Intermittent Preventive Therapy in Pregnancy and Incidence of Low Birth Weight in Malaria-Endemic Countries

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Objectives. To estimate the impact of hypothetical antimalarial and nutritional interventions (which reduce the prevalence of low midupper arm circumference [MUAC]) on the incidence of low birth weight (LBW).

Methods. We analyzed data from 14 633 pregnancies from 13 studies conducted across Africa and the Western Pacific from 1996 to 2015. We calculated population intervention effects for increasing intermittent preventive therapy in pregnancy (IPTp), full coverage with bed nets, reduction in malaria infection at delivery, and reductions in the prevalence of low MUAC.

Results. We estimated that, compared with observed IPTp use, administering 3 or more doses of IPTp to all women would decrease the incidence of LBW from 9.9% to 6.9% (risk difference = 3.0%; 95% confidence interval = 1.7%, 4.0%). The intervention effects for eliminating malaria at delivery, increasing bed net ownership, and decreasing low MUAC prevalence were all modest.

Conclusions. Increasing IPTp uptake to at least 3 doses could decrease the incidence of LBW in malaria-endemic countries. The impact of IPTp on LBW was greater than the effect of prevention of malaria, consistent with a nonmalarial effect of IPTp, measurement error, or selection bias. (*Am J Public Health.* 2018;108:399–406. doi:10.2105/AJPH.2017.304251)

Low birth weight (LBW; < 2500 g) remains a significant global health concern, affecting more than 25 million infants annually.[1,2] Low birth weight is associated with a marked increase in infant mortality and contributes to long-term morbidity.[1] In 2012, the World Health Organization (WHO) endorsed a target of 30% reduction in the incidence of LBW by 2025. As of 2014, the Global Nutrition Report found that there was little progress globally toward this goal.[3] Interventions in low- and middle-income countries (LMICs) to prevent LBW have the potential to produce substantial public health effects, ranging from improved cognitive development to enhanced neonatal survival.[1,2]

Two important risk factors for LBW in many LMICs are maternal malnutrition and malaria infection during pregnancy.[4–6] In malaria-endemic countries, up to 1 in 4 pregnant women are infected with malaria, while up to 20% of women of childbearing age in LMICs suffer undernutrition (body mass index [BMI; defined as weight in kilograms divided by the square of height in meters] < 18.5).[2,5,7] Although these 2 factors are highly prevalent in LMICs, interventions for them are often evaluated independently. Our group, the Maternal Malaria and Malnutrition (M3) Initiative, has endeavored to better understand this coburden of malaria infection and malnutrition during pregnancy. Specifically, in a recent study in which we used data pooled from 13 studies across Africa and the Western Pacific, we found that women who were both infected with malaria and malnourished were at greater risk of delivering a LBW infant than their uninfected, well-nourished counterparts. However, there was no conclusive evidence of synergistic interaction between the 2 risk factors for LBW (i.e., the effects of malaria infection and nutritional status of the mother on LBW were independent of each other).[8]

Although results from this study were informative for furthering our understanding of the biological mechanisms that affect fetal growth and development, policymakers would benefit from knowing how many cases of LBW could be prevented by interventions targeting malaria infection and maternal malnutrition. WHO policy for malaria prevention during pregnancy includes insecticide-treated bed nets, intermittent preventive treatment during pregnancy (IPTp), and prompt and effective case management.[9] Intermittent preventive treatment during pregnancy may also prevent LBW by preventing other infections because of its antibacterial properties, and by possible impacts on maternal nutritional status.[6] Currently, IPTp is recommended as repeated

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sulfadoxine and pryimethamine (SP) doses at least a month apart, starting in the second trimester,[9] but before 2007, only 2 doses of IPTp were recommended. Consistent with the lack of progress toward LBW reduction reported by the Global Nutrition Report, in 2013, an estimated 43% of 35 million eligible pregnant women did not receive any doses of IPTp.[10–12] The WHO endorses balanced energy and protein dietary supplementation during pregnancy among undernourished populations; however, interventions that would ameliorate poor nutrition before conception have received less focus.[2,13]

The objectives of this study were 2-fold. First, we aimed to estimate the impact of implementing hypothetical targeted antimalarial interventions and reductions in the prevalence of low midupper arm circumference (MUAC; a proxy for malnutrition) on population-level estimates of LBW. Second, we aimed to examine whether the introduction of any combination of these hypothetical targeted interventions might meet the WHO goal of a 30% reduction in the incidence of LBW.

