

# Effect of Sulfadoxine-Pyrimethamine Resistance on the Efficacy of Intermittent Preventive Therapy for Malaria Control During Pregnancy

## A Systematic Review

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**I**N MALARIA-ENDEMIC REGIONS, THE burden of disease is primarily in young children and pregnant women. Women are particularly vulnerable to the adverse effects of malaria during their first and second pregnancies.<sup>1</sup> Approximately 50 million women living in malaria-endemic areas become pregnant each year, half in areas of sub-Saharan Africa with stable *Plasmodium falciparum* transmission. In these regions, strategies to control malaria during pregnancy rely on case management of malaria illness and anemia, and a package of preventive measures that consists of insecticide-treated nets (ITNs) and intermittent preventive therapy (IPT) with sulfadoxine-pyrimethamine.<sup>1</sup>

In the mid 1990s, IPT replaced weekly chloroquine prophylaxis as the drug-based strategy for the prevention of malaria during pregnancy and has now been adopted by almost all malaria-endemic countries in Africa. Intermittent preventive therapy during pregnancy consists of administration of treatment doses of an efficacious antimalarial drug given at predefined intervals at least 1 month apart, regardless of the presence of malaria parasitemia at the time of treatment. Intermittent preventive therapy during pregnancy provides intermittent clearance or suppression of existing asymptomatic infections from the

**Context** In malaria-endemic regions, strategies to control malaria during pregnancy rely on case management of malaria illness and anemia, and preventive measures such as insecticide-treated nets and intermittent preventive therapy (IPT).

**Objective** To determine the effect of increasing resistance to sulfadoxine-pyrimethamine on the efficacy of IPT during pregnancy in Africa.

**Data Sources and Study Selection** The 6 databases of MEDLINE, EMBASE, SCOPUS, LILACS, Cochrane CENTRAL, and the trial register and bibliographic database of the Malaria in Pregnancy Library were searched for relevant studies regardless of language, published between 1966 and December 2006. The reference lists of all trials identified were searched and researchers were contacted about relevant data. Nine trials of IPT with sulfadoxine-pyrimethamine during pregnancy in Africa were identified and matched by year and location with treatment studies of sulfadoxine-pyrimethamine among symptomatic children.

**Data Extraction** Data on the efficacy of IPT with sulfadoxine-pyrimethamine on placental and peripheral malaria, birth weight, and hemoglobin level/anemia were independently abstracted by 2 investigators. Sulfadoxine-pyrimethamine resistance was defined as the proportion of total treatment failures in symptomatic children by day 14.

**Data Synthesis** Four trials compared 2-dose IPT with sulfadoxine-pyrimethamine to case management or placebo in women during their first or second pregnancy. The IPT reduced placental malaria (relative risk [RR], 0.48; 95% CI, 0.35-0.68), low birth weight (RR, 0.71; 95% CI, 0.55-0.92), and anemia (RR, 0.90; 95% CI, 0.81-0.99). The effect did not vary by sulfadoxine-pyrimethamine resistance levels (range, 19%-26%). Efficacy of IPT with sulfadoxine-pyrimethamine was lower among women using insecticide-treated nets. Three trials compared 2-dose with monthly IPT with sulfadoxine-pyrimethamine during pregnancy. Among HIV-positive women in their first or second pregnancy, monthly IPT resulted in less placental malaria (RR, 0.34; 95% CI, 0.18-0.64) and higher birth weight (mean difference, 112 g; 95% CI, 19-205 g) over the range of sulfadoxine-pyrimethamine resistance tested (8%-39%). Among HIV-negative women, there was no conclusive additional effect of monthly dosing (2 trials; 24% and 39% resistance).

**Conclusions** In areas in which 1 of 4 treatments with sulfadoxine-pyrimethamine fail in children by day 14, the 2-dose IPT with sulfadoxine-pyrimethamine regimen continues to provide substantial benefit to HIV-negative semi-immune pregnant women. However, more frequent dosing is required in HIV-positive women not using cotrimoxazole prophylaxis for opportunistic infections.

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placenta (the treatment effect) and slowly eliminated drugs, such as sulfadoxine-pyrimethamine, may prevent new infections from occurring for several weeks

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by maintenance of suppressive drug levels (the prophylactic effect). In areas of Africa with stable *P. falciparum* malaria transmission, the World Health Organization (WHO) recommends that at least 2 curative doses of sulfadoxine-pyrimethamine be given during the second and third trimester of pregnancy.<sup>1</sup> More frequent dosing is recommended for women with the human immunodeficiency virus (HIV) who are not taking cotrimoxazole for prophylaxis of opportunistic infections.

Sulfadoxine-pyrimethamine is the only antimalarial drug currently used for IPT during pregnancy.<sup>1</sup> However, sulfadoxine-pyrimethamine efficacy for treatment of symptomatic malaria in children has declined in the last 5 years, raising concerns about its longevity for IPT during pregnancy. Although it is not fully understood how IPT works, it is likely that the prophylactic effect of sulfadoxine-pyrimethamine, as opposed to the treatment effect alone, plays an important role.<sup>2</sup>

Resistance to sulfadoxine-pyrimethamine results from mutations in the dihydrofolate reductase (*DHFR*) gene and the dihydropteroate synthetase (*DHPS*) gene of the parasite. With increasing drug resistance, the minimum inhibitory concentration at which parasite growth is inhibited increases and the time window for drug concentrations to fall below these levels shortens. This results in a progressive shortening of the duration of the suppressive prophylactic effect posttreatment. Parasites with triple *DHFR* mutations have an approximate 1000-fold reduction in susceptibility to pyrimethamine, which translates into a reduction in the duration of posttreatment prophylaxis of 1 month, compromising the efficacy of the 2-dose regimen, which can have a 3-month interval between doses.<sup>2</sup>

Countries with moderate to high levels of sulfadoxine-pyrimethamine resistance urgently require guidance on whether to continue using sulfadoxine-pyrimethamine for IPT during pregnancy. This requires an improved understanding of the relationship between drug resistance and its implications for

IPT during pregnancy. In vivo drug resistance in a population is typically monitored by assessing the treatment response in symptomatic children aged 6 months to almost 5 years (4 years and 11 months), who have acquired little or limited immunity.<sup>3-5</sup> Pregnant women in stable malaria transmission areas have significant levels of acquired immunity to malaria and when infected often have no or few symptoms and low parasite densities. Their response to antimalarial treatment is therefore much better than that in symptomatic young children. A recent meta-analysis illustrated that pregnant women are on average half as likely to fail antimalarial treatment with chloroquine or sulfadoxine-pyrimethamine than children.<sup>6</sup>

We evaluated published and unpublished data to assess the efficacy of IPT with sulfadoxine-pyrimethamine during pregnancy as a function of sulfadoxine-pyrimethamine resistance in the population in Africa. The degree of sulfadoxine-pyrimethamine resistance was determined using the therapeutic response to sulfadoxine-pyrimethamine in children with acute falciparum malaria obtained from concomitant treatment studies conducted in the same time frame and country.

There is an urgent need to explore alternative drugs that can be used for IPT during pregnancy. Such studies are planned or ongoing but the results will not be available for several years.<sup>7</sup> In this review, we therefore also explored whether increasing the frequency of IPT with sulfadoxine-pyrimethamine during pregnancy could provide a temporary respite in areas with increasing sulfadoxine-pyrimethamine resistance by reviewing trials that compared the conventional 2-dose IPT regimens with sulfadoxine-pyrimethamine during pregnancy with monthly regimens.

## METHODS

### Study Eligibility Criteria and Identification of Trials

The 6 databases of MEDLINE, EMBASE, SCOPUS, LILACS, Cochrane CENTRAL, and the trial register and bibliographic database of the Ma-

larial in Pregnancy Library<sup>8</sup> were searched using the strategy of the Cochrane Infectious Diseases Group<sup>9</sup> to identify potentially relevant IPT trials regardless of language, which were published between 1966 and December 2006, using the Medical Subject Headings *malaria, pregnant, prophylaxis, Africa, intermittent, treatment, sulfadoxine, pyrimethamine, efficacy, and resistance*. The reference lists of all trials identified also were searched and researchers in the field were contacted to identify unpublished data. To obtain relevant treatment studies in children, we used the search terms *sulfadoxine, pyrimethamine, malaria, efficacy, resistance, and Africa*.

All trials in sub-Saharan Africa that randomized pregnant women to IPT with sulfadoxine-pyrimethamine and a control group were included. The control group in the included studies could consist of either a placebo or current standard of care, which could include treatment of incident malaria cases only (ie, no preventive intervention), or weekly chloroquine prophylaxis. In studies investigating the efficacy of monthly IPT with sulfadoxine-pyrimethamine during pregnancy, the comparator group was a standard 2-dose IPT with sulfadoxine-pyrimethamine during pregnancy. To estimate the degree of in vivo sulfadoxine-pyrimethamine resistance in the population at the time of the trial of IPT with sulfadoxine-pyrimethamine during pregnancy, treatment studies involving symptomatic children were identified using a similar search strategy.

### Data Extraction

For the trials of IPT with sulfadoxine-pyrimethamine during pregnancy, we recorded information on the recruitment and randomization procedures, supervision of study medications, loss to follow-up, description of the blood test examination, bed net use, number of previous pregnancies, and HIV status.

