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

Kassoum Kayentao, MD
Paul Garner, MD
Anne Maria van Eijk, PhD
Inbarani Naidoo, MSc
Cally Roper, PhD
Abdunoor Mulokozi, PhD
John R. MacArthur, MD
Mari Luntamo, MD
Per Ashorn, PhD
Ogobara K. Doumbo, PhD
Feiko O. ter Kuile, PhD

Importance Intermittent preventive therapy with sulfadoxine-pyrimethamine to control malaria during pregnancy is used in 37 countries in sub-Saharan Africa, and 31 of those countries use the standard 2-dose regimen. However, 2 doses may not provide protection during the last 4 to 10 weeks of pregnancy, a pivotal period for fetal weight gain.

Objective To perform a systematic review and meta-analysis of trials to determine whether regimens containing 3 or more doses of sulfadoxine-pyrimethamine for intermittent preventive therapy during pregnancy are associated with a higher birth weight or lower risk of low birth weight (LBW) (<2500 g) than standard 2-dose regimens.

Data Sources and Study Selection ISI Web of Knowledge, EMBASE, SCOPUS, PubMed, LILACS, the Malaria in Pregnancy Library, Cochrane CENTRAL, and trial registries from their inception to December 2012, without language restriction. Eligible studies included randomized and quasi-randomized trials of intermittent preventive therapy during pregnancy with sulfadoxine-pyrimethamine monotherapy.

Data Extraction Data were independently abstracted by 2 investigators. Relative risk (RR), mean differences, and 95% CIs were calculated with random-effects models.

Results Of 241 screened studies, 7 trials of 6281 pregnancies were included. The median birth weight in the 2-dose group was 2870 g (range, 2722-3239 g) and on average 56 g higher (95% CI, 29-83 g; I^2=0%) in the ≥3-dose group. Three or more doses were associated with fewer LBW births (RR, 0.80; 95% CI, 0.69-0.94; I^2=0%), with a median LBW risk per 1000 women in the 2-dose group (assumed control group risk) of 167 per 1000 vs 134 per 1000 in the ≥3-dose group (absolute risk reduction, 33 per 1000 [95% CI, 10-52]; number needed to treat=31). The association was consistent across a wide range of sulfadoxine-pyrimethamine resistance (0% to 96% dihydropteroate-synthase *K540E* mutations). There was no evidence of small-study bias. The ≥3-dose group had less placental malaria (RR, 0.51; 95% CI, 0.38-0.68; I^2=0%, in 6 trials, 63 vs 32 per 1000; absolute risk reduction, 31 per 1000 [95% CI, 20-39]). In primigravid plus secundigravid women, the risk of moderate to severe maternal anemia was lower in the ≥3-dose group (RR, 0.60; 95% CI, 0.36-0.99; I^2=20%; in 6 trials, 36 vs 22 per 1000; absolute risk reduction, 14 per 1000 [95% CI, 0.4-23]). There were no differences in rates of serious adverse events.

Conclusions and Relevance Among pregnant women in sub-Saharan Africa, intermittent preventive therapy with 3 or more doses of sulfadoxine-pyrimethamine was associated with a higher birth weight and lower risk of LBW than the standard 2-dose regimens. These data provide support for the new WHO recommendations to provide at least 3 doses of intermittent preventive therapy during pregnancy at each scheduled antenatal care visit in the second and third trimester.

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In areas of stable malaria transmission in sub-Saharan Africa, *Plasmodium falciparum* infection in pregnant women is associated with maternal anemia and low birth weight (LBW) (<2500 g),[1-3] especially among primigravida and secundigravida and human immunodeficiency virus (HIV)–infected women.[1] The World Health Organization (WHO) recommended intermittent preventive therapy during pregnancy, consisting of at least 2 full treatment doses of sulfadoxine-pyrimethamine for HIV-negative women and at least 3 doses for HIV-positive women not receiving cotrimoxazole, administered presumptively in the second and third trimesters at least 1 month apart.[4,5] Each dose suppresses or clears any existing asymptomatic infections from the placenta and provides up to 6 weeks of posttreatment prophylaxis.[4,6] Although the stan-

CME available online at www.jamaarchivescme.com and questions on p 614.

Author Affiliations are listed at the end of this article.
Corresponding Author: Feiko O. ter Kuile, PhD, Child and Reproductive Health Group, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, United Kingdom (terkuile@liv.ac.uk).

dard 2-dose regimen provides at most 12 weeks of prophylaxis,[6] it has been shown to be effective in reducing LBW[7-13] and was adopted by 31 of 37 endemic countries in Africa with a policy for intermittent preventive therapy during pregnancy; the remaining countries use a 3-dose or monthly regimen.[14] Nevertheless, reinfections are common with the 2-dose regimen, especially among women who complete their last dose early in the third trimester.[8,9] A previous meta-analysis[7] of 3 trials confirmed that additional doses of sulfadoxine-pyrimethamine may add benefit over 2 doses among HIV-infected primigravida plus secundigravida (G1-G2 women), but there was insufficient evidence on HIV-negative women or intermittent preventive therapy during pregnancy when used in combination with insecticide-treated nets. Furthermore, increasing sulfadoxine-pyrimethamine resistance, which results in a progressive decrease of the duration of the prophylactic effect,[6] may also require more frequent dosing.[7]

The objective of this analysis was to evaluate whether 3 or more doses of intermittent preventive therapy during pregnancy with sulfadoxine-pyrimethamine are associated with higher birth weight or a lower risk of LBW than the current standard 2-dose regimen and to examine whether this is moderated by sulfadoxine-pyrimethamine resistance, HIV status, gravidity, or use of insecticide-treated nets.

METHODS

Eligibility Criteria

Study inclusion criteria, outcomes, and methods for the analysis were prespecified in the protocol. Studies had to be quasi-randomized or randomized controlled trials conducted with pregnant women living in sub-Saharan Africa, comparing the standard 2-dose regimen with sulfadoxine-pyrimethamine with a regimen of intermittent preventive therapy during pregnancy consisting of 3 doses or monthly dosing. Studies or study groups that combined sulfadoxine-pyrimethamine with other antimalarial drugs, such as artemisinin derivatives or azithromycin, or other interventions, such as screening for malaria, were excluded. Use of mosquito nets was not an exclusion criterion. Trial inclusion was unrestricted by gravida group, HIV status, and type of outcomes reported.

Study Selection

Studies were identified by searching PubMed, SCOPUS, ISI Web of Knowledge, EMBASE, LILACS, Cochrane CENTRAL, the Malaria in Pregnancy Library,[15] WHO's International Clinical Trials Registry Platform, and the Cochrane Central Register of Controlled Trials from their inception to December 11, 2012, without language restrictions; scanning reference lists of articles; and consultation with experts in the field (see eFigure 1 and eMethods, available at http://www.jama.com). For trial selection, 2 authors (K.K. and A.M.v.E.) independently screened and assessed trials for eligibility and final inclusion in the analysis in a standardized manner. Disagreement between reviewers was resolved through consensus after discussion and consultation with the senior author (F.O.t.K.).