METHODS

The study population comprised 14 633 live birth pregnancies among women enrolled in 1 of 13 studies conducted from 1996 to 2015 in sub-Saharan Africa (7 countries) and the Western Pacific (1 country).[14]

Outcome and Exposures

The main outcome of interest was LBW. Every study measured birth weight within 1 week of delivery, and birth weights measured after 24 hours (13% of weights) were adjusted by using a regression model to account for changes in weight during the first week of life.[15] In a sensitivity analysis, we excluded weights measured after 24 hours. We considered 2 secondary outcomes: small-for-gestational age (a birth weight less than the 10th percentile of the INTERGROWTH-21st reference) and preterm birth (gestational age < 37 weeks), among a subset of studies with ultrasound-dated gestational age.[16] Malaria diagnostics at study enrollment and delivery were available; however, this analysis focused on malaria infection at delivery because malaria infection at delivery had a stronger effect on LBW than malaria infection at enrollment in this data set.[8] Presence of malaria parasites in peripheral blood or in the placenta at delivery was assessed with light microscopic examination of a Giemsa-stained peripheral or placental smear or placental histology (active or past infection) or both.[17]

Information on how many doses of IPTp women received was available for 92% of the study population, and self-reported bed net ownership at study enrollment was ascertained in 9 of the 13 studies. Bed net ownership did not distinguish between untreated and insecticide-treated bed nets, although most recent studies will have included the latter. Currently, the WHO recommends IPTp with SP, which is what the majority (64%) of the women received, but some women in the clinical trials received IPTp with SP plus azithromycin (16%), SP plus chloroquine (15%), or dihydroartemisinin-piperaquine (5%).[9] We used MUAC at study enrollment as our primary measure of maternal malnutrition, categorizing women with an MUAC less than 23 centimeters as malnourished.[18] In a sensitivity analysis, we used gestational age–adjusted BMI less than 18.5 as an alternative anthropometric indicator of malnutrition. We adjusted maternal weight measured in the second or third trimesters by using a cubic regression model to account for gestational weight gain.[19]

Population Intervention Effects

Table 1 and Table A (available as a supplement to the online version of this article at http://www.ajph.org) describe a series of contrasts between observed and counterfactual population distributions of malaria infection, IPTp dosage, bed net ownership, and MUAC. The first 2 contrasts compare the risk of LBW (1) if the population were all infected with malaria at delivery or (2) given the observed distribution of malaria infection, both compared with if none of the population had been infected. Although not based on a specific antimalarial intervention, these contrasts inform on the etiologic effect of malaria infection at delivery and provide a best estimate about what would happen if malaria infection at delivery in the study populations was completely eliminated. In a sensitivity analysis, we explored using an aggregate measure of malaria infection during pregnancy, "any malaria," defined as a positive microscopy test, rapid diagnostic tests, or polymerase chain reaction at enrollment, delivery, or during pregnancy (in 5 studies with repeat malaria diagnostics throughout pregnancy). To better guide policies for specific evidence-based interventions, we also assessed the impact of scaling up existing malaria-prevention efforts implemented in the pooled studies, specifically (1) bed net ownership and (2) IPTp during pregnancy (Table 1 and Table A, scenarios 3 and 4).