An eligible treatment study in children was considered a match with a trial of IPT with sulfadoxine-pyrimethamine during pregnancy if it was con-

ducted within the same country and during the same period (maximum of 2 years difference).<sup>6</sup> From the matching treatment studies, we recorded loss to follow-up, inclusion and exclusion criteria, and the response to treatment with sulfadoxine-pyrimethamine.

The quality of each IPT during pregnancy trial was assessed based on the methods for the generation of the allocation sequence and concealment, the degree of blinding,<sup>10</sup> and the degree of loss to follow-up reported for the primary end point. This was scored using a modified version of the Jadad scale.<sup>11</sup> Blinding of the quality assessment could not be achieved because the reviewers were familiar with all of the included studies.

### Data Analysis

The relationship between the effect of IPT with sulfadoxine-pyrimethamine during pregnancy and drug resistance was assessed using 2 different approaches: the comparison with the control group and the proportional reduction of peripheral parasitemia within each IPT with sulfadoxine-pyrimethamine treatment group.

In the first set of analyses, efficacy of IPT with sulfadoxine-pyrimethamine during pregnancy was expressed as a relative risk (RR) and compared with the control groups. Placental malaria, the most malaria-specific end point, was the primary outcome. It was used as a primary outcome in all but 2 trials. Secondary outcome measures included maternal peripheral parasitemia at delivery, low birth weight, mean birth weight, all-cause maternal anemia, and mean hemoglobin level.

These analyses were categorized into 3 main groups according to the control group: (1) studies that compared 2-dose IPT with sulfadoxine-pyrimethamine during pregnancy with chloroquine prophylaxis, (2) studies that compared 2-dose IPT with sulfadoxine-pyrimethamine during pregnancy with placebo or case management, and (3) studies that compared 2-dose IPT with 3 or more doses of IPT with sulfadoxine-pyrimethamine during pregnancy

(monthly IPT regimen). The relationship between efficacy of IPT and the degree of drug resistance was then assessed by comparing the protective efficacy of IPT during pregnancy as a function of the treatment failure rate with sulfadoxine-pyrimethamine observed in children. Assessment of the treatment response in children was based on standard WHO criteria and defined as the proportion of total treatment failure by day 14, which combines clinical and parasitological failure.<sup>4,5</sup>

We used fixed-effects models and assessed heterogeneity by the  $I^2$  test with values greater than 50% representing significant heterogeneity using RevMan version 4.2 (Cochrane Collaboration's Information Management System, Oxford, England).<sup>12</sup> When heterogeneity between studies was found to be significant, pooled estimates were based on random-effect models.<sup>13</sup>

The second analytical approach expressed efficacy of IPT with sulfadoxine-pyrimethamine during pregnancy as the reduction in the proportion of women with peripheral parasitemia at delivery compared with the proportion at enrollment. This was assessed within each IPT group (ie, not relative to a control group). For example, if 60% of the women in the 2-dose IPT group were parasitemic at enrollment and only 20% of the group were parasitemic at delivery this was considered as a 67% reduction in peripheral parasitemia. This method was used to combine results from all trials regardless of the type of control group used and allowed assessment of the impact of drug resistance over a wider range of sulfadoxine-pyrimethamine resistance.

Analyses were subdivided a priori by 2 gravidity groups: first and second pregnancy, who are most at risk for and benefit most from successful prevention of malaria; and third or more pregnancies, henceforth referred to as multiple previous pregnancies. The analysis of 2-dose vs monthly IPT with sulfadoxine-pyrimethamine was stratified by HIV status because HIV is known to moderate the effect of IPT during pregnancy.<sup>14</sup> We had hoped to explore heterogeneity by

gravidity but data were insufficient because almost all studies were conducted only among women during their first and second pregnancies.

## RESULTS

### IPT During Pregnancy Studies

Nine randomized controlled trials of IPT with sulfadoxine-pyrimethamine during pregnancy were identified (TABLE 1). Two of these trials compared IPT with sulfadoxine-pyrimethamine during pregnancy with weekly chloroquine prophylaxis<sup>15,29</sup>; 5 trials compared IPT with sulfadoxine-pyrimethamine with placebo or case management<sup>17,21,24,27,30</sup>; and 3 trials compared IPT with 2 doses of sulfadoxine-pyrimethamine with monthly IPT (ie,  $\geq 3$  doses)<sup>17,32</sup> (D. H. Hamer, MD, unpublished data, 2006), 1 of which also contained a case management group (ie, 3 groups).<sup>17</sup> One trial used a factorial design with ITNs in which women were allocated to receive IPT during pregnancy, placebo IPT during pregnancy, ITNs plus IPT during pregnancy, or ITNs plus placebo IPT during pregnancy.<sup>24</sup> Seven of the 9 trials restricted enrollment to women during their first or second pregnancy. One trial recruited women of all pregnancy order (D. H. Hamer, MD, unpublished data, 2006), and another recruited only women who had at least 1 previous pregnancy (multigravida).<sup>30</sup> One study recruited HIV-positive women only (D. H. Hamer, MD, unpublished data, 2006). The HIV-positive women in these trials were not receiving cotrimoxazole prophylaxis. In all trials of sulfadoxine-pyrimethamine, intake was supervised. Placental malaria was the primary outcome in 7 of the 8 trials that included its assessment.

Two trials were considered low quality (22%). These 2 studies were conducted in the early and mid 1990s,<sup>15,17</sup> before the introduction of the Consolidated Standards for Reporting of Trials (CONSORT) guidelines for clinical trials in 1996.<sup>35</sup> One compared 2-dose IPT with sulfadoxine-pyrimethamine during pregnancy with chloroquine prophylaxis, and the other trial compared 2-dose IPT with sulfadoxine-pyrimethamine during pregnancy with monthly IPT and with case management (3 groups) (Table 1).

**Table 1.** Characteristics of Included Randomized Controlled Trials

Trial of Pregnant Women; Location	No. of Women	Trial Quality Score; Comments*	Comparison of Regimens During Pregnancy	Bed Net, %	EIR, per Year	Matched Treatment Studies in Symptomatic Children	Resistance to Sulfadoxine-Pyrimethamine, %†
Schultz et al, <sup>15</sup> 1994; Malawi	109‡	1; Allocation to treatment group based on day of clinic attendance, not blinded, low follow-up	2-dose IPT with sulfadoxine-pyrimethamine vs chloroquine prophylaxis	Unknown	18-27	Nwanyanwu et al <sup>16</sup>	5.5
Parise et al, <sup>17</sup> 1998; Kenya	672‡	1; Allocation to treatment group based on day of clinic attendance, not blinded, low follow-up	2-dose IPT with sulfadoxine-pyrimethamine vs case management; 2-dose IPT with sulfadoxine-pyrimethamine vs monthly IPT with sulfadoxine-pyrimethamine	ITN: 11; Any net: 39 in 1997-2000 <sup>18</sup>	60-300	Van Dillen et al <sup>19</sup> Omar et al <sup>20</sup>	23.8§
Shulman et al, <sup>21</sup> 1999; Kenya	401	9; Adequate generation of allocation sequence and concealment, placebo-controlled, adequate follow-up	IPT vs placebo; No. of doses dependent on gestational age at enrollment (64% received 2 doses)	ITN: 26	10	Adjuik et al <sup>22</sup> Amukoye et al <sup>23</sup>	19.3§
Njagi, <sup>24</sup> 2002 and Njagi et al, <sup>25</sup> 2003; Kenya	624‡	7; Adequate generation of allocation sequence, inadequate allocation concealment, placebo-controlled, moderate follow-up	2-dose IPT with sulfadoxine-pyrimethamine vs placebo	ITN: 50¶	60-300	Obonyo et al <sup>26</sup>	25.5
Challis et al, <sup>27</sup> 2004; Mozambique	244‡#	6; Adequate generation of allocation sequence, inadequate allocation concealment, placebo-controlled, low follow-up	2-dose IPT with sulfadoxine-pyrimethamine vs placebo	ITN: Unknown; Any net: 15	12	Abacassamo et al <sup>28</sup>	21.4
Kayentao et al, <sup>29</sup> 2005; Mali	722‡	6; Adequate generation of allocation sequence and concealment, open label, no assessor blinding, adequate follow-up	2-dose IPT with sulfadoxine-pyrimethamine vs chloroquine prophylaxis	Unknown	17-150	MRTC/CDC (unpublished)	2.9
Mbaye et al, <sup>30</sup> 2006; Gambia	2002**	8; Adequate generation of allocation sequence and concealment, placebo-controlled, moderate follow-up	IPT vs placebo; No. of doses dependent on gestational age at enrollment (58% received >2 doses)	ITN: 61; Any net: 78	10	Dunyo et al <sup>31</sup>	9.5
Filler et al, <sup>32</sup> 2006; Malawi	498‡	6; Adequate generation of allocation sequence and concealment, open label, assessor blinded, moderate follow-up	2-dose IPT with sulfadoxine-pyrimethamine vs monthly IPT with sulfadoxine-pyrimethamine; stratified by HIV status	ITN: 15.3	18-27	Plowe et al <sup>33</sup> Plowe et al (unpublished) Plowe et al (unpublished)	38.9††
Hamer et al (unpublished); Zambia	359‡‡	8; Adequate generation of allocation sequence and concealment, placebo-controlled, moderate follow-up	2-dose IPT with sulfadoxine-pyrimethamine vs monthly IPT with sulfadoxine-pyrimethamine	ITN: 24.8	Unknown	NMCH/CBH <sup>34</sup>	7.7

Abbreviations: EIR, entomological inoculation rate; HIV, human immunodeficiency virus; IPT, intermittent preventive therapy; ITN, insecticide-treated net; MRTC/CDC, Malaria Research and Training Center/CDC, Centers for Disease Control and Prevention; NMCH/CBH, National Malaria Control Center/Central Board of Health.