Data Collection and Analysis

Data extraction was conducted independently by 2 unblinded investigators (K.K. and A.M.v.E.) using pretested standardized data extraction forms. Authors of primary studies were contacted for missing information or if reported data did not fit the required format. For each study, the following information was extracted: first author, publication year, year of study start and end, study design, randomization procedures, inclusion criteria (eg, any restrictions by gravidity, age, or HIV status), insecticide-treated net or bed net use, folate supplementation and dosage, local malaria transmission, details of study groups, number of women enrolled, and outcomes assessed, including adverse events overall and stratified by subgroup. The Cochrane Collaboration's tool for assessing the risk of bias[16] was used to determine the quality of included trials as low (high risk of bias), high (low risk of bias), or unclear. Uncertainties were resolved by consensus and by contacting the corresponding authors.[17]

Time- and location-matched data on molecular resistance to sulfadoxine-pyrimethamine were obtained from published articles, as described previously,[18] and through correspondence with the authors of the trials. The prevalence of the *K540E* mutation in the dihydropteroate synthase (*DHPS*) gene was used as a proxy for the prevalence of the combined dihydrofolate reductase *DHFR* (N51I, C59R, and S108N)/*DHPS* (A437G, K540E) quintuple genotype that is strongly associated with treatment failure of sulfadoxine-pyrimethamine.[19]

Synthesis

The primary outcome measures were LBW and mean birth weight. Secondary outcomes included maternal hemoglobin level, maternal anemia (hemoglobin level $<$11 g/dL) and moderate to severe anemia (defined by the individual trials as hemoglobin level $<$6, 7, or 8 g/dL) at term or delivery, maternal malaria infection (peripheral blood) at delivery, placental malaria infection (all species), preterm delivery ($<$37 weeks' gestation), spontaneous miscarriage, stillbirth, and neonatal death (death within 0-27 days in live-born infants). All analyses were stratified a priori by HIV status and gravidity status (G1-G2 vs $\geq$G3 pregnancies [multigravida]), with the aim to provide independent subgroup estimates and overall estimates of the pooled data.

We used both random-effects (primary method) and fixed-effects models to calculate the summary relative risks (RRs) for dichotomous outcomes (Mantel-Haenszel) or differences in means for continuous outcomes (inverse variance) and we prespecified that any heterogeneity would be investigated by subgroup analysis. To provide estimates of absolute risk and effect, values for the assumed control-group risk in 2-dose recipients and the

corresponding intervention-group risk and 95% CI in ≥3-dose recipients were computed as assumed control-group risk = median risk (expressed per 1000 women) across the included trials in the 2-dose group; corresponding intervention-group risk = assumed control-group risk × RR (95% CI), where the RR was taken from random-effects models.[20] The absolute risk reduction was calculated as the assumed control-group risk × (1 − RR) and expressed per 1000 women. Similar methods were used with the lower and upper CI of the RR to obtain the 95% CI of the absolute risk reduction. The number needed to treat (NNT) for LBW (the primary end point) was computed as NNT = 1/(assumed control-group risk × [1 − RR]).[20] For the continuous end points, the observed median birth weight or hemoglobin concentration in the 2-dose group was reported as the assumed control-group median. The corresponding value in ≥3-dose recipients was expressed as the corresponding intervention-group median and 95% CI, which were computed as the assumed control-group median + mean difference (95% CI).

Heterogeneity was quantified with the I^2 statistic and χ^2 test.[21] The Deeks and Higgens method was used to test for heterogeneity between the different summary estimates across subgroups.[22] Publication and small-study bias was assessed by visual inspection of funnel plots and the Harbord test. To evaluate the change in pooled summary estimates for the RR with addition of new evidence, we created cumulative meta-analysis plots.[23] Prespecified sensitivity analysis for the primary outcomes was performed by excluding all studies that were scored as low quality for allocation concealment or other sources of bias.[16] Further sensitivity analysis was conducted to test the effect of each study on the pooled

Table 1. Characteristics of Included Trials

Source	Parise et al[12]	Filler et al[24]	Hamer et al[25]	Luntamo et al[26]	Valea et al[28]	Diakite et al[9]	MacArthur et al[29]
Country	Kenya	Malawi	Zambia	Malawi	Burkina Faso	Mali	Tanzania
Year published	1998	2006	2007	2010	2010	2011	Unpublished[a]
Study, years	1994-1996	2002-2005	2003-2004	2003-2006	2006-2008	2006-2008	2003-2006
Gravidity	G1-G2	G1-G2	All	All	All	All	G1-G2
No. of women							
≥3-Dose group	661	351	224	441	656	413	400
2-Dose group	680	347	232	436	640	401	399
Total (G1-G2)	1341 (1341)	698 (698)	456 (251)	877 (381)	1296 (536)	814 (339)	799 (799)
Intervention regimen	Monthly	Monthly	Monthly	Monthly	3 dose[b]	3 dose	Monthly
No. of doses in ≥3 group, median (range)	3 (1-5)	5 (1-5)	4 (1-6)	4 (1-6)	2 (1-3)[b]	3 (1-3)	3 (1-5)
No. of ANC visits by dose, median (range)	Designed to be equal[c]	Designed to be equal[c]	Designed to be equal[c]				
≥3-Dose group				4 (1-9)	4 (1-7)	3 (1-6)	4 (1-6)
2-Dose group				4 (1-9)	4 (1-6)	3 (1-6)	3 (1-7)
HIV status	Positive + negative	Positive + negative	Positive only	Positive + negative[d]	All[e]	All[e]	Positive + negative[f]
Malaria transmission[g]	Holoendemic	Holoendemic	Holoendemic[h]	Holoendemic	Hyperendemic	Hyperendemic	Holoendemic
Entomologic inoculation rate/y[i]	60-300	18-27	NA	NA	NA	NA	367
SP resistance, No. (% *DHPS K540E*)[j]	77 (14)[30]	76 (96)[31]	24 (46)[32]	88 (86)[33]	80 (0)[34]	9 (0)[9]	120 (46)[35]
Folic acid dose, mg/d	5	0.5	5	0.25	0.4	0.4	0.4
Insecticide-treated net coverage, No. (%)	148 (11)	105 (15)	114 (25)	530 (60)	40 (14)[36]	138 (17)	296 (37)
Random sequence generation	Not random	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
Sequence allocation	By day of visit	Inadequate	Adequate	Adequate	Adequate	Adequate	Adequate
Open label/placebo-controlled	Open label	Open label	Placebo	Open label	Open label	Open label	Open label
Assessor blinding birth weight	No	No	Yes	Yes	No	Yes	Yes
Loss to follow-up, No. (%)	478 (36)	143 (22)	68 (15)	86 (10)	259 (20)	73 (9)	56 (7)

