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.

*Lauren M Cohee, Miriam K Laufer
Center for Vaccine Development and Global Health, School of Medicine, University of Maryland, Baltimore, MD 21201, USA
lcohee@som.umaryland.edu

We declare no competing interests.

1 O'Meara WP, Bejon P, Mwangi TW, et al. Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. *Lancet* 2008; **372:** 1555–62.
2 Ceesay SJ, Casals-Pascual C, Erskine J, et al. Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis. *Lancet* 2008; **372:** 1545–54.
3 Muhindo MK, Jagannathan P, Kakuru A, et al. Intermittent preventive treatment with dihydroartemisinin–piperaquine and risk of malaria following cessation in young Ugandan children: a double-blind, randomised, controlled trial. *Lancet Infect Dis* 2019; published online July 12. http://dx.doi.org/10.1016/S1473-3099(19)30299-3.
4 Jagannathan P, Bowen K, Nankya F, et al. Effective antimalarial chemoprevention in childhood enhances the quality of CD4+ T cells and limits their production of immunoregulatory interleukin 10. *J Infect Dis* 2016; **214:** 329–38.
5 Bigira V, Kapisi J, Clark TD, et al. Protective efficacy and safety of three antimalarial regimens for the prevention of malaria in young Ugandan children: a randomized controlled trial. *PLoS Med* 2014; **11:** e1001689.
6 Cissé B, Ba EH, Sokhna C, et al. Effectiveness of seasonal malaria chemoprevention in children under ten years of age in Senegal: a stepped-wedge cluster-randomised trial. *PLoS Med* 2016; **13:** e1002175.
7 Staedke SG, Maiteki-Sebuguzi C, Rehman AM, et al. Assessment of community-level effects of intermittent preventive treatment for malaria in schoolchildren in Jinja, Uganda (START-IPT trial): a cluster-randomised trial. *Lancet Glob Health* 2018; **6:** e668–79.

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

Published Online July 25, 2019 http://dx.doi.org/10.1016/S1473-3099(19)30390-1

See Articles page 973

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

positive by rapid diagnostic test at enrolment in the single screening and treatment (SST) and intermittent screening and treatment (IST) groups. On the basis of these data, the ethics committee in Indonesia suspended recruitment in Sumba but allowed researchers to re-calculate the sample size for Papua to ensure enough statistical power. Overall, the intention-to-treat analysis showed that malaria prevalence in mothers at delivery was 20·2% (128 of 633) in the SST clusters versus 11·8% (84 of 713) in the IST clusters (relative risk 0·56, 0·40–0·77; p=0·0005) and 11·6% (61 of 528) in the IPT clusters (0·59, 0·42–0·83; p=0·0022). Adjusted analysis found IPT to be significantly more effective at preventing malaria infections than IST (0·69, 0·48–1·00; p=0·050, $p_{adjusted}$=0·0044). These findings suggest that monthly dosing with dihydroartemisinin–piperaquine might be required to clear new *P falciparum* and *P vivax* infections and keep relapses of *P vivax* infection in check. A larger trial of IPT is needed to establish whether monthly IPT with dihydroartemisinin–piperaquine will translate into better birth outcomes relative to SST.

Results from Sumba indicate there is a threshold of malaria transmission intensity below which IST and IPT with dihydroartemisinin–piperaquine is no more protective than SST against malaria and, potentially, adverse pregnancy outcomes. By contrast, IPT with sulphadoxine–pyrimethamine in Africa remains protective against low birthweight even in areas where malaria prevalence is extremely low.[9] A meta-regression analysis of IPT studies in Africa was not able to detect a cutoff of malaria transmission below which sulphadoxine–pyrimethamine no longer protects against low birthweight.[10] This finding might be explained, in part, by evidence that IPT with sulphadoxine–pyrimethamine, despite concerning amounts of parasite resistance, confers protection against adverse pregnancy outcomes among women with malaria, as well as among those with curable sexually transmitted infections and reproductive tract infections.[11] Dihydroartemisinin–piperaquine alone—as SST, IST, or IPT—is unlikely to provide similar dual-protection, although this might be inconsequential in Indonesia if co-infection is less common than in Africa.[12] However, pregnant women in Papua New Guinea probably shoulder a dual-burden of infection,[13,14] similar to their African counterparts.[15] Nonetheless, the evidence presented by Ahmed and colleagues is important and shows that IPT with dihydroartemisinin–piperaquine might help to shape a WHO strategy that protects pregnant women in the Asia-Pacific region against *P falciparum* and *P vivax* infections.