\*Trial quality was assessed using a modified version of the Jadad scale.<sup>11</sup> Adequacy of the generation of allocation sequence and its concealment was assessed as described by Jüni et al.<sup>10</sup> Follow-up was scored as adequate (>85%), moderate (70%-85%), and low (<70%) for the primary end point in each of these studies, which was placental malaria with the exception of Mbaye et al<sup>30</sup> (birth weight) and Shulman et al<sup>21</sup> (anemia in the third trimester). All authors were contacted if the information provided in the publication was not clear or not provided. The highest trial quality score that could be obtained was 9. Trials rated 6 or more were considered high quality.

†Defined as the proportion of total treatment failure in symptomatic children by day 14.

‡Study included women during their first or second pregnancy.

§The mean of 2 studies was used.

|| Study included only women during their first pregnancy.

¶Study had factorial design with 4 treatment groups: IPT; placebo IPT; ITN plus IPT; or ITN plus placebo IPT.

#Study enrolled only women during their first or second pregnancy if younger than 21 years.

\*\*Study included only women during their second pregnancy or higher.

††Mean of 3 studies was used (all 3 studies by Plowe et al).

‡‡Study included only HIV-infected women and those of any pregnancy order (enrollment not limited by number of previous pregnancies).

### Matched Treatment Studies in Children

Thirteen studies in children were identified that matched the 9 prevention studies in pregnant women by country and study period (TABLE 2). All matched studies included symptomatic children younger than 5 years, except 1 study in Kenya that included infants and children younger than 6 years, and 1 study in the Gambia that included children aged 6 months to 10 years.<sup>31</sup> In all matched treatment studies, sulfadoxine-pyrimethamine was taken under supervision. The matching quality was considered good in 7 of 9 IPT studies (Table 2). For all IPT with sulfadoxine-pyrimethamine during pregnancy studies, a matching treatment study could be identified that was conducted at the same location (n=5) or within 100 miles of the IPT study site (n=4). The treatment studies in children overlapped in time with 5 of the 9 IPT during pregnancy trials. For the remaining 4, the maximum time difference was 2 years. For 2 of these, 2 matches were identified; 1 before and 1 after the IPT during pregnancy trial, and the midpoint was used. For both trials that involved chloroquine prophylaxis, additional treatment studies with chloroquine could be identified to define the degree of chloroquine resistance at the time of the study.

### Protective Efficacy of 2-Dose IPT During Pregnancy by Level of Drug Resistance Compared With Weekly Chloroquine Prophylaxis

The 2 IPT with sulfadoxine-pyrimethamine trials using chloroquine prophylaxis as the comparator were conducted among women during their first and second pregnancies, 1 in Malawi and 1 in Mali.<sup>15,29</sup> The 2-dose IPT with sulfadoxine-pyrimethamine regimen resulted in greater reductions in malaria infection and low birth weight than weekly chloroquine but the difference was only statistically significant for low birth weight (FIGURE 1). Because both studies were from areas with low sulfadoxine-pyrimethamine resistance (5% in Malawi and 3% in Mali) and different degrees of chloroquine resistance, no

trend analysis could be conducted by degree of sulfadoxine-pyrimethamine resistance.

The differences in the effect of IPT with sulfadoxine-pyrimethamine during pregnancy vs weekly chloroquine were greatest in the study in Malawi, which had much higher levels of chloroquine resistance at the time of the study than was present in Mali (86% treatment failure with chloroquine in children at day 7 in Malawi vs 9% in Mali).<sup>36,37</sup> The differences between these 2 studies in the efficacy of IPT with sulfadoxine-pyrimethamine relative to chloroquine prophylaxis were statistically significant for placental malaria and maternal parasitemia as indicated by the  $I^2$  score greater than 80% (Figure 1). A sensitivity analysis that included only high-quality trials was not possible because only 1 of the trials fulfilled the high-quality criteria.

### IPT Compared With Case Management or Placebo Among Women With 1 or More Previous Pregnancies

Of the 5 trials comparing the standard 2-dose IPT with sulfadoxine-pyrimethamine regimen with case management or placebo, 1 was conducted in women with 1 or multiple previous pregnancies only (ie, this study did not include women during their first pregnancy).<sup>30</sup> This study from the Gambia compared IPT with sulfadoxine-pyrimethamine during pregnancy with placebo and was conducted in an area with low sulfadoxine-pyrimethamine resistance (9.5% treatment failure by day 14)<sup>30</sup>; 78% of the women also used a bed net. The number of doses received was dependent on the time of enrollment; 58% received more than 2 doses. Although a protective effect was seen on maternal peripheral parasitemia at delivery, no significant effect was detected on any other outcome measure, except in women not using a bed net (data not shown).<sup>30</sup>

### Women During Their First and Second Pregnancies

The remaining 4 studies were all conducted among women during their first

and second pregnancies in areas with 19% to 26% sulfadoxine-pyrimethamine resistance.<sup>17,21,24,27</sup> The 2-dose IPT with sulfadoxine-pyrimethamine regimen was very effective in preventing placental malaria, peripheral parasitemia, anemia, and low birth weight (FIGURE 2) and was associated with a mean increase of 0.38 g/dL in hemoglobin level and 79 g in birth weight (FIGURE 3). The forest plots suggested heterogeneity of effect, which was statistically significant for placental malaria ( $I^2$  score of 52.1%) and mean birth weight and maternal anemia ( $I^2$  scores of 50.8% and 59.9%, respectively). The heterogeneity for placental malaria and birth weight could be explained by inclusion of the trial by Njagi et al<sup>24,25</sup> in western Kenya that used a factorial design and co-randomized half of the women to also receive ITNs. This study showed that effect of IPT with sulfadoxine-pyrimethamine during pregnancy was significantly modified by the presence of ITNs.

Intermittent preventive therapy with sulfadoxine-pyrimethamine during pregnancy had significantly less effect on placental malaria if women were randomized to ITNs (RR of 0.79 [95% confidence interval {CI}, 0.50-1.24] vs 0.44 [95% CI, 0.28-0.70];  $I^2=68.5%$ ). The effect of IPT during pregnancy on mean birth weight also differed significantly between the group with ITNs and the group without ITNs (-14 vs 83 g;  $I^2=52.7%$ ). With the exception of mean hemoglobin level for which low and nonstatistically significant residual heterogeneity remained (21.7%), all  $I^2$  values were 0 after exclusion of women randomized to ITNs, indicating homogeneity of effect across trials and resistance levels. These results were the same whether the low-quality trial<sup>17</sup> was included or excluded.

### Protective Efficacy of Monthly vs 2-Dose IPT by Level of Drug Resistance

Three trials compared monthly with 2-dose IPT with sulfadoxine-pyrimethamine during pregnancy (D. H. Hamer, MD, unpublished data, 2006).<sup>17,32</sup> Two trials included both HIV-positive and

HIV-negative women during their first and second pregnancies and were conducted in areas with sulfadoxine-pyrimethamine resistance of 24% in Kenya and 39% in Malawi. The rate of treatment failure in Malawi was the highest recorded in this review. The third trial included HIV-positive women only, and unlike the other 2 trials included women of all pregnancy order and was conducted in an area of low sulfadoxine-pyrimethamine resistance (8%) (D. H. Hamer, MD, unpublished data, 2006). The monthly regimen resulted in women receiving between 3 and 7 doses of sulfadoxine-pyrimethamine depending on the gestational age at enrollment. The median number of doses in Kenya was 3 (60% received 3 doses, 17% received 4 doses, and 3% received 5 doses)<sup>17</sup>; the median number of doses was 5 in Malawi (80% received >3 doses)<sup>32</sup>; and the median number of doses was 4 in Zambia (D. H. Hamer, MD, unpublished data, 2006).

Among HIV-positive women in their first and second pregnancies (3 studies), the monthly regimens resulted consistently in greater reductions in placental malaria (RR, 0.34; 95% CI, 0.18-

0.64) and greater increases in mean birth weight (mean difference, 112 g) at all 3 levels of sulfadoxine-pyrimethamine resistance (TABLE 3). This was not associated with a significant beneficial effect on low birth weight. Monthly dosing was not associated with better hemoglobin levels or less anemia. Exclusion of the low-quality trial<sup>17</sup> did not alter the conclusion.

Among HIV-positive women with multiple previous pregnancies, monthly IPT with sulfadoxine-pyrimethamine did not provide any additional benefit over 2-dose IPT (data not shown; D. H. Hamer, MD, unpublished data, 2006).