Abbreviations: ANC, antenatal clinic; *DHPS*, dihydropteroate synthase; G1-G2, first and second pregnancies; HIV, human immunodeficiency virus; NA, not available.
[a] All information was provided by 2 of the coauthors (A.M., J.R.M.).
[b] Drug administration was provided as directly observed therapy in the home environment. However, because of logistic reasons, only 149 of the women (23%) in the 3-dose group received the third sulfadoxine-pyrimethamine dose and only 261 (41%) in the 2-dose group received a second sulfadoxine-pyrimethamine dose.
[c] Actual number of visits not reported, but the studies were designed to have identical antenatal care schedules in both groups.
[d] The HIV-negative group includes 81 women (41 in the ≥3-dose group) with unknown/undetermined HIV status.
[e] HIV screening and testing not conducted, but HIV prevalence in the general ANC population was 1.0% and 1.3% in the study sites in Burkina Faso[28] and Mali,[9] respectively.
[f] HIV screening and testing conducted, but HIV results were not available.
[g] Holoendemic: malaria transmission occurs all year long; hyperendemic: intense but with periods of no malaria transmission during the dry season.
[h] Transmission during the study period was reported to be lower than usual, described as "mild malaria transmission."
[i] The entomologic inoculation rate is a measure of malaria transmission intensity and is the number of infectious bites per person per unit of time (usually expressed per year). It is the product of the biting rate and the sporozoite rate.
[j] Sulfadoxine-pyrimethamine resistance data matched for time and location (≤100 km) and defined as the proportion of symptomatic children younger than 5 or 12 years carrying *DHPS K540E* mutations for sulfadoxine-pyrimethamine resistance, except for the studies by Diakite et al[9] in Mali and Lin et al[33] in Malawi, which were based on samples from women attending antenatal care before receiving their first dose of sulfadoxine-pyrimethamine. The No. represents the total number of samples tested in the matched study (denominator).

estimates and heterogeneity by removing one study at a time from the meta-analysis. We used $P<.05$ to indicate statistical significance (2-sided tests). Data were analyzed with Review Manager version 5.2, GradePro version 3.6, and Stata version 12.

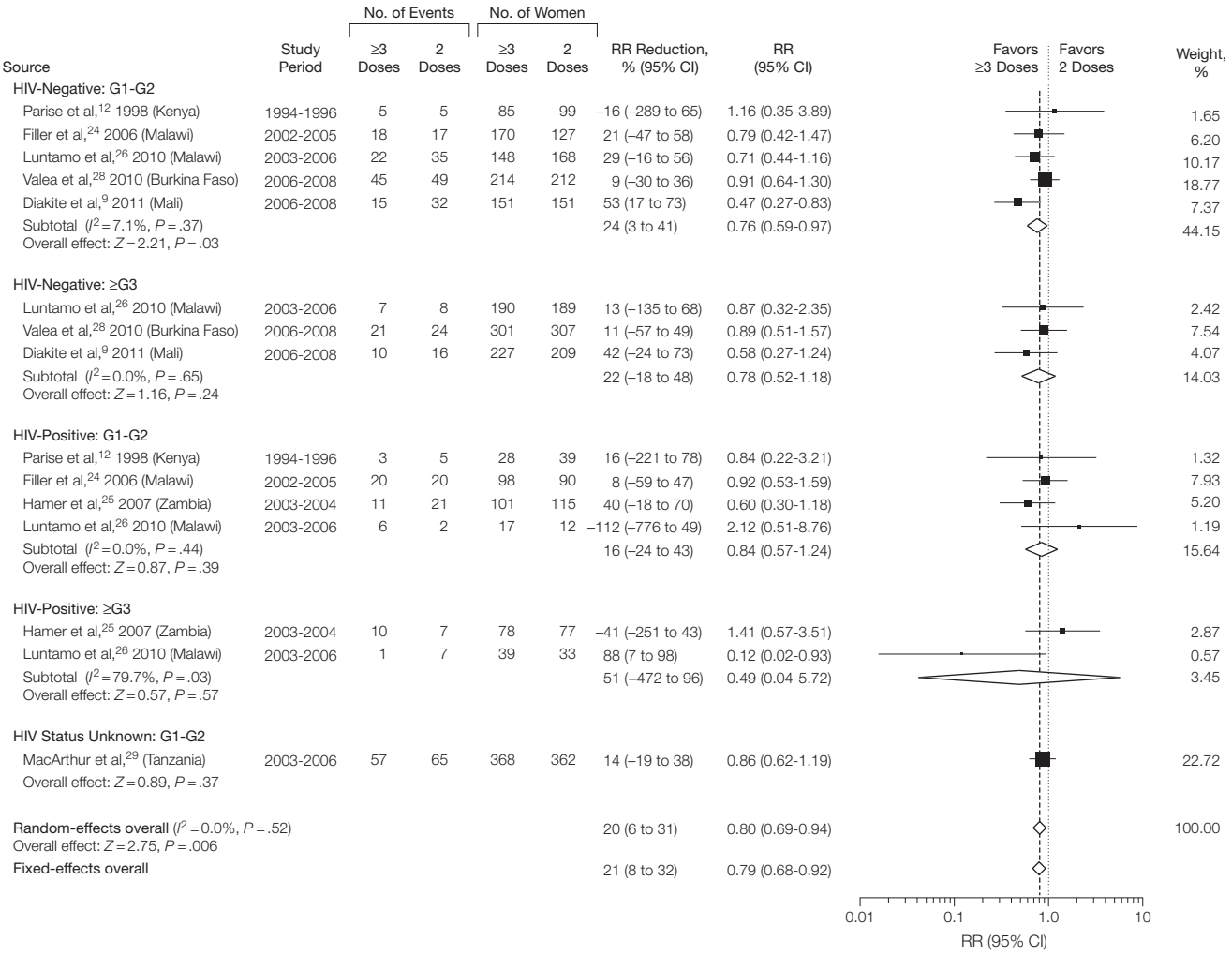
RESULTS

Studies and Outcomes

A total of 241 studies were screened, and 7 trials including a total of 6281 pregnancies were included (eFigure 1),[9,12,24-29] one of which was unpublished[29] (TABLE 1). Authors of all primary studies provided further unpublished information where available. Five trials compared monthly sulfadoxine-pyrimethamine against the standard 2-dose regimen and the remaining 2 compared 3- vs 2-dose intermittent preventive therapy during pregnancy with sulfadoxine-pyrimethamine.[9,28] Sulfadoxine-pyrimethamine intake was supervised in all trials.