We took a similar approach for estimating population-level contrasts for distribution of low MUAC, first comparing the risk of LBW if all women had MUAC less than 23 centimeters, and second comparing the observed distribution of malnutrition, to the study population if all women had MUAC at or more than 23 centimeters (Table 1 and Table A, scenarios 5 and 6). It is unrealistic to expect that an intervention could increase the MUAC of all malnourished women. Therefore, we also simulated a hypothetical intervention that would reduce the prevalence of low MUAC at study enrollment in each separate study to 5% (the lowest prevalence of malnutrition from any of our studies). In a sensitivity analysis, an equivalent approach was taken when we used gestational age–adjusted BMI to define malnutrition.

Statistical Analysis

We used the parametric g-formula to estimate the aforementioned population intervention effects.[20,21] The parametric g-formula, which has also been described as a substitution estimator by Ahern et al.,[22] allows estimation of how the distribution of LBW would be different if we were able to alter malaria infection at delivery, the number of doses of IPTp received during pregnancy, the level of bed net ownership, and the prevalence of low MUAC.

First, we modeled the effect of each exposure (malaria, malnutrition, bed net ownership, or IPTp dosage) on LBW. We used logistic regression models, with control for known and measured confounders, and generalized estimating equations to account for within-study correlation. We determined confounders from a causal directed acyclic graph[23] based on previous literature on the

TABLE 1—Population Average Causal Effects, Population Attributable Effects, and Generalized Intervention Effects for the Risk of Low Birth Weight Associated With Malaria Infection and Malnutrition During Pregnancy: Africa and Western Pacific, 1996–2015

Exposure(s)	Contrasts	Intervention
Malaria interventions		
Malaria infection at delivery	Population average causal effect: the population with everyone infected with malaria at delivery compared with the population of women with no infection	NA
Malaria infection at delivery	Population attributable effect: the observed distribution of malaria infection at delivery compared with the population of women with no infection	Hypothetical complete and instant eradication of malaria infection at delivery
Bed net ownership at enrollment	Population attributable effect: the observed distribution of bed net ownership compared with the population of women in which everyone owns a bed net	Scaling up of existing bed net intervention
Number of IPTp doses	Generalized intervention effect: the observed distribution of IPTp doses compared with the population in which (1) everyone has at least 2 doses of IPTp, (2) everyone has at least 3 doses of IPTp, or (3) at least 80% of the study population has at least 3 doses of IPTp	Scaling up of existing IPTp interventions
Malnutrition interventions		
Malnutrition at enrollment	Population average causal effect: the population with everyone malnourished at enrollment compared with the population of women with no malnutrition	NA
Malnutrition at enrollment	Population attributable effect: the observed distribution of malnutrition (MUAC < 23 cm) compared with the population of women with no malnutrition	Hypothetical complete and instant eradication of malnutrition before pregnancy or in early pregnancy
Malnutrition at enrollment	Generalized intervention effect: the observed distribution of malnutrition (MUAC < 23 cm) compared with the population in which only 5% of each separate study population is malnourished	Hypothetical intervention with a nonspecific mechanism that would reduce malnutrition prevalence in each study in M3 to 5% (prevalence in FSP/MISAME-Burkina Faso study)

Note. FSP/MISAME = Micronutriments-Sante de la Mere et de l'Enfant; IPTp = intermittent preventive therapy during pregnancy; LBW = low birth weight; M3 = Maternal Malaria and Malnutrition Initiative; MUAC = midupper arm circumference; NA = not applicable. For example, the second scenario depicts the population attributable effect for malaria infection at delivery, comparing the risk of LBW under the observed distribution of malaria infection at delivery in the study population to the risk under a counterfactual setting in which there is hypothetical complete and instant eradication of malaria.