Among HIV-negative women during their first and second pregnancies (2 studies), the effect on placental malaria of monthly IPT with sulfadoxine-pyrimethamine differed significantly between the 2 studies ( $I^2=63.7%$ ) (FIGURE 4); whereas there was no evidence for any additional effect on placental (RR, 1.33; 95% CI, 0.50-3.52) or peripheral malaria (RR, 1.02; 95% CI, 0.39-2.69) of monthly dosing in the study in Kenya (conducted at 24% sulfadoxine-pyrimethamine resistance),<sup>17</sup> monthly dosing resulted in

greater reductions in peripheral parasitemia (RR, 0.39 [95% CI, 0.17-0.90];  $P=.03$ ) in Malawi (39% resistance)<sup>32</sup> (FIGURE 5). There was also a 63% greater reduction in placental malaria with monthly dosing in Malawi and a greater increase in birth weight (mean difference, 80 g), but none of these differences was statistically significant (Table 3).<sup>32</sup>

**Proportional Reduction of Peripheral Parasitemia**

For 7 of the 9 studies, it was possible to assess the proportional reduction of peripheral parasitemia at delivery compared with enrollment in women during their first or second pregnancy (FIGURE 6). Studies among HIV-negative or women with unknown HIV status showed a lower proportional reduction with 2-dose regimen with an increasing level of sulfadoxine-pyrimethamine resistance in the area (Figure 6). However, the reduction associated with 2-dose IPT with sulfadoxine-pyrimethamine during pregnancy remained greater than 60% in the range of resistances evaluated (3%-39%).

**Table 2.** Matched Treatment Studies Among Symptomatic Children

Trial of Symptomatic Children	Age of Children, y	Reported No. of Treatment Failures/Total	Day of Assessment	Treatment Failure at Day 14, %	Trial of Pregnant Women Receiving Intermittent Preventive Therapy	Quality of Trial Match*		
						Difference in Study Period	Locations	Overall
Nwanyanwu et al, <sup>16</sup> 1996	<5	7/69	28	5.5†	Schultz et al, <sup>15</sup> 1994	<2 y	Overlap	Moderate
Van Dillen et al, <sup>19</sup> 1999	<5	19/55	14	34.5	Parise et al, <sup>17</sup> 1998	<2 y	<100 miles	Good
Omar et al, <sup>20</sup> 2001	<5	9/69	14	13.0	Parise et al, <sup>17</sup> 1998	<2 y	<100 miles	Good
Adjuik et al, <sup>22</sup> 2004	<5	53/189	14	28.0	Shulman et al, <sup>21</sup> 1999	<2 y	Overlap	Good
Amukoye et al, <sup>23</sup> 1997	<6	28/142	28	10.6†	Shulman et al, <sup>21</sup> 1999	<2 y	Overlap	Good
Obonyo et al, <sup>26</sup> 2003	<5	49/192	14	25.5	Njagi, <sup>24</sup> 2002	Overlap	Overlap	Good
Abacassamo et al, <sup>28</sup> 2004	<5	15/70	14	21.4	Challis et al, <sup>27</sup> 2004	Overlap	<100 miles	Good
MRTC/CDC (unpublished)	<5	3/56	28	2.9†	Kayentao et al, <sup>29</sup> 2005	Overlap	Overlap	Good
Dunyo et al, <sup>31</sup> 2006	6 mo to 10	22/124	28	9.5†	Mbaye et al, <sup>30</sup> 2006	<2 y	Overlap	Moderate
Plowe et al, <sup>33</sup> 2004‡	<5	48/133	14	36.1	Filler et al, <sup>32</sup> 2006	Overlap	<100 miles	Good
Plowe et al (unpublished)‡	<5	34/121	14	28.1	Filler et al, <sup>32</sup> 2006	Overlap	<100 miles	Good
Plowe et al (unpublished)‡	<5	40/76	14	52.6	Filler et al, <sup>32</sup> 2006	Overlap	<100 miles	Good
NMCH/CBH, <sup>34</sup> 2002	<5	4/52	14	7.7	Hamer et al (unpublished)	Overlap	<100 miles	Good

Abbreviations: MRTC/CDC, Malaria Research and Training Center/Centers for Disease Control and Prevention; NMCH/CBH, National Malaria Control Center, Ministry of Health/Central Board of Health.

\*A match was considered good if both time and location matching were good, and moderate if either the time match or location match was moderate. Location matching was considered moderate if the study sites were more than 100 miles apart but within the same country, and good if they were within 100 miles or overlapped. Time matching was considered good if the study period overlapped or if the midpoint of 2 matching studies overlapped with the intermittent preventive therapy study period.

†Data extrapolated to day 14 by dividing the day 28 failure rate by 1.86 based on published data from a meta-analysis of 5 randomized controlled treatment trials (N = 852) involving infants and children aged 6 months to almost 5 years (4 years and 11 months) with acute falciparum malaria treated with sulfadoxine-pyrimethamine in sub-Saharan Africa.<sup>22</sup>

‡Data from 2002 was extracted for children younger than 5 years from the publication quoted.<sup>33</sup> Data from 2004 was collected in an identical way in the same study site as the publication quoted and data from 2005 were from a subsequent trial conducted using similar but not identical methods in the same study site.

Among HIV-positive women during their first or second pregnancy, the proportional reduction with the 2-dose IPT with sulfadoxine-pyrimethamine regimen declined from 56% at 8% resistance (1 study) and 68% at 24% resistance (1 study) to only 21% in the area with the highest resistance (1 study at 39% resistance). By contrast, in these same studies the monthly dosing regimens maintained good efficacy (79%) even at the 39% resistance level (Figure 6).

**Adverse Events**

In the 9 trials, a total of at least 11 379 sulfadoxine-pyrimethamine treatments among 4911 women were observed, of which 1898 sulfadoxine-pyrimethamine treatments were given to 652 known HIV-positive women (TABLE 4). Adverse events were not common and did not appear to be more common in the participants receiving 2 doses of sulfadoxine-pyrimethamine compared with participants in the control group, or in

participants receiving monthly doses compared with 2 doses of sulfadoxine-pyrimethamine (insufficient details were provided to allow a meta-analysis of the data).

Maternal adverse drug reactions may be more common among HIV-positive women. In the study by Parise et al,<sup>17</sup> 3.2% of HIV-positive women had an adverse drug reaction after the first dose compared with 0.4% of HIV-negative women ( $P=.08$ ). In contrast, no difference was reported in the study by Filler et al.<sup>32</sup>

Of the 21 reported maternal deaths (10 in the IPT with sulfadoxine-pyrimethamine groups [2-dose or monthly], 9 in placebo groups, and 2 in unknown groups); 1 death was due to a severe cutaneous adverse drug reaction to sulfadoxine-pyrimethamine. This death occurred in an HIV-positive woman who was randomized to monthly sulfadoxine-pyrimethamine; however, symptoms started 3 weeks after the first dose of sulfadoxine-pyrimethamine and she did not

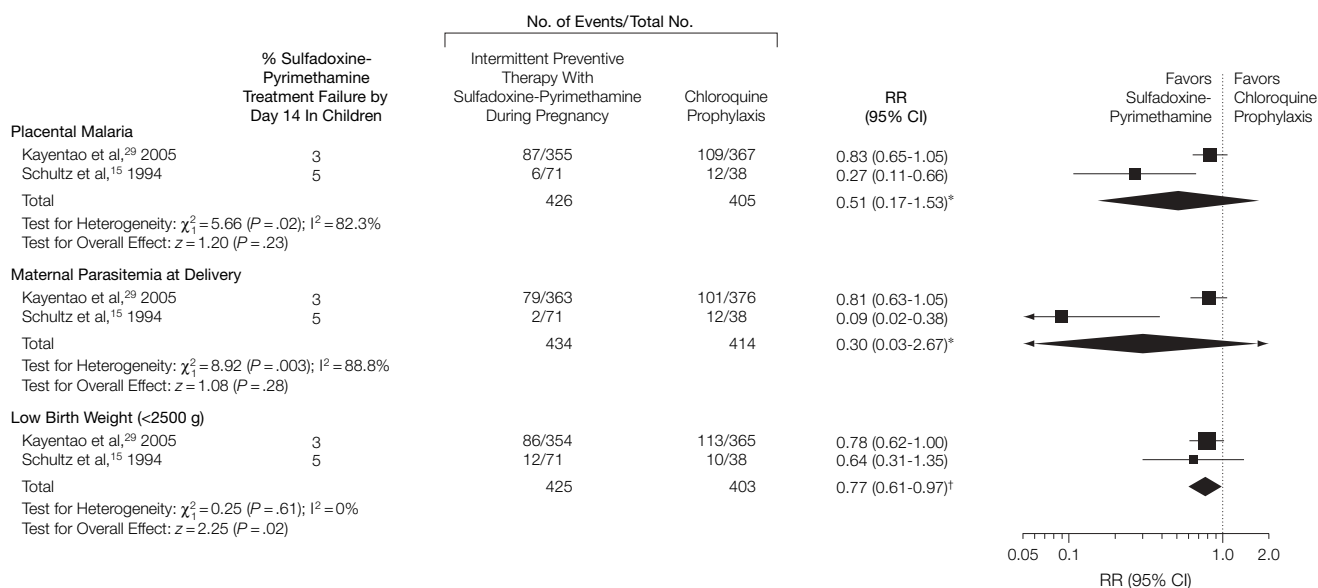
receive a second dose (D. H. Hamer, MD, unpublished data, 2006).

**COMMENT**

The deleterious effects of malaria during pregnancy can be substantially reduced by using IPT in pregnant women. Sulfadoxine-pyrimethamine is currently the only single-dose long-acting antimalarial drug that has ideal properties (low cost, documented safety, and ease of use) for use as IPT during pregnancy.<sup>1</sup> The current appraisal of available data on the efficacy of IPT with sulfadoxine-pyrimethamine as a function of sulfadoxine-pyrimethamine treatment responses in children provides policy makers with a clearer understanding of the value of different IPT regimens with sulfadoxine-pyrimethamine during pregnancy in the context of increasing sulfadoxine-pyrimethamine resistance.