Three trials in Kenya and Malawi involved both HIV-infected and uninfected women,[12,24,26] and 1 trial in Zambia involved HIV-infected women only.[25] In 3 other trials, the HIV status was unknown,[9,28,29] 2 of which were from areas with very low HIV prevalence among pregnant women (1% in Burkina Faso and 1.3% in Mali)[9,28]; results were therefore pooled with those of the HIV-negative women. The third trial from Tanzania[29] was conducted in an area with high HIV prevalence and

Figure 1. Meta-analysis of the Risk of Low Birth Weight in Trials Comparing the Standard 2-Dose vs 3 or More Doses of Intermittent Preventive Therapy During Pregnancy With Sulfadoxine-Pyrimethamine



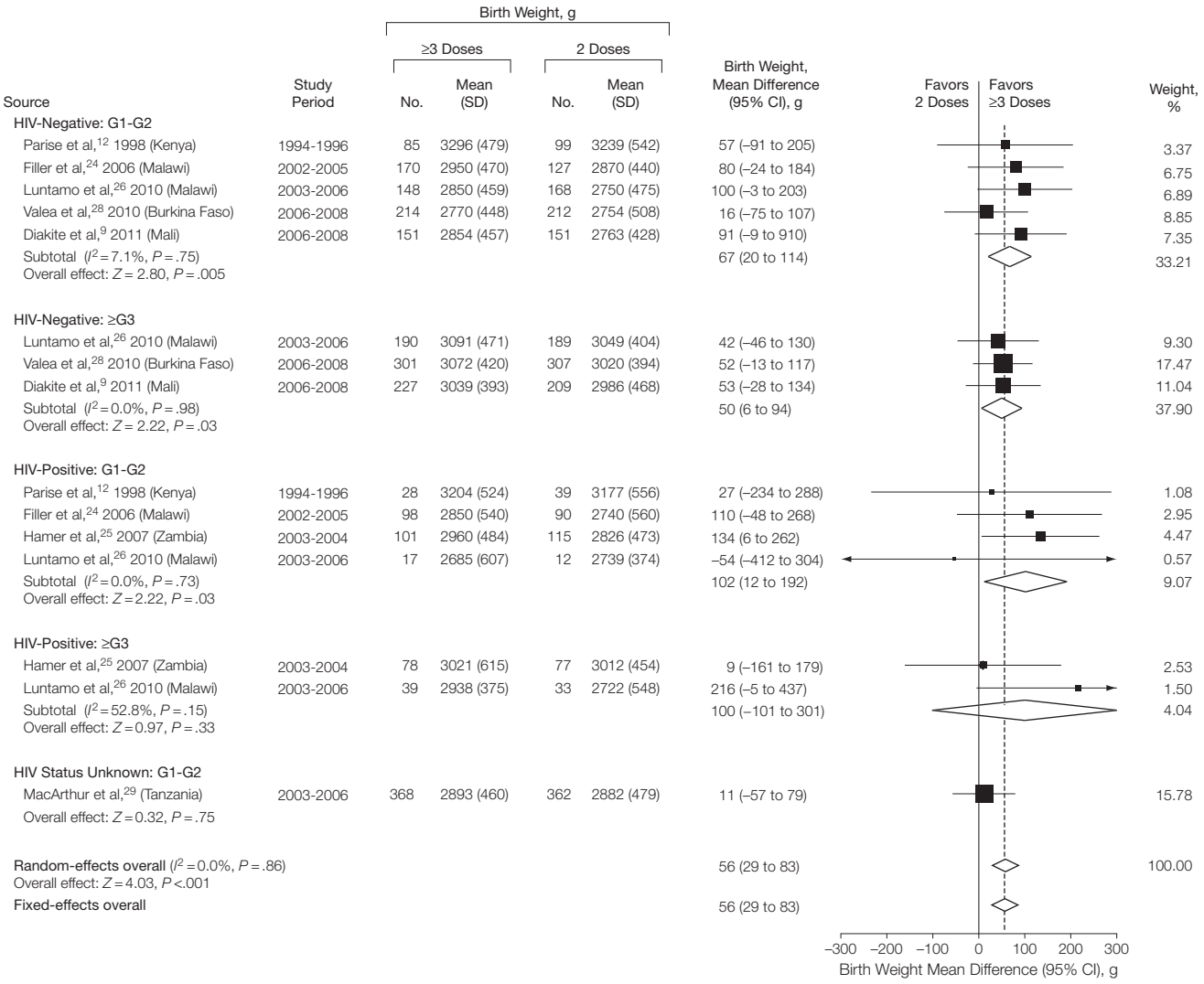
G1-G2 indicates first and second pregnancies; ≥G3, 2 or more previous pregnancies; HIV, human immunodeficiency virus; RR, relative risk. *P* values after the I^2 statistics represent the χ^2 test for heterogeneity. Dersimonian-Laird method used to calculate random-effects models; Mantel-Haenszel for fixed-effects models. Weights are from random-effects analysis. Data marker sizes indicate the weight applied to each study with random-effects meta-analysis. Test for subgroup differences: χ^2_4=0.62, P=.96, I^2=0.0%.

analyzed as a separate "HIV status unknown" stratum. Two of the 7 trials were considered of low quality (eFigure 2), including a trial in Burkina Faso, in which two-thirds of participants did not receive the intended regimen.[28] The other study was a quasi-randomized trial[12] conducted before the introduction of the Consolidated Standards of Reporting Trials (CONSORT) guidelines for clinical trials[37] (Table 1).

Primary Outcomes: Birth Weight

Women in the ≥3-dose group had fewer infants with LBW (random-effects model RR = 0.80; 95% CI, 0.69-0.94; $P = .006$; $I^2 = 0\%$) (FIGURE 1), corresponding to an RR reduction (RR reduction = 100% × [1 − RR]) of 20% (95% CI, 6-31). The absolute risk reduction was 33 per 1000 women (95% CI, 10-52), from a median risk of 167 per 1000 in the 2-dose group (assumed control-group risk) to 134 per 1000 in the ≥3-dose recipients (NNT = 31). The median birth weight in the 2-dose group was 2870 g (range, 2722-3239 g) and on average 56 g (95% CI, 29-83 g) higher in the ≥3-dose group (FIGURE 2, TABLE 2). Analyses by gravida and HIV subgroup showed that the mean difference in birth weight was statistically significant in HIV-negative women (random-effects mean

Figure 2. Meta-analysis of Mean Birth Weight in 7 Trials Comparing the Standard 2-Dose vs 3 or More Doses of Intermittent Preventive Therapy During Pregnancy With Sulfadoxine-Pyrimethamine



G1-G2 indicates first and second pregnancies; ≥G3, 2 or more previous pregnancies; HIV, human immunodeficiency virus status. *P* values after the I^2 statistics represent the χ^2 test for heterogeneity. Dersimonian-Laird method used for random-effects models; inverse-variance method used in the fixed-effects models. Weights are from random-effects analysis. Data marker sizes indicate the weight applied to each study with random-effects meta-analysis. Test for subgroup differences: $\chi^2_4 = 3.14$, $P = .53$, $I^2 = 0.0\%$.