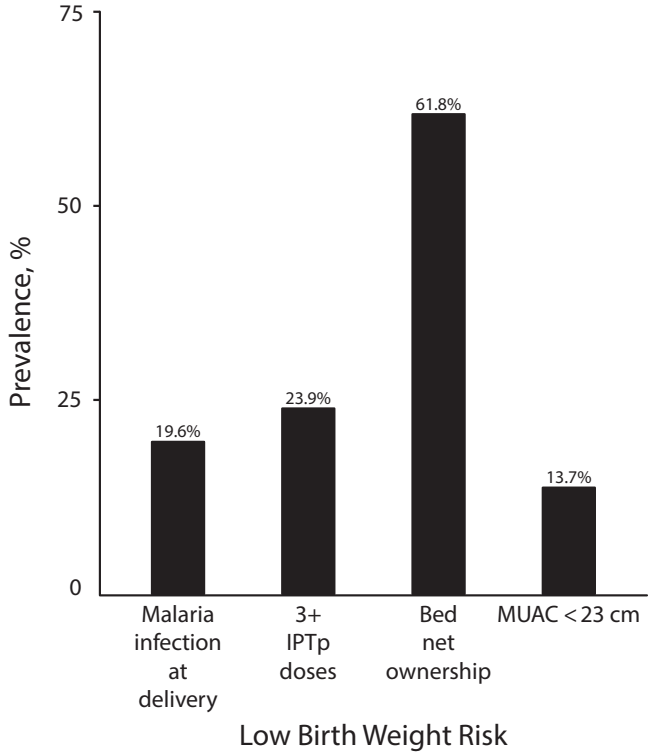
relationship between covariates. Known confounders for the malaria–LBW relationship were study site, maternal age, gravidity, rural versus urban residence, malnutrition (MUAC when available, otherwise BMI), HIV infection, anemia at enrollment, malaria infection at enrollment, and the number of IPTp doses. Confounders for the malnutrition–LBW relationship were study site, maternal age, gravidity, rural versus urban residence, anemia at enrollment, and HIV infection. Confounders for the bed net–LBW relationship were study site, rural versus urban residence, gravidity, and number of IPTp doses. Confounders for the IPTp–LBW relationship were study site, HIV infection, bed net ownership, rural versus urban residence, and gravidity. We conducted a complete case analysis for each model, and the sample sizes for each analysis depended on the availability of data on relevant variables.

Second, we "set" (i.e., coded) the exposure to the level specified for the particular hypothesized intervention (Table 1 and Table A). With this exposure set (sometimes counter to the fact of the observed exposure), we predicted the probability of having a LBW infant for each individual.

Third, we averaged the imputed probabilities for having a LBW infant for each individual across the population, for each set level of exposure. Comparison of the average outcomes for the different set exposure provides us with a population-standardized risk difference (RD) for LBW when changing exposure prevalence. We estimated the number needed to treat for each contrast of set exposures as the reciprocal of the absolute value of the RD. We calculated confidence intervals (CIs) by using a nonparametric bootstrap (200 samples with replacement from original data set).[24]

RESULTS

Characteristics of the 14 633 women participating in the 13 M3 studies have been reported previously and are included in Table B, available as a supplement to the online version of this article at http://www.ajph.org.[8] As illustrated in Figure 1, 2312 (20%) of the 11 826 women with malaria diagnostics were infected with malaria at delivery and 1224 (14%) of the 8963 women with MUAC measured were malnourished at enrollment. The median gestational age at enrollment was 20 weeks (interquartile range = 17–24). These prevalences varied greatly by study site, with the prevalence of malaria at delivery ranging from less than 1% (0.3%) to 57% and the prevalence of malnutrition ranging from 5% to 54% (Table B). The median number of IPTp doses among the 12 280 women with IPTp dosage information was 1 (interquartile



Note. IPTp = intermittent preventive therapy during pregnancy; MUAC = midupper arm circumference. Malaria infection at delivery: n = 11 826; 3 or more doses of IPTp: n = 12 280; bed net ownership at study enrollment: n = 8516; and low maternal MUAC: n = 8963.

