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Reply to Harrington et al

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To the Editor

We thank Harrington et al for pointing out the differences between our 2 studies [1, 2], including a concern that the small number of women who did not receive antenatal sulfadoxine-pyrimethamine (SP) prevents meaningful conclusions about the effects of receiving SP for intermittent preventive treatment for malaria in pregnancy (SP-IPTp) relative to not receiving it. We noted in our article that the small number of women unexposed to SP was a limitation of our study; however, this does not negate our finding that we did not observe the same relationship in Malawi when comparing outcomes between recent SP users and early SP users as reported by Harrington et al. In Figure 3 of their article, they showed clear differences in placental parasite densities between recent SP users (14.1% [10]), early SP users (6.4% [77]), and women who did not receive SP (1.9% [17]) [1]. The main value of our study is to show that, in Malawi, where the *dhfr-dhps* quintuple mutant is also ubiquitous but where the additional *dhps* A581G mutation is not, we did not observe an analogous relationship between parasite densities and SP timing (Table 1), A581G-bearing parasites, or birth outcomes. Our findings suggest that, under these conditions, there was no evidence that parasite growth was fueled by the presence of SP.

However, similar to Harrington et al, we found higher parasite densities in women infected with *Plasmodium falciparum* bearing *dhps* A581G than in those infected with parasites bearing wild-type *dhps*; this finding suggests that SP is less able to clear these highly resistant infections or suppress parasite densities. We fully agree that this is a cause for concern and that there is an urgent need to identify new drugs for the prevention of malaria in pregnancy. Unfortunately, recent trials have shown that, when given as IPTp, neither mefloquine, amodiaquine, nor the fixed-dose combination of chloroquine-azithromycin were superior to IPTp-SP for the prevention of low birth weight. Furthermore, these regimens were poorly tolerated by asymptomatic women [3–5].To address this, we and others are

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conducting trials with dihydroartemisinin-piperaquine, provided either as part of intermittent screening and treatment or as IPTp in Malawi (ISRCTN: 69800930), Uganda (ClinicalTrials.gov identifier: NCT02163447), and Kenya (ClinicalTrials.gov identifier: NCT01669941). Results should be available soon.

To date, the observation that SP may be harmful to women infected with highly resistant parasites has been found in a single study [1]. These mutant lineages emerged independently from similar lineages elsewhere [6], and other mutations may be present in the Tanzanian parasites that uniquely modify parasite fitness when exposed to SP. Although the findings of potential harm are clearly of concern, our results and those of others have not found evidence of harm in areas with either lower [7, 8] or similar levels [9] of the *dhps* A581G mutation. We do agree that, in highly resistant areas in northern Tanzania, a new approach to antenatal malaria prevention is needed. To this end, Tanzania recently introduced screening of pregnant women at the first antenatal care visit and treating test-positive women with an effective artemisinin-based combination therapy; test-negative women receive SP. This hybrid strategy may address some concerns by treating highly resistant patent infections early in pregnancy, until the results of new trials with dihydroartemisinin-piperaquine are available.

But what is the evidence that SP is truly failing overall? Several reports are cited by Harrington et al as evidence of IPTp-SP failure; each of these studies report effect estimates on low birth weight in favor of IPTp-SP (adjusted odds ratio [aOR], 0.71 [95% confidence interval {CI}, .33–1.54] [10]; aOR, 0.90 [95% CI, .78–1.03] [11]; aOR, 0.88 [95% CI, .57–1.38] after exclusion of human immunodeficiency virus–positive women [12]; and low-birth-weight frequency, 11.8% in the full IPTp group vs 15.8% in the suboptimal IPTp group [7]). Although each is statistically nonsignificant, the consistently lower risk of low birth rate among infants delivered by women who received IPTp-SP suggests that the drug retains clinically relevant efficacy. Furthermore, these data were generated under policies recommending only 2 doses of SP. The World Health Organization now recommends at least 3 doses of SP, as this improves birth weight more than the original 2-dose regimen, even in areas where quintuple-mutant parasites are highly prevalent [13]. Thus, on balance, IPTp-SP appears to continue to offer some benefit to pregnant women overall, even where the quintuple mutant is fixed but the additional *dhps* A581G mutation remains infrequent [13, 14].

We agree that a shift in paradigm is needed. More specifically, this must include both a search for new strategies for areas with highly resistant parasites and for areas with very low malaria transmission, as well as optimization of IPTp-SP policies and practices in the majority of Africa where SP still appears to remain efficacious for this indication.

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Table 1

Geometric Mean Parasite Densities (GMPDs), Stratified by Timing of Sulfadoxine-Pyrimethamine (SP) Receipt

Variable	Timing of SP Receipt, GMPD (95% CI)			*P* Value
	None Received (n = 4)	≤4 wk Before Delivery (n = 149)	>4 wk Before Delivery (n = 49)	
Maternal specimens	29 (2–344)	34 (22–52)	31 (15–65)	.97
Placental specimens	36 (2–620)	17 (12–25)	14 (8–25)	.44

Both maternal peripheral and placental parasite densities were similar among women who did not receive any SP, compared to those who received SP, regardless of the timing of the last dose of SP.

Abbreviation: CI, confidence interval.