difference = 58 g; 95% CI, 26-90 g), HIV-positive women (mean difference = 97 g; 95% CI, 22-172) (Table 2), G1-G2 women (mean difference = 57 g; 95% CI, 22-93 g) (eTable 1), and multigravida (mean difference = 53 g; 95% CI, 11-95 g) (eTable 2) (between-subgroup difference, $I^2 = 0\%$; $P = .53$) (Figure 2). The RR estimates for LBW, however, were significant only in HIV-negative women (RR = 0.77 [95% CI, 0.63-0.94] [Table 2]; assumed control-group risk = 106 per 1000; absolute risk reduction = 24 per 1000 [95% CI, 6-39]; NNT = 42) and G1-G2 women (RR = 0.80 [95% CI, 0.68-0.95] [eTable 1]; assumed control-group risk = 181 per 1000; absolute risk reduction = 36 per 1000 [95% CI, 9-58]; NNT = 28) but not in HIV-positive women (RR = 0.86 [95% CI, 0.53-1.39] [Table 2]; assumed control-group risk = 175 per 1000; absolute risk reduction = 24 per 1000 [95% CI, −68 to 82]; NNT = 42) or multigravida (RR = 0.79 [95% CI, 0.49-1.27] [eTable 2]; assumed control-group risk = 78 per 1000; absolute risk reduction = 16 per 1000 [95% CI, −21 to 40]; NNT = 63). The difference in the RR estimates between the subgroups was not significant (between-subgroup difference $I^2 = 0\%$; $P = .96$) (Figure 1). The results of fixed-effects models overall and by gravidity or HIV groups were mostly identical or very similar (eTable 3).

There was no evidence for publication bias after visual inspection of funnel plots or with the Harbord modified test for small-study effects ($P = .72$) (eFigure 3). Cumulative meta-analysis, ordered by publication date,

Table 2. Random-Effects Meta-analysis of Trials Comparing the Standard 2-Dose vs ≥3 Doses of Sulfadoxine-Pyrimethamine for Intermittent Preventive Therapy During Pregnancy by HIV Status

		2 Doses			≥3 Doses			Random-Effects Model			
	No. of Studies	No. Events	Total No.	ACR per 1000 or ACM (Range)[a]	No. Events	Total No.	CIR per 1000 or CIM (95% CI)[a]	Relative Risk (95% CI)[b]	ARR per 1000 or Mean Difference (95% CI)[c]	*P* Value[b]	I^2, %
Primary End Points											
Low birth weight											
HIV+	4	62	366	175 (91-222)	51	361	151 (93-243)	0.86 (0.53-1.39)	24 (−68 to 82)	.54	33
HIV−	5	186	1462	106 (42-231)	143	1486	82 (67-100)	0.77 (0.63-0.94)	24 (6 to 39)	.01	0
Unknown	1	65	362	180[d]	57	368	155 (112-214)	0.86 (0.62-1.19)	25 (−34 to 68)	.37	[d]
Overall	7	313	2190	167 (42-231)	251	2215	134 (115-157)	0.80 (0.69-0.94)	33 (10 to 52)	.006	0
Birth weight, g											
HIV+	4		366	2783 (2722-3177)		361	2880 (2805-2955)		97 (22 to 172)	.01	0
HIV−	5		1462	2928 (2750-3239)		1486	2986 (2954-3018)		58 (26 to 90)	<.001	0
Unknown	1		362	2882[d]		368	2893 (2825-2961)		11 (−57 to 79)	.75	[d]
Overall	7		2190	2870 (2722-3239)		2215	2926 (2899-2953)		56 (29 to 83)	<.001	0
Secondary End Points											
Maternal hemoglobin, g/dL											
HIV+	4		349	11.0 (9.7-11.4)		327	11.1 (10.9-11.4)		0.11 (−0.15 to 0.37)	.40	0
HIV−	5		1395	10.8 (10.2-11.6)		1461	11.0 (10.8-11.1)		0.15 (0.04 to 0.26)	.009	0
Unknown	1		344	11.1[d]		340	11.1 (10.8-11.4)		0 (−0.31 to 0.31)	1	[d]
Overall	7		2088	10.9 (9.7-11.6)		2128	11.0 (10.9-11.1)		0.13 (0.03 to 0.22)	.009	0
Maternal anemia, <11 g/dL											
HIV+	4	214	349	582 (333-795)	190	327	559 (506-623)	0.96 (0.87-1.07)	23 (−41 to 76)	.51	0
HIV−	5	665	1395	473 (269-660)	682	1461	459 (426-492)	0.97 (0.90-1.04)	14 (−19 to 47)	.37	0
Unknown	1	175	344	509[d]	152	340	448 (382-524)	0.88 (0.75-1.03)	61 (−15 to 127)	.11	[d]
Overall	7	1054	2088	509 (269-795)	1024	2128	484 (458-514)	0.95 (0.90-1.01)	25 (−5 to 51)	.10	0
Moderate/severe maternal anemia (<8, 7, or 6 g/dL)											
HIV+	2	7	124	0 (0-65)	3	135	0 (0-0)	0.60 (0.06-5.85)	0 (0 to 0)	.66	48
HIV−	4	38	1296	38 (9-63)	27	1376	27 (14-52)	0.70 (0.36-1.36)	11 (−14 to 24)	.29	34
Unknown	2[e]	25	776	32 (30-35)	21	771	27 (15-48)	0.85 (0.48-1.50)	5 (−16 to 17)	.57	0
Overall	6	70	2196	34 (0-65)	51	2282	25 (16-38)	0.73 (0.48-1.11)	9 (−4 to 18)	.14	15
Maternal parasitemia											
HIV+	4	51	338	112 (0-359)	13	328	29 (17-52)	0.26 (0.15-0.46)	83 (60 to 95)	<.001	0
HIV−	5	265	1407	104 (31-350)	234	1445	89 (77-105)	0.86 (0.74-1.01)	15 (−1 to 27)	.06	0
Unknown	1	7	351	20[d]	2	349	6 (1-27)	0.29 (0.06-1.37)	14 (−7 to 19)	.12	[d]
Overall	7	323	2096	92 (0-359)	249	2122	63 (48-82)	0.68 (0.52-0.89)	29 (10 to 44)	.005	47
Placental malaria											
HIV+	4	39	338	102 (0-256)	14	320	39 (21-70)	0.38 (0.21-0.69)	63 (32 to 81)	.001	0
HIV−	4	82	753	67 (0-201)	47	782	38 (26-55)	0.57 (0.39-0.82)	29 (12 to 41)	.003	9
Unknown	1	7	345	20[d]	4	344	11 (3-39)	0.57 (0.17-1.94)	9 (−19 to 17)	.37	[d]
Overall	6	128	1436	63 (0-256)	65	1446	32 (24-43)	0.51 (0.38-0.68)	31 (20 to 39)	<.001	0

(continued)

showed that a significant association with LBW emerged with the addition of new evidence from trials reported since 2010 (eFigures 4 and 5). Sensitivity analysis showed that after removal of both low-quality studies,[12,28] the point estimates for LBW and mean birth weight were RR=0.76 (95% CI, 0.61-0.93), I^2=16%; and mean difference=62 g (95% CI, 29-95 g), I^2=0%. Removal of any individual trial also had relatively little effect and pooled results remained statistically significant at $P<.05$ for all 7 analyses with fixed-effects models and at $P=.06$ with random-effects models (eFigures 6 and 7).