FIGURE 1—Distribution of Malaria Infection at Delivery, Intermittent Preventive Therapy During Pregnancy, Bed Net Ownership at Study Enrollment, and Low Midupper Arm Circumference Among Women in the Maternal Malaria and Malnutrition (M3) Initiative: Africa and Western Pacific, 1996–2015

range = 0–6), and 5260 (62%) of the 8516 women reported owning a bed net (Figure 1). The prevalence of LBW was 9% (range = 5%–15%). Among 9 studies with ultrasound-dated gestational age, the prevalence of small-for-gestational age was 19% (range = 13%–25%) and the prevalence of preterm birth was 11% (range = 3%–20%).

As reported in Table 2 and Table C (available as a supplement to the online version of this article at http://www.ajph.org), the RD for LBW when we compared the population in which everyone was infected with malaria at delivery with that in which no one was infected was 2.0% (95% CI = 0.8%, 3.4%). The population-attributable RD was smaller (RD = 0.5%; 95% CI = 0.2%, 0.8%) because it compared the observed prevalence of malaria (only 20% of participants were infected) to complete elimination of malaria infection.

The RD for the comparison of observed bed net ownership to the population had everyone owned a bed net was 0.3% (95% CI = –0.3%, 0.8%; Table 2 and Table C). The RD for 2 or more doses of IPTp compared with the observed distribution was modest (0.9%; 95% CI = –0.8%, 1.7%), but the effect for increasing the dosage to 3 or more doses for all women was markedly stronger (RD = 3.0%; 95% CI = 1.7%, 4.0%; number needed to treat: 33; 95% CI = 25, 60). This number needed to treat suggests that increasing the IPTp dosage to 3 or more doses in 33 pregnant women would result in 1 fewer infant born LBW. A similar increase for 80% of the study population also produced a substantial impact on LBW (RD = 2.1%; 95% CI = 1.0%, 2.7%). These results did not qualitatively change when we excluded women with other IPTp regimens (i.e., SP plus azithromycin, SP plus chloroquine, or dihydroartemisinin-piperaquine; RD = 3.2%; 95% CI = 1.3%, 4.4%) and when we excluded infants with birth weight measured after 24 hours (Table D, available as a supplement to the online version of this article at http://www.ajph.org).

The risk difference for LBW when we compared the population if everyone had low MUAC at study enrollment versus if all of the population had MUAC of 23 or more centimeters was 4.0% (95% CI = 3.0%, 5.1%; Table 2 and Table C). The risk differences for LBW were smaller when we compared the observed distribution of MUAC with the population had there been no malnutrition (RD = 0.3%; 95% CI = 0.2%, 0.4%) or with the population in which only 5% of each study was malnourished (RD = 0.2%; 95% CI = 0.2%, 0.3%). The population-standardized risk differences when we used BMI as an anthropometric indicator of maternal malnutrition were similar but weaker (Table E, available as a supplement to the online version of this article at http://www.ajph.org).

DISCUSSION

We calculated estimates for the potential impact of interventions that reduce malaria infection at delivery, including scale-up of bed net ownership and IPTp during pregnancy and interventions to improve maternal nutritional status among malnourished women (according to MUAC measured at first antenatal visit) on the risk of delivering a LBW infant. We combined data from 13 studies in malaria-endemic countries in Africa and the Western Pacific. Calculation of interventional effects is rarely done in epidemiological studies, despite the utility of such results from a policy and public health perspective.[21,25–27] Overall, these results showed that increasing uptake of IPTp to 3 or more doses could markedly reduce the number of infants born with LBW in malaria-endemic countries. If all women received 3 or more doses of IPTp, the incidence of LBW would be reduced from 9.9% to 6.9%, a 3.0% absolute reduction in LBW incidence and a 30% (95% CI = 16%, 40%) relative reduction, matching the WHO 2025 Global Nutrition Target of a 30% reduction in LBW.[1] Even 80% coverage of 3 or more doses was estimated to result in a 21% (95% CI = 9%, 28%) relative reduction in LBW. By contrast, completely eliminating malaria

TABLE 2—Estimated Population-Level Low Birth Weight Risk Differences for Malaria Infection at Delivery, Bed Net Ownership, Intermittent Preventive Therapy During Pregnancy Dosage, and Low Midupper Arm Circumference Among Women in the Maternal Malaria and Malnutrition (M3) Initiative: Africa and the Western Pacific, 1996–2015