R Matthew Chico, Jorge Cano
Department of Disease Control, Faculty of Infectious & Tropical Diseases, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK
matthew.chico@lshtm.ac.uk

We declare no competing interests.

1 Rogerson SJ, Desai M, Mayor A, Sicuri E, Taylor SM, van Eijk AM. Burden, pathology, and costs of malaria in pregnancy: new developments for an old problem. *Lancet Infect Dis* 2018; **18:** e107–18.
2 Kakuru A, Jagannathan P, Muhindo MK, et al. Dihydroartemisinin–piperaquine for the prevention of malaria in pregnancy. *N Engl J Med* 2016; **374:** 928–39.
3 Kajubi R, Ochieng T, Kakuru A, et al. Monthly sulfadoxine–pyrimethamine versus dihydroartemisinin–piperaquine for intermittent preventive treatment of malaria in pregnancy: a randomised controlled trial. *Lancet* 2019; **393:** 1428–39.
4 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 sulfadoxine–pyrimethamine for the control of malaria during pregnancy in western Kenya: an open-label, three-group, randomised controlled superiority trial. *Lancet* 2016; **386:** 2507–19.
5 Verdrager J. Epidemiology of the emergence and spread of drug-resistant falciparum malaria in South-East Asia and Australasia. *J Trop Med Hyg* 1986; **89:** 277–89.
6 Rijken MJ, McGready R, Boel ME, et al. Malaria in pregnancy in the Asia-Pacific region. *Lancet Infect Dis* 2012; **12:** 75–88.
7 Hill J, Landuwulang CU, Hoyt J, et al. Evaluation of the national policy of single screening and treatment for the prevention of malaria in pregnancy in two districts in Eastern Indonesia: health provider perceptions. *Malaria J* 2018; **17:** 309.
8 Ahmed R, Poespoprodjo JR, Syafruddin D, et al. Efficacy and safety of intermittent preventive treatment and intermittent screening and treatment versus single screening and treatment with dihydroartemisinin–piperaquine for the control of malaria in pregnancy in Indonesia: a cluster-randomised, open-label, superiority trial. *Lancet Infect Dis* 2019; published online July 25. http://dx.doi.org/10.1016/S1473-3099(19)30156-2.
9 Stoner MC, Vwalika B, Smid M, et al. Dosage of sulfadoxine–pyrimethamine and risk of low birth weight in a cohort of Zambian pregnant women in a low malaria prevalence region. *Am J Trop Med Hyg* 2017; **96:** 170–77.
10 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; **20:** 1621–33.
11 Chico RM, Chaponda EB, Ariti C, Chandramohan D. Sulfadoxine–pyrimethamine exhibits dose-response protection against adverse birth outcomes related to malaria and sexually transmitted and reproductive tract infections. *Clin Infect Dis* 2017; **64:** 1043–51.
12 Chaponda EB, Chico RM, Bruce J, et al. Malarial infection and curable sexually transmitted and reproductive tract infections among pregnant women in a rural district of Zambia. *Am J Trop Med Hyg* 2016; **95:** 1069–76.
13 Mueller I, Rogerson S, Mola GD, Reeder JC. A review of the current state of malaria among pregnant women in Papua New Guinea. *P N G Med J* 2008; **51:** 12.
14 Vallely LM, Toliman P, Ryan C, et al. Prevalence and risk factors of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis* and other sexually transmissible infections among women attending antenatal clinics in three provinces in Papua New Guinea: a cross-sectional survey. *Sex Health* 2016; **13:** 420–27.
15 Chico RM, Mayaud P, Ariti C, Mabey D, Ronsmans C, Chandramohan D. Prevalence of malaria and sexually transmitted and reproductive tract infections in pregnancy in sub-Saharan Africa: a systematic review. *JAMA* 2012; **307:** 2079–86.