Secondary Outcomes

The median maternal hemoglobin level at term in the 2-dose group was 10.9 g/dL (range, 9.7-11.6 g/dL), and this was on average 0.13 g/dL higher (95% CI, 0.03-0.22 g/dL) in the ≥3-dose group (Table 2, eFigure 8). This group had a lower risk of moderate to severe maternal anemia, but this was evident only in G1-G2 women (RR=0.60 [95% CI, 0.36-0.99]; I^2=20%) (eTable 1), not overall (RR=0.73 [95% CI, 0.48-1.11]; I^2=15%) (Table 2 and eFigure 9). Women in the ≥3-dose group were approximately half as likely to have placental malaria (6 studies) compared with those in the 2-dose group, regardless of HIV status (RR=0.51 [95% CI, 0.38-0.68]; I^2=0%) (Table 2, eFigure 10), but this was evident only in G1-G2 women (RR=0.50 [95% CI, 0.35-0.70]; I^2=0%) (eTable 1), not in multigravida (RR=0.71 [95% CI, 0.26-1.95]; I^2=21%) (eTable 2). Similarly, ≥3 doses were associated with less peripheral (maternal) malaria (RR=0.68 [95% CI, 0.52-0.89]; I^2=47%) (Table 2), but this was evident in G1-G2 women only (RR=0.54 [95% CI, 0.37-0.80]; I^2=56%) (eTable 1), not in multigravida (RR=0.97 [95% CI, 0.75-1.24]; I^2=0%) (eTable 2). No difference in preterm delivery was detected (RR=0.95 [95% CI, 0.80-1.12]; I^2=35%) or in the number of stillbirths (RR=1.14 [95% CI, 0.85-1.55]; I^2=0%), miscarriages (RR=1.43 [95% CI, 0.88-2.33]; I^2=0%), or neonatal deaths (RR=0.88 [95% CI, 0.57-1.35]; I^2=0%) (Table 2).

Stratified Analysis for LBW and Mean Birth Weight

There was no clear correlation between resistance level and the strength of the association between treatment

Table 2. Random-Effects Meta-analysis of Trials Comparing the Standard 2-Dose vs ≥3 Doses of Sulfadoxine-Pyrimethamine for Intermittent Preventive Therapy During Pregnancy by HIV Status (continued)

		2 Doses			≥3 Doses			Random-Effects Model			
	No. of Studies	No. Events	Total No.	ACR per 1000 or ACM (Range)[a]	No. Events	Total No.	CIR per 1000 or CIM (95% CI)[a]	Relative Risk (95% CI)[b]	ARR per 1000 or Mean Difference (95% CI)[c]	*P* Value[b]	I^2, %
Secondary End Points											
Preterm delivery											
HIV+	3	130	331	306 (46-655)	113	340	278 (211-370)	0.91 (0.69-1.21)	28 (−64 to 95)	.51	32
HIV−	4	209	1479	107 (16-248)	191	1554	93 (72-122)	0.87 (0.67-1.14)	14 (−15 to 35)	.32	41
Unknown	2[e]	51	769	61 (21-102)	66	777	78 (55-111)	1.28 (0.90-1.82)	−17 (−50 to 6)	.17	1
Overall	7	390	2579	122 (16-655)	370	2671	116 (98-137)	0.95 (0.80-1.12)	6 (−15 to 24)	.52	35
Miscarriage											
HIV+	2	3	147	0 (0-30)	5	171	0 (0-0)	1.54 (0.38-6.28)	0 (0 to 0)	.55	[d]
HIV−	4	19	1515	0 (0-29)	28	1587	0 (0-0)	1.31 (0.64-2.70)	0 (0 to 0)	.46	20
Unknown	2[e]	5	809	6 (0-12)	9	809	11 (4-32)	1.80 (0.61-5.34)	−5 (−26 to 2)	.29	[d]
Overall	6	27	2471	0 (0-30)	42	2567	0 (0-0)	1.43 (0.88-2.33)	0 (0 to 0)	.15	0
Stillbirth											
HIV+	3	11	352	40 (0-56)	8	362	27 (11-70)	0.68 (0.27-1.74)	13 (−30 to 29)	.43	0
HIV−	4	44	1515	30 (15-53)	60	1587	40 (27-59)	1.33 (0.90-1.95)	−10 (−29 to 3)	.15	0
Unknown	2[e]	24	809	30 (25-34)	24	809	29 (13-68)	0.97 (0.42-2.27)	1 (−38 to 17)	.95	54
Overall	7	79	2676	30 (0-56)	92	2758	34 (26-46)	1.14 (0.85-1.55)	−4 (−16 to 4)	.38	0
Neonatal death[f]											
HIV+	2	10	137	77 (29-167)	6	160	39 (14-112)	0.51 (0.18-1.45)	38 (−35 to 63)	.21	0
HIV−	4	25	1472	19 (8-31)	32	1549	23 (13-39)	1.19 (0.69-2.05)	−4 (−20 to 6)	.54	0
Unknown	2[e]	14	796	18 (14-22)	7	800	8 (2-33)	0.47 (0.12-1.84)	10 (−15 to 16)	.28	37
Overall	6	49	2405	21 (8-167)	45	2509	18 (12-28)	0.88 (0.57-1.35)	3 (−7 to 9)	.55	0

Abbreviations: ACM, assumed control-group median; ACR, assumed control-group risk; ARR, absolute risk reduction (risk difference); CIM, corresponding intervention-group median; CIR, corresponding intervention-group risk; HIV, human immunodeficiency virus.

[a] ACR represents the observed median risk (range) (expressed per 1000 women) across the trials in the 2-dose group (the range is only provided to illustrate low- and high-risk populations, whereas the median risk is illustrative of a population with a moderate risk); the CIR (and 95% CI) is based on the assumed risk in ≥3 dose recipients, computed as ACR×RR (95% CI).[20] For the 2 continuous end points, the ACM represents the median birth weight or hemoglobin concentration in the 2-dose arm. The CIM values were computed as the ACM + mean difference (95% CI).

[b] Effect size, 95% CIs, and *P* values for the overall effect (last rows) and for each HIV-status subgroup were obtained from random-effects models and are adjusted for gravidity group (all estimates [G1-G2, ≥G3]) and HIV status (for last rows representing the overall effect) by using the independent subgroups as the unit of analysis.

[c] The ARR was calculated as the ACR×(1 − RR) and expressed per 1000 women.

[d] Range or heterogeneity cannot be estimated because the data contain only a single trial in the subgroup or no events occurred in 1 of the 2 included studies.[12]

[e] Results for the study by Parise et al[12] in Kenya were not reported by HIV status for these end points.