Contrast	Risk of LBW, %	Risk Difference, % (95% CI)	No. Needed to Treat (95% CI)
Malaria infection at delivery (n = 11 826 [2312 infected])			
Population average causal effect			
All exposed	9.8	2.0 (0.8, 3.4)	
None exposed	7.7		
Population attributable effect			
Observed	8.2	0.5 (0.2, 0.8)	210 (130, 543)
None exposed	7.7		
Bed net ownership (n = 8516 [5260 owned bed net])			
Population attributable effect			
Observed	9.5	0.3 (–0.3, 0.8)	396 (–320, 119)[a]
All exposed	9.3		
IPTp dosage (n = 12 280 [average 1.5 doses])			
Population attributable effect			
Observed (n = 2935 [24%] with ≥ 3 doses)	9.9		
All ≥ 2 doses	9.0	0.9 (–0.8, 1.7)	115 (–124, 61)[a]
All ≥ 3 doses	6.9	3.0 (1.7, 4.0)	33 (25, 60)[a]
80% of each study 3+ doses	7.8	2.1 (1.0, 2.7)	48 (37, 100)[a]
Maternal malnutrition (n = 8963 [1224 with low MUAC])			
Population average causal effect			
All exposed	13.6	4.0 (3.0, 5.1)	
None exposed	9.6		
Population attributable effect			
Observed	9.9	0.3 (0.2, 0.4)	312 (243, 424)[a]
None exposed	9.6		43 (34, 63)[b]
Generalized intervention effect			
Observed	9.9	0.2 (0.2, 0.3)	446 (336, 579)[a]
Exposure reduced to realistic lower bound (5%)[c]	9.7		61 (47, 90)[b]

Note. CI = confidence interval; IPTp = intermittent preventive therapy during pregnancy; LBW = low birth weight; MUAC = midupper arm circumference.

[a]Number needed to treat, assuming an intervention that is administered to all women.

[b]Number needed to treat, assuming an intervention that is administered to women who were malnourished at baseline.

[c]The lowest prevalence of malnutrition (MUAC < 23 cm) within the pooled M3 data set was observed in the Intermittent Screening and Treatment or Intermittent Preventive Treatment for the Control of Malaria in Pregnancy (STOPMIP)-Kenya cohort (5%).

infection at delivery, increasing bed net ownership to 100%, or abolishing low MUAC at study enrollment had a less than 1% reduction on the risk for LBW.

The hypothetical effects for IPTp were stronger than the estimated effect of complete elimination of malaria infection at delivery, which is counterintuitive if one assumes that IPTp prevents LBW solely through treating and preventing malaria infection. One explanation might be that increased IPTp coverage would control malaria through much of pregnancy and not just at delivery. This was not something we captured in our main malaria analysis, but a sensitivity analysis examining the effect of any malaria infection detected during pregnancy found weaker intervention effects than our analysis of malaria infection at delivery, although repeat malaria diagnostics were not available for all studies (Table F, available as a supplement to the online version of this article at http://www.ajph.org).

An alternative hypothesis is that the apparent effect of IPTp may be attributable to mechanisms additional to the prevention of malaria. As it is a broad-spectrum antibiotic, SP may improve LBW through clearance of other pathogens associated with fetal growth restriction and preterm birth and may decrease chronic maternal inflammation.[28] In a sensitivity analysis, increased doses of IPTp had a greater effect on preventing preterm birth than small-for-gestational age, which supports the hypothesis that IPTp is functioning to clear pathogens that can cause preterm birth (Table G, available as a supplement to the online version of this article at http://www.ajph.org).