There were only a small number of trials and several different comparator groups. Only 4 trials compared the 2-dose IPT regi-

**Figure 1.** Effect of 2-Dose Intermittent Preventive Therapy With Sulfadoxine-Pyrimethamine Among Women During Their First or Second Pregnancy vs Chloroquine Prophylaxis on Placental Malaria, Maternal Malaria, and Low Birth Weight



Both studies were conducted in areas of low to moderate sulfadoxine-pyrimethamine treatment failure among symptomatic children by day 14 (3% and 5%). However, chloroquine treatment failure in children was much lower in Mali (8.9% at day 7)<sup>36</sup> than in Malawi (85.7% at day 7).<sup>37</sup> The effect on mean birth weight, hemoglobin level, and anemia were reported only for the study in Mali (not shown). The size of the square data markers reflects the relative weight of each study. The diamonds represent summary effect estimates. CI indicates confidence interval; RR, relative risk.

\*Indicates random-effects model was used.  
†Indicates fixed-effects model was used.

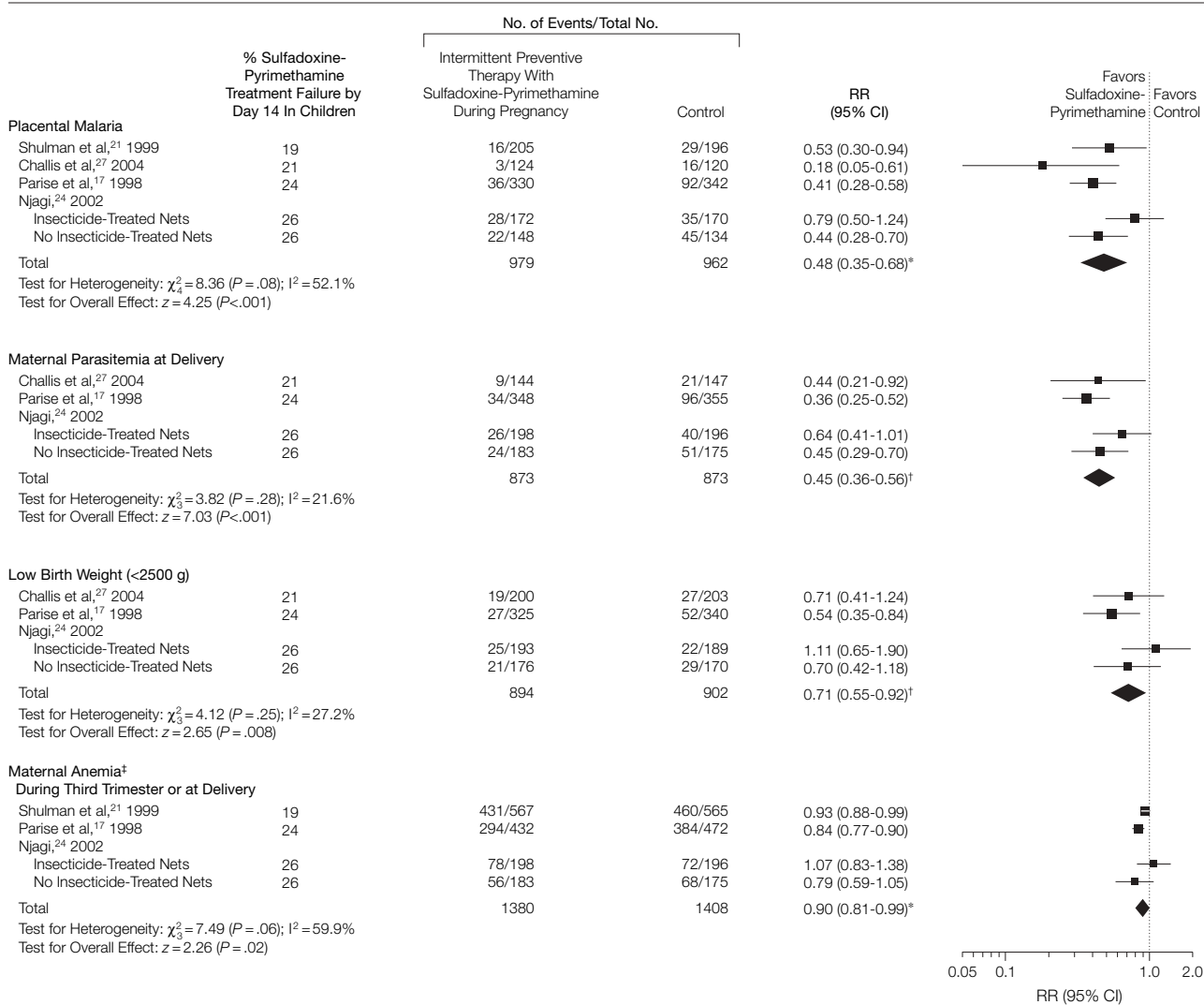
men with sulfadoxine-pyrimethamine with placebo or case management in women during their first or second pregnancy, and the range of sulfadoxine-pyrimethamine resistance in this group was narrow (19%-26%), which limited trend analysis. Only a single trial was conducted at higher levels of resistance (the study in Malawi comparing 2-dose with monthly IPT with sulfadoxine-pyrimethamine during pregnancy with a

39% treatment failure), and no trial has yet been conducted in areas with a greater than 40% failure rate by day 14.

The pooled analysis of the 4 studies that use placebo or case management as a control show that the 2-dose regimen of IPT with sulfadoxine-pyrimethamine continues to provide a substantial benefit to semi-immune, HIV-negative pregnant women in their first or second pregnancy even in areas

where sulfadoxine-pyrimethamine resistance is well established and fails to cure 1 in 4 malaria infections in symptomatic children by day 14. A 25% threshold has been used by the WHO as the cut-off for policy change in areas with high transmission such as Africa.<sup>5</sup> Our analysis of the proportional reduction in peripheral parasitemia, which allowed assessment of the effect of IPT during pregnancy over a wider range

**Figure 2.** Effect of 2-Dose Intermittent Preventive Therapy With Sulfadoxine-Pyrimethamine Among Women During Their First or Second Pregnancy vs Case Management or Placebo (Control) on Placental Malaria, Maternal Parasitemia, Low Birth Weight, and Maternal Anemia



In the study by Shulman et al,<sup>21</sup> the number of sulfadoxine-pyrimethamine (or placebo) doses depended on gestational age at enrollment; the majority of women (64%) received 2 doses. The size of the square data markers reflects the relative weight of each study. The diamonds represent summary effect estimates. CI indicates confidence interval; RR, relative risk.

\*Indicates random-effects model was used.

†Indicates fixed-effects model was used.

‡Hemoglobin level lower than 10 g/dL<sup>17,21</sup> or lower than 11 g/dL.<sup>24</sup>

of drug resistance (7 studies), also indicates there is no evidence of a marked decline in efficacy of the 2-dose regimen between areas with as little as 3% treatment failure in children by day 14 to areas with 39% treatment failure. The clear exception were HIV-infected women during their first and second pregnancies among whom clearance of peripheral parasitemia with the 2-dose regimen declined from 83% at 9.5% sulfadoxine-pyrimethamine resistance to 21% at 39% resistance.

Three studies assessed whether more frequent dosing of IPT with sulfadoxine-pyrimethamine during pregnancy could enhance the efficacy over the standard 2-dose regimen. Among HIV-positive women, monthly IPT with sulfadoxine-pyrimethamine provided no additional benefit to women with multiple previous pregnancies (1 trial; D. H. Hamer, MD, unpublished data, 2006) but among HIV-positive women during their first and second pregnancies monthly IPT