[f] Death of a live-born infant within the first 28 days of life. One study assessed early neonatal death only (death within 7 days of life).[29]

regimen and LBW or mean birth weight; the point estimates were similar in areas with less than 50% *DHPS*-K540E mutations (5 trials) and areas with 50% or more *DHPS*-K540E (2 trials) (eFigures 11 and 12). There was also no evidence that intensity of malaria transmission or the median number of sulfadoxine-pyrimethamine doses in the ≥3-dose group modified the association ($P > .17$ for all tests for subgroup differences). There was no clear difference in the association between the dose group and the risk of LBW or mean birth weight in the 2 trials that used high-dose folate supplementation (5 mg/d)[12,25] (which has since been contraindicated) vs the standard dose (0.25-0.5 mg/d). Three studies reported results stratified by insecticide-treated net use[9,26,29]; the associations with LBW and mean birth weight were statistically significant in the nonusers only. There was no evidence for an association with LBW in insecticide-treated net users (eFigures 11 and 12).

Adverse Events

The risks of neonatal icterus and congenital malformation were comparable between the groups, as were the number of adverse events in the mother. One study reported a case of Stevens-Johnson syndrome, which occurred in the 3 or more dose group, 3 weeks after the first dose (**Table 3**).[25]

COMMENT

This meta-analysis of 7 trials demonstrated that regimens of intermittent preventive therapy during pregnancy consisting of ≥3 doses of sulfadoxine-pyrimethamine were well tolerated and, compared with the standard 2-dose regimen, were associated with higher mean birth weight, less LBW, and less placental and maternal malaria at delivery. The ≥3-dose regimen was also associated with slightly higher mean maternal hemoglobin levels at term overall, but a significant association with moderate to severe maternal anemia was observed only in G1-G2 women. The associations with birth weight were consistent across trials despite variations in study design, malaria endemicity, and the degree of sulfadoxine-pyrimethamine resistance. Although the number of trials was limited, there was no suggestion of publication or other small-study bias. There was also no suggestion that the results were affected by the weight of a single influential study. Two of the trials were classified as low quality, but sensitivity analysis indicated that their effect on the overall pooled estimate for LBW was minor. The consistency of these findings across the trials suggests the results are generalizable.

Although the summary point estimates of the association with mean birth weight were modest (56-g difference overall and 67 g among HIV-negative G1-G2 women), these were associated with clinically relevant changes in the risk of LBW, particularly among HIV-negative G1-G2 women (RR reduction = 25%) (eTable 1). These estimates were comparable to that reported in previous studies for 2-dose intermittent preventive therapy during pregnancy relative to none (mean difference = 79 g; RR reduction = 29%) and for insecticide-treated nets alone (mean difference = 55 g; RR reduction = 23%).[7,38] The magnitude of the observed association is remarkable, given that approximately 28% of women were protected by insecticide-treated nets in these 7 trials and considering that the control group benefited from protection of the 2-dose intermittent preventive therapy during pregnancy with sulfadoxine-pyrimeth-

Table 3. Summary of Adverse Events in Women and Neonates After Intermittent Preventive Therapy During Pregnancy With ≥3 Doses vs 2 Doses of Sulfadoxine-Pyrimethamine During Pregnancy

	Sulfadoxine-Pyrimethamine Treatment		No./No. (%)						
			Neonatal Icterus		Congenital Abnormalities		Maternal Drug Reaction		
Source	No. of Courses	No. of Women	≥3 Doses	2 Doses	≥3 Doses	2 Doses	≥3 Doses	2 Doses	Severe Skin Reactions
Parise et al,[12] 1998	2276	1086[a]	60/431 (14)	69/432 (15)	Not reported		7/661 (1.4)	14/680 (2.3)	None observed[b]
Filler et al,[24] 2006	1734	641[a]	0.4%[c]		Not reported		<1%[c]		None observed
Hamer et al,[25] 2007	1039	456	1/189 (0.5)	0/198 (0)	Not reported		1.13 (0.56 to 2.18)[d]		1 Case reported in the monthly group[e]
Luntamo et al,[26] 2010	2603	877	Not reported		3/443 (0.7)	4/439 (0.9)	Not reported		Not reported
Valea et al,[28] 2010	2213	1296	Not reported		Not reported		Not reported		Not reported
Diakite et al,[9] 2011	1997	814	11/400 (2.7)	10/383 (2.5)	1/400 (0.3)	3/383 (0.8)	0/413 (0)	0/401 (0)	None observed
McArthur et al[29]	1692	799	14/272 (5.1)	21/290 (7.2)	5/383 (1.3)	7/384 (1.8)	23/399 (5.7)[f]	28/400 (6.7)[f]	None observed
Relative risk (95% CI)			0.87 (0.66 to 1.14)		0.65 (0.28 to 1.50)		0.73 (0.46 to 1.15)		
I^2 (95% CI), %			0 (0 to 61)		0 (0 to 53)		0 (0 to 0)		
P value for heterogeneity			.76		.80		.38		

[a] Reported only for women followed up prospectively.
[b] In 193 treatment episodes in 94 HIV-positive women and 502 treatment episodes in 230 HIV-negative women. Cases were assessed during the study but not observed by investigators, but 2 of 94 HIV-positive (2%) and 0 of 230 HIV-negative women had sulfadoxine-pyrimethamine withheld due to adverse drug reactions (mild rash or oral lesions).
[c] Reported only for all groups pooled, but no statistical difference was observed between treatment groups.
[d] Numerator and denominators were not reported.
[e] The case of Stevens-Johnson syndrome reported in the monthly arm occurred 3 weeks after the first dose of sulfadoxine-pyrimethamine.
[f] Maternal drug reactions collected from the first dose (enrollment) to the last dose, including diarrhea, rash, weakness, seizures, sleepiness, and difficulty walking.

amine. The association mainly reflects an association with fetal growth, rather than with preterm delivery, and indicates that more complete protection in the second and third trimesters, including the last 6 to 10 weeks of pregnancy, may be pivotal for fetal growth. This result is consistent with observations in healthy pregnancies, which show that of the total fetal weight gain, 28% and 55% of it occurs during the last 6 and 10 weeks of pregnancy, respectively.[39]

Although the lack of heterogeneity across the sulfadoxine-pyrimethamine resistance range is encouraging, it does not imply that sulfadoxine-pyrimethamine efficacy is unaffected at higher levels of resistance. A possible explanation is that the extra doses compensate for any reductions in efficacy of the 2-dose regimen resulting from a progressive decrease of the duration of posttreatment prophylaxis.

The association with placental infections is an expected outcome because the 3 or more dose group received their last dose on average 1 month closer to delivery and is likely to reflect clearance of existing infections near term and prevention of new infections by the extra period of prophylaxis. However, the association with mean birth weight among multigravida was unexpected because most multigravida in endemic countries have acquired a pregnancy-specific protective immunity during exposures in previous pregnancies. Overall, the evidence for a beneficial association in multigravida was weak, and the finding in this study may therefore reflect a chance observation (eg, because of multiple comparisons) or mechanisms other than the prevention of malaria. Although the point estimates for LBW (RR reduction 21%) and placental malaria (RR reduction 29%) were in the same direction as those observed in primigravida and secundigravida, none were statistically significant and there was no suggestion that ≥3 doses were associated with less maternal malaria or moderate to severe anemia. On the other hand, the lack of significant association with LBW may reflect lack of power because only 4 of the 7 studies included multigravida.

