatment of Malaria in Pregnancy: A Randomised Controlled Non-Inferiority Trial. *PLoS ONE* 2010; **5**(12): e14425.

3. Gonzalez R, Mombo-Ngoma G, Ouedraogo S, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-negative women: a multicentre randomized controlled trial. *PLoS Med* 2014; **11**(9): e1001733.

4. World Health Organization. A Strategic Framework for Malaria Prevention and Control During Pregnancy in the Africa Region: World Health Organization Regional Office for Africa; 2004.

5. Roper C, Pearce R, Bredenkamp B, et al. Antifolate antimalarial resistance in southeast Africa: a population-based analysis. *Lancet* 2003; **361**(9364): 1174-81.

6. Kayentao K, Garner P, van Eijk AM, et al. Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. *JAMA* 2013; **309**(6): 594-604.

7. Gutman J, Kalilani L, Taylor S, et al. The A581G Mutation in the Gene Encoding Plasmodium falciparum Dihydropteroate Synthetase Reduces the Effectiveness of Sulfadoxine-Pyrimethamine Preventive Therapy in Malawian Pregnant Women. *J Infect Dis* 2015.

8. Desai M, Gutman J, L’lanziva A, et al. Intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin–piperaquine versus intermittent preventive treatment with sulphadoxine–pyrimethamine for the control of malaria during pregnancy in western Kenya: an open-label, three-group, randomised controlled superiority trial. *The Lancet* 2015; (published online 29 Sept 2015): <http://dx.doi.org/10.1016/S0140-6736(15)00310-4>.

9. Schurmann D, Bergmann F, Albrecht H, et al. Effectiveness of twice-weekly pyrimethamine-sulfadoxine as primary prophylaxis of Pneumocystis carinii pneumonia and toxoplasmic encephalitis in patients with advanced HIV infection. *Eur J Clin Microbiol Infect Dis* 2002; **21**(5): 353-61.

10. World Health Organization. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults. Recommendations for a public health approach. Geneva, Switzerland: World Health Organization, 2006.

11. Bhattacharyya MN, Jones BM. Haemophilus vaginalis infection. Diagnosis and treatment. *J Reprod Med* 1980; **24**(2): 71-5.

12. Chico RM, Hack BB, Newport MJ, Ngulube E, Chandramohan D. On the pathway to better birth outcomes? A systematic review of azithromycin and curable sexually transmitted infections. *Expert Rev Anti Infect Ther* 2013; **11**(12): 1303-32.

13. Chico RM, Cano J, Ariti C, et al. Influence of Malaria Transmission Intensity and the 581G Mutation on the Efficacy of Intermittent Preventive Treatment in Pregnancy: Systematic Review and Meta-analysis. *Trop Med Int Health* 2015; (10.1111/tmi.12595).