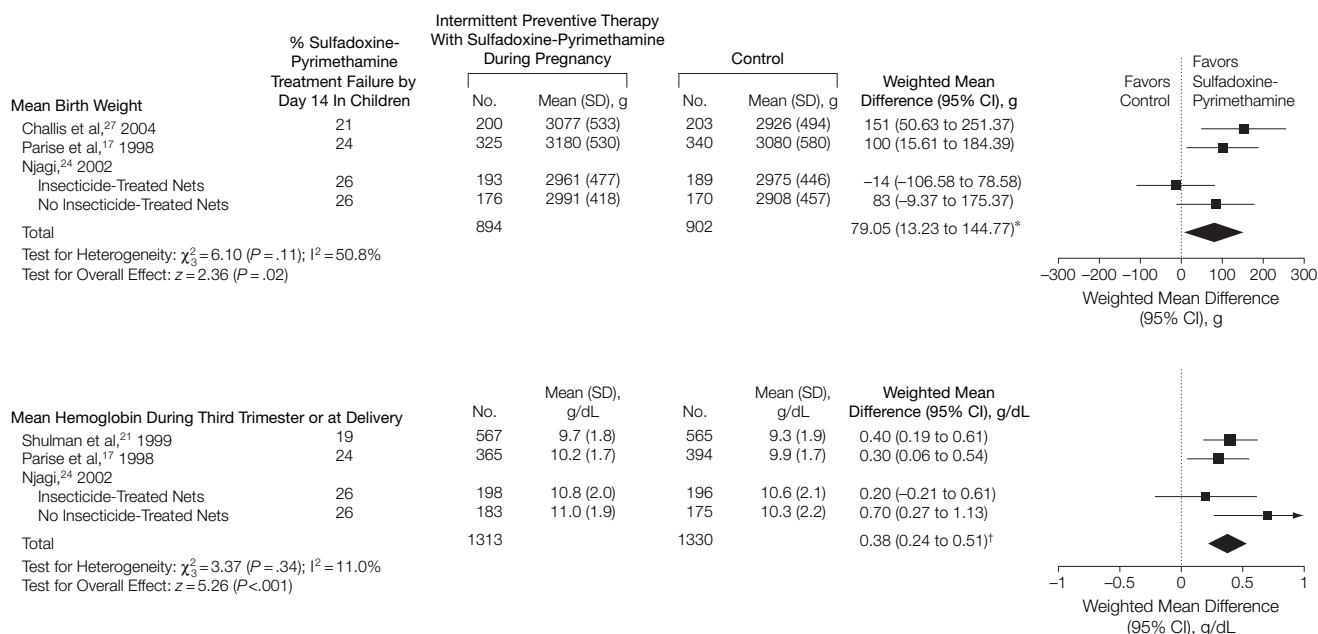
with sulfadoxine-pyrimethamine was consistently more effective than the 2-dose regimen in terms of reductions in placental malaria, peripheral malaria, and increase in mean birth weight (all 3 trials). The considerable beneficial impact on birth weight (112 g;  $P=.02$ ) is an important finding.

Although the WHO has recommended more than 2 doses of IPT during pregnancy for HIV-infected women for some years now, few countries have introduced this as their policy. These recommendations were based on the results of the first study<sup>17</sup> from western Kenya that compared monthly IPT with sulfadoxine-pyrimethamine during pregnancy and 2-dose IPT with sulfadoxine-pyrimethamine with no IPT and showed that monthly dosing was required in HIV-positive women to obtain the same beneficial effect as 2-doses in HIV-negative women. However, none of the observed differences between the monthly and 2-dose regi-

men were statistically significant.<sup>17</sup> The second trial also failed to detect a statistically significant effect on birth weight.<sup>32</sup> It has been argued that in the absence of a benefit on birth weight and other relevant clinical measures, the absence of parasites in blood tests or the placenta may simply reflect that women in the monthly dosing group received their last dose of sulfadoxine-pyrimethamine much closer to delivery and does not necessarily reflect clinical benefit to the mother or the infant.<sup>38</sup>

It is also not known whether radical clearance of parasites is required or whether a suppressive effect (dampening existing parasitemia) from a prophylactic effect may be sufficient. With the pooled information from these 3 trials, it is now clear that monthly regimens add significant benefit over the 2-dose regimen among HIV-positive women during their first and second pregnancies in increasing mean birth

**Figure 3.** Effect of 2-Dose Intermittent Preventive Therapy With Sulfadoxine-Pyrimethamine Among Women During Their First or Second Pregnancy vs Case Management or Placebo (Control) on Mean Birth Weight and Hemoglobin Level



In the study by Shulman et al,<sup>21</sup> the number of sulfadoxine-pyrimethamine (or placebo) doses depended on gestational age at enrollment; the majority of women (64%) received 2 doses. The size of the square data markers reflects the relative weight of each study. The diamonds represent summary effect estimates. CI indicates confidence interval.

\*Indicates random-effects model was used.  
†Indicates fixed-effects model was used.

weight. Importantly, this effect was not dependent on the degree of sulfadoxine-pyrimethamine resistance and was observed in all 3 studies conducted over a range of 8% to 39% resistance. Monthly dosing was not associated with more frequent or more severe adverse reactions in the limited sample. This supports the earlier recommendation by the WHO to use more frequent dosing in HIV-positive women in Africa who are not protected by cotrimoxazole prophylaxis for opportunistic infections (cotrimoxazole also has antimalarial properties).

Among HIV-negative women, the beneficial effect of monthly dosing is less clear. There was no indication that 3 or more doses were superior to the 2-dose regimen among HIV-negative women in the study in Kenya in the mid 1990s, when sulfadoxine-pyrimethamine resistance was 24%. Eight years later in Malawi, sulfadoxine-pyrimethamine resistance was 39% and the direction of the effects favored the monthly regimen and the effects were of similar magnitude as among HIV-positive women. However, with the exception of peripheral parasitemia, none

of the differences was statistically significant.<sup>32</sup> Further studies will need to clarify whether the difference between these 2 studies implies that among HIV-negative women the additional benefits of monthly dosing only become apparent when sulfadoxine-pyrimethamine resistance is well established (eg, >25% by day 14). Two such studies comparing the 2-dose regimen with monthly IPT with sulfadoxine-pyrimethamine during pregnancy are ongoing in Malawi and Tanzania and the results will become available later in 2007 and in 2008. Another ex-

**Table 3.** Summary Effect Measures of 3 Trials Comparing 2-Dose vs Monthly Intermittent Preventive Therapy With Sulfadoxine-Pyrimethamine During First or Second Pregnancy\*

	Placental Malaria	Maternal Parasitemia at Delivery	Birth Weight, g†	Low Birth Weight (<2500 g)	During Third Trimester or at Delivery	
					Hemoglobin Level†	Anemia (<11 g/dL)
<b>HIV-Positive Women</b>						
All studies (pooled estimate) Effect (95% CI)	0.34 (0.18 to 0.64)	0.24 (0.14 to 0.44)	112 (19 to 205)	0.77 (0.51 to 1.15)	0.09 (-0.21 to 0.38)	0.93 (0.82 to 1.05)
<i>P</i> value	<.01	<.01	.02	.21	.57	.21
Hamer et al (unpublished) (8% sulfadoxine-pyrimethamine resistance) Effect (95% CI)	0.35 (0.08 to 1.66)	0.25 (0.06 to 1.15)	134 (6 to 262)	0.60 (0.30 to 1.18)	0.04 (-0.42 to 0.50)	0.79 (0.58 to 1.08)
<i>P</i> value	.19	.07	.04	.18	0.86	.14
Parise et al, <sup>17</sup> 1998 (24% sulfadoxine-pyrimethamine resistance) Effect (95% CI)	0.28 (0.07 to 1.17)	0.20 (0.03 to 1.53)	27 (-234 to 288)	0.84 (0.22 to 3.21)	0.20 (-0.69 to 1.09)	0.90 (0.68 to 1.19)
<i>P</i> value	.08	.12	.84	.79	.66	.46
Filler et al, <sup>32</sup> 2006 (39% sulfadoxine-pyrimethamine resistance) Effect (95% CI)	0.36 (0.17 to 0.79)	0.25 (0.13 to 0.49)	110 (-48 to 268)	0.92 (0.53 to 1.59)	0.10 (-0.33 to 0.53)	1.02 (0.88 to 1.17)
<i>P</i> value	.01	<.01	.17	.76	.65	.82
<b>HIV-Negative Women‡</b>						
All studies (pooled estimate) Effect (95% CI)	0.73 (0.21 to 2.58)	0.61 (0.24 to 1.55)	72 (-13 to 157)	0.86 (0.50 to 1.50)	0.22 (-0.07 to 0.50)	0.99 (0.87 to 1.13)
<i>P</i> value	.63§	.30	.10	.60	.14	.94
Parise et al, <sup>17</sup> 1998 (24% sulfadoxine-pyrimethamine resistance) Effect (95% CI)	1.33 (0.50 to 3.52)	1.02 (0.39 to 2.69)	57 (-91 to 205)	1.16 (0.35 to 3.89)	0 (-0.55 to 0.55)	1.05 (0.83 to 1.32)
<i>P</i> value	.56	.97	.45	.80	>.99	.70
Filler et al, <sup>32</sup> 2006 (39% sulfadoxine-pyrimethamine resistance) Effect (95% CI)	0.37 (0.11 to 1.19)	0.39 (0.17 to 0.90)	80 (-24 to 184)	0.79 (0.42 to 1.47)	0.30 (-0.04 to 0.64)	0.97 (0.83 to 1.13)
<i>P</i> value	.09	.03	.13	.46	.11	.70

\*The effect measure is relative risk unless otherwise indicated. The effect model is fixed unless otherwise indicated. The *I*<sup>2</sup> test for heterogeneity value was 0 unless otherwise indicated.  
 †The effect measure is weighted mean difference.  
 ‡Hamer et al (unpublished) included HIV-positive women only.  
 §Because the value for the *I*<sup>2</sup> test for heterogeneity was 63.7%, a random-effects model was used. A value greater than 50% reflects significant heterogeneity between studies.  
 ||Because the value for the *I*<sup>2</sup> test for heterogeneity was 53.5%, a random-effects model was used.