The intervention estimates for IPTp did not account for regional drug resistance, which could have biased our findings; however, previous

studies have found that IPTp–SP remains associated with reductions in LBW even in areas of SP resistance.[29,30] In addition, women who more frequently access antenatal care, and so receive more doses of IPTp, are potentially healthier because of associated health-promoting behaviors and related socioeconomic status.[31]

Limitations

Our inability to control for these potential unmeasured confounders and selection biases indicates that our intervention effects may be biased and that the impact of IPTp may not be as great as we have estimated. Unmeasured healthy behaviors that are promoted or interventions that are provided at the same antenatal care visits as SP provision may be reducing the risk of LBW instead of SP; however, previous studies that controlled for the number of antenatal visits were consistent with an effect of SP that is independent of the number of antenatal visits.[32,33] Further studies are warranted to elucidate the mechanisms of action for SP and to untangle the effects of increased dosage from the potential selection bias related to more frequent antenatal care.

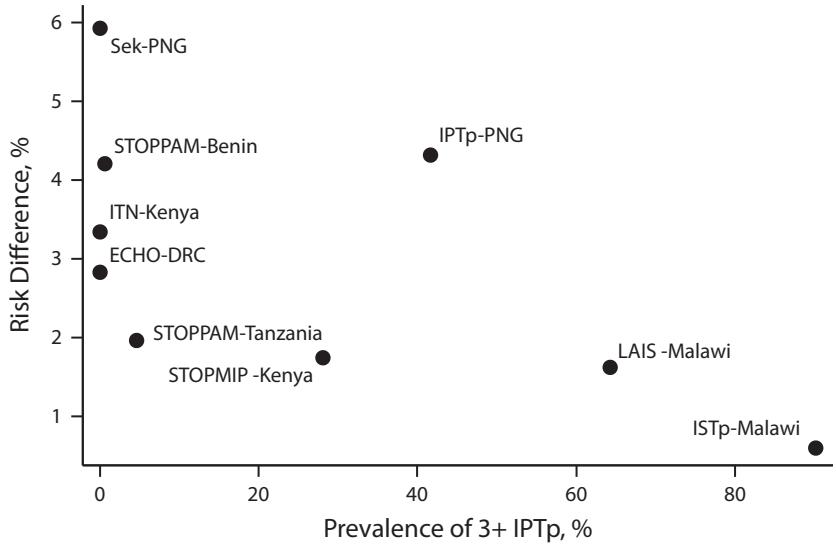
In addition, women that did not have information on the number of IPTp doses were on average younger, and had lower prevalences of anemia, malaria infection, and low MUAC; only analyzing women with measured IPTp could have led to selection bias if these factors modify the relationship between IPTp and LBW (Table H, available as a supplement to the online version of this article at http://www.ajph.org).

Benefits of Interventions

Despite these limitations, these findings are consistent with previous evidence on the importance of multiple doses of IPTp during pregnancy.[30,34] Our estimates agree with a mathematical model that estimated that 215 000 (95% credible interval = 128 000, 318 000) LBW deliveries in Africa in 2015 could have been prevented by women taking IPTp–SP during at least 3 antenatal care visits.[30] Despite the evidence regarding the benefits of IPTp, coverage is presently inadequate.[10–12] Concerns around SP drug resistance have contributed to this low level of coverage; however, the synthesis of current evidence supports the benefits of increasing IPTp dosage even when accounting for SP resistance.[29,30]

Whereas scaling up IPTp had notable impacts on LBW incidence, the population attributable effect for bed net ownership was weak: we estimated that 100% uptake of bed net ownership would only result in a 0.3% absolute reduction in LBW prevalence compared with current levels over all studies in this cohort. However, in our pooled data set, 62% of women with available information reported owning a bed net at enrollment. Coverage is likely lower among pregnant women outside of a research setting: in 2010, insecticide-treated bed net coverage in sub-Saharan Africa was only 41%.[10,11] If bed net ownership is overestimated, the actual population intervention estimate is likely greater than we estimated. In addition, although we adjusted our model for study site, we did not have more detailed information on malaria transmission, regional insecticide resistance, actual bed net usage, and whether the bed nets were untreated or insecticide-treated, all of which may influence the validity of our results. Given the limitations surrounding our measurement of bed net usage, we urge caution in the interpretation of the bed net results, emphasizing that insecticide-treated bed nets remain a valuable tool for preventing malaria and improving fetal development in malaria-endemic countries.[35] However, the weak population attributable effect for bed nets is aligned with evidence of increased insecticide resistance in many regions of sub-Saharan Africa.[36]