Our meta-analysis has some limitations. First, although all trials were designed to standardize the number of visits and antenatal care (eg, hematinic supplementation) between the 2 groups, in one trial in Tanzania the women in the ≥3-dose group had on average 1 extra visit compared with the 2-dose group and thus potentially better antenatal care.[29] However, exclusion of this study in the sensitivity analysis did not change the conclusion (eFigures 6 and 7). Second, only 1 of the 7 trials was placebo controlled, which may have biased the results and affected some outcomes because of lack of expectations in a 2-dose group or differential behaviors across intervention groups. We did not use blinding in the selection, evaluation, and data abstraction phases, and because the authors were familiar with all included studies, this could have introduced bias.[40] Third, none of the trials were conducted in regions where additional *DHFR* 164L or *DHPS* 581G mutations are prevalent, as reported from parts of Rwanda, Uganda, and northern Tanzania, conferring the highest level of sulfadoxine-pyrimethamine resistance.[18,41-43] Last, only 3 trials reported results stratified by insecticide-treated net use, limiting our evaluation of the potential modifying role of insecticide-treated nets. In this smaller subgroup of studies, significant associations with LBW and mean birth weight were observed among the nonusers of insecticide-treated nets only, consistent with results of previous evaluations of 2-dose intermittent preventive therapy during pregnancy against placebo.[15,44,45]

Only 1 serious cutaneous reaction was reported in the current meta-analysis involving 13 554 sulfadoxine-pyrimethamine treatments among 6281 pregnancies, and this occurred in an HIV-positive woman 3 weeks after she received her first dose of sulfadoxine-pyrimethamine for intermittent preventive therapy during pregnancy.[25] We found no indication that more frequent dosing (ie, resulting in doses administered closer to delivery) was associated with increased risk of neonatal jaundice, the main safety signal of interest in neonates. Sulfonamides have the potential to displace unconjugated bilirubin from albumin, which could increase a newborn's risk of kernicterus if received near delivery. Our observations, combined with the evidence reviewed by Peters et al[44] from the experience with sulfonamides for rheumatic fever prophylaxis, urinary tract infections, and congenital toxoplasmosis (which involve higher doses and prolonged use of sulfadoxine-pyrimethamine), suggest that concerns regarding kernicterus should not restrict the use of monthly sulfadoxine-pyrimethamine for intermittent preventive therapy during pregnancy. There was no indication that ≥3-dose regimens increased or reduced the risk of stillbirth or neonatal death. The risk of spontaneous miscarriages in G1-G2 women was higher among the 3-dose group (RR=1.78, P=.046 with fixed-effects models and RR=1.75, P=.06 with random-effects models). These miscarriages, however, were not associated with the third dose because in 3 of the 4 trials that contributed 80% of the study weight, they occurred before 28 weeks of gestation when the third dose had not yet been provided.[9,24,28] In the fourth trial, the risk of miscarriage was 2.0% with a monthly regimen, higher than the 1.1% in the 2-dose group but similar to the 2.3% in a third control group consisting of women randomized to passive case detection only instead of intermittent preventive therapy during pregnancy.[12]

Since the strategic framework for the control of malaria in pregnancy in sub-Saharan Africa was first developed, at least 3 doses of sulfadoxine-pyrimethamine for intermittent preventive therapy during pregnancy has been recommended by WHO for HIV-infected women or for all women in high-HIV-prevalence areas (>10%) where screening for HIV is not conducted. Some countries, such as Cameroon,[45] Ghana, Zambia, and Zimbabwe, selected 3

doses of sulfadoxine-pyrimethamine in their policy for all pregnant women, but most other countries, including many high-HIV-prevalence countries, implemented the 2-dose regimen and use cotrimoxazole for HIV-infected women.[14] However, more recently other countries, including Kenya and Malawi, implemented a monthly regimen among HIV-negative women mainly because of concerns about sulfadoxine-pyrimethamine resistance and for pragmatic reasons to minimize the risk for missed opportunities to deliver a second dose[46] and to achieve better alignment with WHO's focused antenatal care schedule (a goal-oriented antenatal care approach consisting of 4 visits providing essential evidence-based interventions). In southern Malawi, this has resulted in a marked increase in the uptake of 2 or more doses of sulfadoxine-pyrimethamine.[47]

Our cumulative meta-analysis showed that, with the accumulation of results from the 4 most recent trials reported since 2010, evidence has emerged that 3-dose or monthly sulfadoxine-pyrimethamine for intermittent preventive therapy during pregnancy was associated with a higher birth weight and lower risk of LBW than the standard 2-dose regimens among pregnant women in sub-Saharan Africa. These data provide support for the new WHO recommendation that intermittent preventive therapy during pregnancy with sulfadoxine-pyrimethamine be provided at each scheduled focused antenatal-care visit in the second and third trimesters in all settings in which intermittent preventive therapy during pregnancy with sulfadoxine-pyrimethamine is recommended.[48] Future research should focus on how best to implement the updated WHO guidelines for intermittent preventive therapy during pregnancy with sulfadoxine-pyrimethamine[48] and specifically their integration with focused antenatal care. Continued monitoring of the association between population-level sulfadoxine-pyrimethamine resistance and the effectiveness of intermittent preventive therapy during pregnancy is required.

Author Affiliations: Liverpool School of Tropical Medicine, Liverpool, United Kingdom (Drs Kayentao, Garner, van Eijk, and ter Kuile); Malaria Research and Training Centre, Department of Epidemiology of Parasitic Diseases, Faculty of Medicine, Pharmacy and Dentistry, University of Bamako, Bamako, Mali (Drs Kayentao and Doumbo); Malaria Research Unit, Medical Research Council, Overport, South Africa (Ms Naidoo); London School of Hygiene and Tropical Medicine, London, United Kingdom (Dr Roper); Ifakara Health Research and Development Centre, Dar es Salaam, Tanzania (Dr Mulokozi); Malaria Branch, Centers for Disease Control and Prevention, Atlanta, Georgia (Dr MacArthur); and the Department of International Health, University of Tampere School of Medicine, Tampere, Finland (Drs Luntamo and Ashorn).

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Study concept and design: Kayentao, Garner, ter Kuile.
Acquisition of data: Kayentao, Garner, van Eijk, Naidoo, Roper, Mulokozi, MacArthur, Luntamo, Ashorn, Doumbo, ter Kuile.
Analysis and interpretation of data: Kayentao, Garner, van Eijk.
Drafting of the manuscript: Kayentao, Garner, ter Kuile.
Critical revision of the manuscript for important intellectual content: Kayentao, Garner, van Eijk, Naidoo, Roper, Mulokozi, MacArthur, Luntamo, Ashorn, Doumbo, ter Kuile.
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