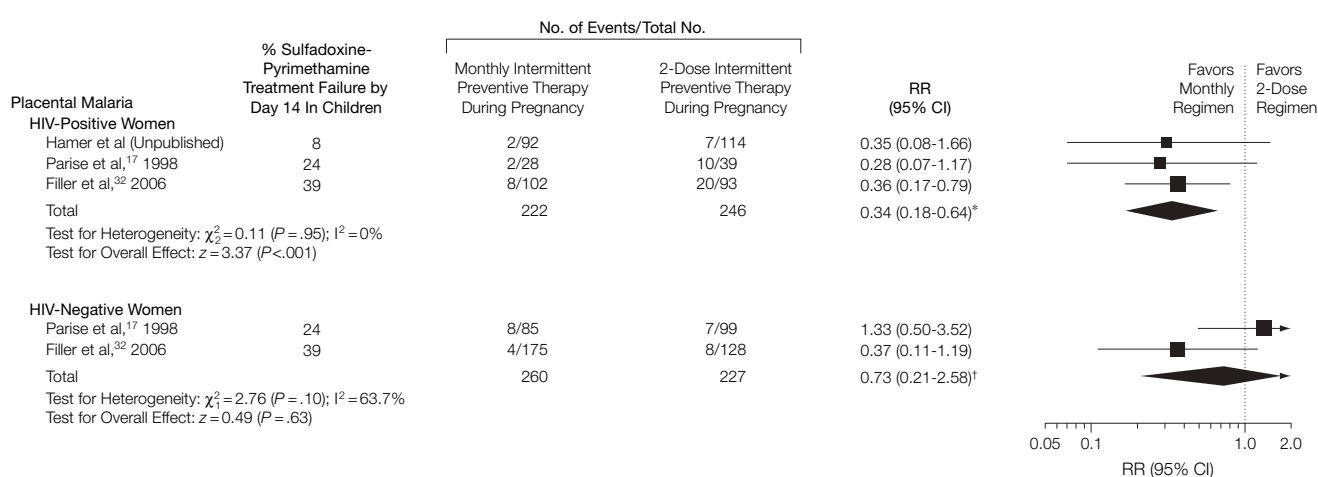
planation for the observed differences in the treatment effect between the 2-dose and monthly regimen among HIV-negative women may be the difference in the median number of doses received by the women in Kenya (3

doses) and Malawi (5 doses) and the difference in the quality between the trials. There was no evidence for a publication bias.

There are several limitations to note. Two of the studies included in our

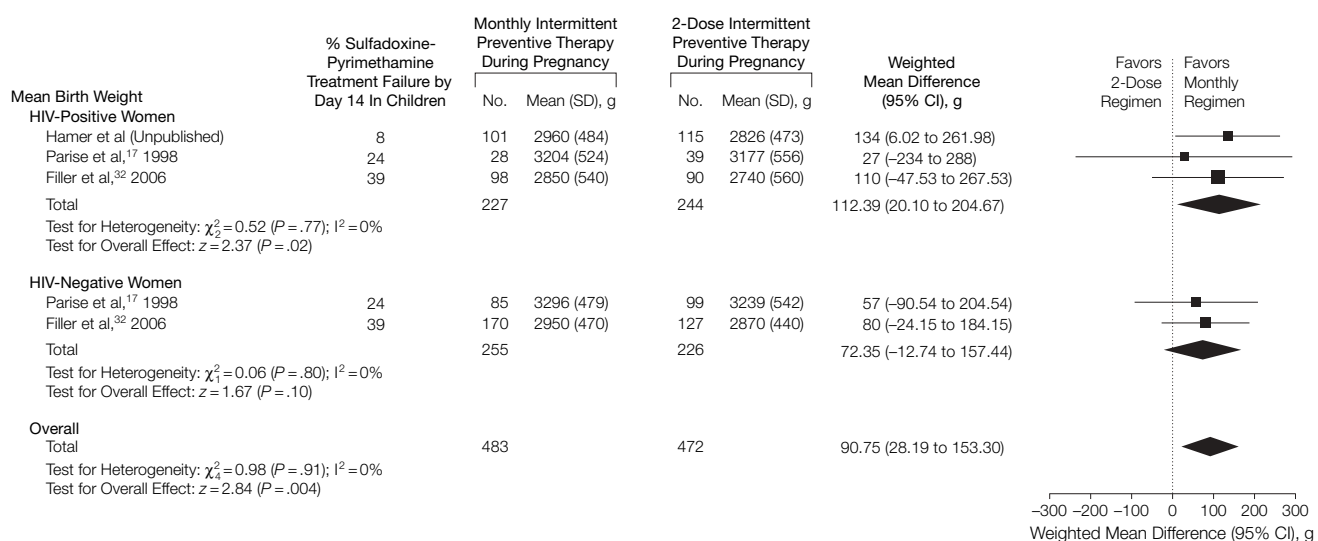
analysis are from western Kenya<sup>24,25</sup> and the Gambia<sup>30</sup> and indicate that IPT with sulfadoxine-pyrimethamine during pregnancy provides less benefit to women who are also protected by ITNs. However, with the exception of these

**Figure 4.** Effect of Monthly vs 2-Dose Intermittent Preventive Therapy With Sulfadoxine-Pyrimethamine Among Women During Their First or Second Pregnancy by HIV Status and Level of Drug Resistance on Placental Malaria



Only data from women during their first or second pregnancy are presented from the study by Hamer et al (unpublished) to allow comparison with the other 2 studies. The size of the square data markers reflects the relative weight of each study. The diamonds represent summary effect estimates. CI indicates confidence interval; HIV, human immunodeficiency virus; RR, relative risk.  
\*Indicates fixed-effects model was used.  
†Indicates random-effects model was used.

**Figure 5.** Effect of Monthly vs 2-Dose Intermittent Preventive Therapy With Sulfadoxine-Pyrimethamine Among Women During Their First or Second Pregnancy by HIV Status and Level of Drug Resistance on Mean Birth Weight



Only data from women during their first or second pregnancy are presented from the study by Hamer et al (unpublished) to allow comparison with the other 2 studies. The size of the square data markers reflects the relative weight of each study. The diamonds represent summary effect estimates. CI indicates confidence interval; HIV, human immunodeficiency virus.

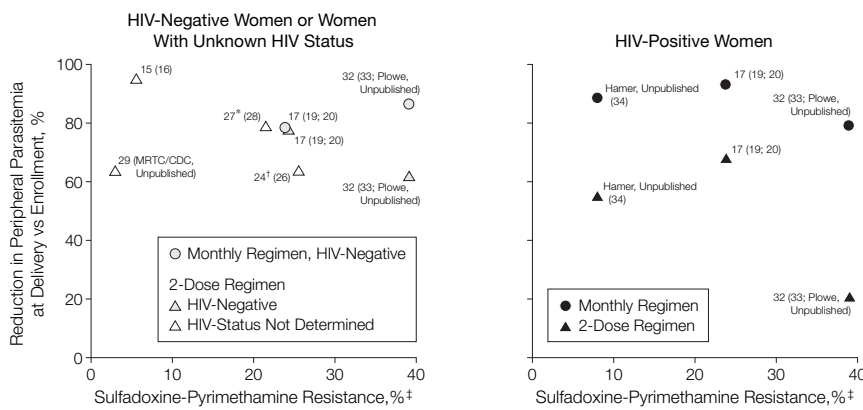
2 studies, insufficient information was available from the other studies to allow further stratified analysis by ITNs. Overall, ITN use in these other stud-

ies (when known) ranged from 12% to 26%. Thus, our analysis is valid for areas with low ITN coverage among pregnant women, which, with the excep-

tion of a handful of countries, is representative of the current coverage in this risk group in sub-Saharan Africa, where the coverage between 2001 and 2005 was estimated to be 17.4% for any nets and 3% for ITNs.<sup>39</sup> The coverage is likely to increase over the next 5 years as a result of several large-scale malaria-control initiatives<sup>40-42</sup> and further studies need to establish whether this could mitigate some of the effects of increasing sulfadoxine-pyrimethamine resistance on the efficacy of IPT with sulfadoxine-pyrimethamine during pregnancy or may reduce the need for frequent dosing in HIV-infected women.

We relied on retrospective matching of the IPT during pregnancy trials against sulfadoxine-pyrimethamine treatment studies in children with acute falciparum malaria to define the degree of resistance. Drug resistance may be focal and may vary between different parts of a single country and this may have affected the accuracy of the resistance estimates. Although few of the IPT with sulfadoxine-pyrimethamine during pregnancy studies reported the degree of drug resistance in the area at the time of the study, good

**Figure 6.** Relationship Between the Sulfadoxine-Pyrimethamine Treatment Response in Symptomatic Children at Day 14 and the Reduction in the Proportion of Women With Peripheral Parasitemia at Delivery vs Enrollment Among Women During Their First or Second Pregnancy



The reduction in the proportion of women with peripheral parasitemia is calculated as the percentage of women with peripheral parasitemia at enrollment minus the percentage with peripheral parasitemia at delivery divided by the percentage of peripheral parasitemia at enrollment divided by 100. The reference numbers in the figure indicate the reference of the trial (first number) and the reference of the matching study among children (numbers in parentheses). HIV indicates human immunodeficiency virus.

\*The study population is pregnant women who are younger than 21 years during their first or second pregnancy.

†Women randomized to insecticide-treated nets were excluded.

‡Resistance to sulfadoxine-pyrimethamine was defined as the proportion of total treatment failure in symptomatic children by day 14.