For malaria, we were able to use information on real interventions (IPTp and bed nets), but we were unable to assess a real nutritional intervention, relying instead on a hypothetical intervention that affected maternal MUAC. Although low MUAC at study enrollment was a strong predictor of LBW, our intervention effects illustrate that a hypothetical periconceptional intervention that would completely or partially reduce the prevalence of MUAC by the first antenatal care visit would have only minor population-level impacts on LBW. Because our nutritional assessments were made at antenatal enrollment, our nutrition models required the assumption that an intervention could be implemented that would target malnutrition before pregnancy or in early pregnancy. For example, an effective community-based antimalnutrition



Note. DRC = Democratic Republic of Congo; IPTp = intermittent preventive therapy during pregnancy; ISTp = Intermittent Screening and Treatment; ITN = Insecticide-Treated Bed Nets; LAIS = Lungwena Antenatal Intervention Study; PNG = Papua New Guinea; STOPMIP = Intermittent Screening and Treatment or Intermittent Preventive Treatment for the Control of Malaria in Pregnancy; STOPPAM = Strategies to Prevent Pregnancy Associated Malaria.

FIGURE 2—The Population Attributable Effect of Increasing Intermittent Preventive Therapy During Pregnancy Dosage to at Least 3 Doses for All Pregnancies, Stratified by the Prevalence of at Least 3 Doses of IPTp: Africa and Western Pacific, 1996–2015

campaign targeted at women of reproductive age could potentially produce the changes in maternal malnutrition that we model. Future studies may wish to estimate impacts of hypothetical nutritional interventions that would improve gestational weight gain during pregnancy, which is a strong predictor of birth weight.[37]

In all analyses, the extent of unmeasured confounding is unknown. Potential unmeasured confounders include helminth infection, sexually transmitted infections, environmental pollutants, or micronutrient deficiencies. In addition, all of the intervention effects reported are a function of background prevalences of the exposure of interest in each analysis; thus, they may not be generalizable to settings with dramatically different baseline prevalences. Figure 2 and Figure A (available as a supplement to the online version of this article at http://www.ajph.org) illustrate that the LBW risk difference associated with increasing IPTp dosage to 3 or more doses for all pregnancies is greatest among studies with low levels of IPTp coverage and high levels of malaria prevalence at delivery.

Public Health Implications

In conclusion, of the interventions we evaluated, 3 or more doses of IPTp appear to offer the greatest potential for achieving the WHO's Global Nutrition Target of a 30% reduction in LBW by 2025. Although the IPTp estimates were notably strong, hypothetical interventions to eliminate malaria infection at delivery or to increase MUAC at study enrollment did not appear to have strong impacts on population-level incidence of LBW. Although we cannot discount potential unmeasured confounding and selection bias of the IPTp estimates, our findings suggest that IPTp–SP prevents LBW through mechanisms beyond malaria treatment and prevention. AJPH

CONTRIBUTORS

H. W. Unger, S. Meshnick, and S. J. Rogerson were involved in design and supervision of data collection of the parent studies. S. J. Rogerson and H. W. Unger were involved in the conceptualization of the Maternal Malaria and Malnutrition (M3) initiative. J. E. Cates, H. W. Unger, D. Westreich, M. Bauserman, L. Adair, S. R. Cole, S. Meshnick, and S. J. Rogerson conceptualized the analyses. J. E. Cates carried out the analyses and drafted the initial article. All authors, including the collaborators in the M3 initiative, critically revised this article and approved the final version of the article.

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HUMAN PARTICIPANT PROTECTION

All studies received approval by their local ethics board and obtained informed consent from all participants.

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