**Table 4.** Summary of Adverse Outcomes Comparing Intermittent Preventive Therapy With 2 Doses of Sulfadoxine-Pyrimethamine With Placebo, Case Management, Chloroquine Prophylaxis, or Monthly Sulfadoxine-Pyrimethamine\*

	Neonatal Icterus, %		Any Maternal Adverse Drug Reaction, %		Estimated No. of Sulfadoxine-Pyrimethamine Doses Given†	No. of Women	Severe Skin Reactions to Sulfadoxine-Pyrimethamine
	Sulfadoxine-Pyrimethamine	Control	Sulfadoxine-Pyrimethamine	Control			
Schultz et al <sup>15,‡</sup>			Not reported	Not reported	192	121	None detected
Kayentao et al <sup>29</sup>	0.6	1.8	2.8	4.4	738	369	None detected
Challis et al <sup>27</sup>	3.1§	7.2§	0.5	1.3	288	144	None detected
Parise et al <sup>17</sup>	15	17	2.3	3.3	2276	1086	None detected
Njagi <sup>24</sup>	Not reported	Not reported	Not reported	Not reported	762	381	Not reported
Shulman et al <sup>21</sup>	0.2¶	0.7¶	0.7	0.5	1153	567	None detected
Mbaye et al <sup>30</sup>	Not reported	Not reported	Not reported	Not reported	3149	1179	Not reported
Filler et al <sup>32,#</sup>					1734	641	None detected
Hamer et al (unpublished)**	0.5	0			1087	423	1 After first dose††

\*Meta-analysis to provide pooled estimates could not be conducted because of the lack of sufficient details for neonatal icterus or maternal adverse drug reactions.

†Total estimated doses of sulfadoxine-pyrimethamine in the study, not just doses of sulfadoxine-pyrimethamine in the intermittent preventive therapy with sulfadoxine-pyrimethamine group.

‡Total percentage for neonatal icterus is 2.8. Values were not reported by group in this study.

§Neonatal adverse event defined as the need for neonatal unit care.

||The drug was withheld from 7 women after minor adverse effects (rash, oral lesions) after the first dose. There were no significant differences in the proportion of women reporting adverse drug reactions in the treatment groups by human immunodeficiency virus status.<sup>17</sup>

¶Neonatal deaths caused by icterus.

#Total percentage for neonatal icterus is 0.4. Total percentage for any maternal adverse drug reaction is less than 1. Values were not reported by group in this study.

\*\*The relative risk for any maternal adverse drug reaction is 1.10 (95% confidence interval, 0.56-2.18). Values were not reported by group in this study.

††One woman with the human immunodeficiency virus died of Stevens Johnson syndrome. The symptoms started 3 weeks after her first sulfadoxine-pyrimethamine dose (D. H. Hamer, MD, unpublished data, 2006).

quality matching, defined as overlapping study periods and overlapping site or location within 100 miles, was possible for all the 7 key studies that provide the core of our analysis (Figure 3, Figure 4, and Table 3). For the 2 studies that did not overlap in time, the time window between matched studies was a maximum of 2 years. While drug resistance may have changed during this time window, we have no reason to believe that this has biased the analyses because 2 matching treatment studies (1 before and 1 after) could be identified for each and the midpoint was used.

The analysis of proportional reduction of maternal peripheral parasitemia allowed assessment over a wider resistance range. The clinical implications of clearing peripheral parasitemia however are unclear and is at best a proxy for placental infection and possibly low birth weight. Nevertheless, the observed relationship with sulfadoxine-pyrimethamine resistance using this type of analysis provides further support for our conclusion that 2-dose IPT with sulfadoxine-pyrimethamine during pregnancy maintains its efficacy and that the potential added benefit of monthly dosing in HIV-infected women.

Despite these caveats, this compilation currently provides the information needed by policy makers to define the role of sulfadoxine-pyrimethamine as IPT during pregnancy in the face of increasing drug resistance. The results have been used by the African Regional Office of the WHO to issue a statement on the continued use of sulfadoxine-pyrimethamine for IPT during pregnancy.<sup>43</sup> However, with the emerging spread of high-grade resistance to sulfadoxine-pyrimethamine,<sup>44-47</sup> high priority must be given to determining safe and affordable alternatives. A series of multicenter trials are planned<sup>7</sup> but it will take several years for the results to become available. In the mean time, increasing the frequency of IPT with sulfadoxine-pyrimethamine during pregnancy to 3 or more doses, particularly in areas with a high HIV prevalence, may provide temporary respite.

The WHO recommends a schedule of 4 antenatal care visits, with 3 visits after quickening. The delivery of IPT with each scheduled visit after quickening may help ensure that a high proportion of women receive at least 2 doses. Data from 2 other ongoing trials of monthly dosing may shed further light in 2008 on the optimal frequency of IPT dosing in HIV-negative women protected by ITNs in the context of sulfadoxine-pyrimethamine resistance. The data from the 2 trials that stratified the results by bed nets also strongly support the use of ITNs, which is particularly important in the face of increasing sulfadoxine-pyrimethamine resistance.

Reserving the use of sulfadoxine-pyrimethamine for IPT during pregnancy and for infants may reduce drug pressure and may prolong longevity of this valuable drug. Almost all countries in Africa are taking this course and have either implemented or are in the process of implementing the use of combination therapy for first-line treatment in the population, mostly with artemisinin-based combinations. This will also limit the options to monitor the degree of sulfadoxine-pyrimethamine resistance in treatment studies in children in vivo, and future studies that aim to determine the effect of sulfadoxine-pyrimethamine resistance on the efficacy of IPT with sulfadoxine-pyrimethamine during pregnancy may need to rely on molecular markers.

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**Author Contributions:** Drs ter Kuile and van Eijk had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** ter Kuile.

**Acquisition of data:** ter Kuile, van Eijk, Filler.

**Analysis and interpretation of data:** ter Kuile, van Eijk, Filler.

**Drafting of the manuscript:** ter Kuile.

**Critical revision of the manuscript for important intellectual content:** ter Kuile, van Eijk, Filler.

**Statistical analysis:** ter Kuile, van Eijk.

**Obtained funding:** ter Kuile.

**Administrative, technical, or material support:** ter Kuile, van Eijk.

**Study supervision:** ter Kuile.

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## REFERENCES

1. World Health Organization Regional Office for Africa. *A Strategic Framework for Malaria Prevention and Control During Pregnancy in the African Region*. Brazzaville, Congo: World Health Organization Regional Office for Africa; 2004.
2. White NJ. Intermittent presumptive treatment for malaria. *PLoS Med*. 2005;2:e3.
3. World Health Organization. *Susceptibility of Plasmodium falciparum to Antimalarial Drugs: Report on Global Monitoring 1996-2004*. Geneva, Switzerland: World Health Organization; 2005.
4. World Health Organization Regional Office for Africa. *Assessment of Therapeutic Efficacy of Antimalarial Drugs for Uncomplicated Falciparum Malaria in Areas With Intense Transmission*. Brazzaville, Congo: World Health Organization Regional Office for Africa; 1996.
5. World Health Organization. *Assessment and Monitoring of Antimalarial Drug Efficacy for the Treatment of Uncomplicated Falciparum Malaria*. Geneva, Switzerland: World Health Organization; 2003.
6. Kalanda GC, Hill J, Verhoeff FH, Brabin BJ. Comparative efficacy of chloroquine and sulfadoxine-pyrimethamine in pregnant women and children: a meta-analysis. *Trop Med Int Health*. 2006;11:569-577.
7. Menéndez C, D'Alessandro U, ter Kuile FO. Reducing the burden of malaria in pregnancy by preventive strategies. *Lancet Infect Dis*. 2007;7:126-135.
8. Update Software Web site. Malaria in pregnancy library [March 2007]. <http://www.update-software.com/publications/malaria/>. Accessed March 23, 2007.
9. The Cochrane Library. Optimal search strategy for RCTs: Appendix C. In: *Cochrane Reviewers' Handbook 4.2.0*. Chichester, England: John Wiley & Sons Ltd; 2003.
10. Jüni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ*. 2001;323:42-46.
11. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1-12.
12. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
13. Deeks JJ, Higgins JPT, Altman DG. Analysing and presenting results. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions 4.2.5*. Chichester, England: John Wiley & Sons Ltd; 2005.
14. ter Kuile FO, Parise ME, Verhoeff FH, et al. The burden of co-infection with human immunodeficiency virus type 1 and malaria in pregnant women

- in sub-saharan Africa. *Am J Trop Med Hyg.* 2004;71 (suppl):41-54.
15. Schultz LJ, Stetekee RW, Macheso A, Kazembe P, Chitsulo L, Wirima JJ. The efficacy of antimalarial regimens containing sulfadoxine-pyrimethamine and/or chloroquine in preventing peripheral and placental *Plasmodium falciparum* infection among pregnant women in Malawi. *Am J Trop Med Hyg.* 1994;51: 515-522.
  16. Nwanyanwu OC, Ziba C, Kazembe P, et al. Efficacy of sulphadoxine/pyrimethamine for *Plasmodium falciparum* malaria in Malawian children under five years of age. *Trop Med Int Health.* 1996;1:231-235.
  17. Parise ME, Ayisi JG, Nahlen BL, et al. Efficacy of sulfadoxine-pyrimethamine for prevention of placental malaria in an area of Kenya with a high prevalence of malaria and human immunodeficiency virus infection. *Am J Trop Med Hyg.* 1998;59:813-822.
  18. van Eijk AM, Ayisi JG, Slutsker L, et al. Effect of haematinic supplementation and malaria prevention on maternal anaemia and malaria in western Kenya. *Trop Med Int Health.* 2007;12:342-352.
  19. van Dillen J, Custers M, Wensink A, et al. A comparison of amodiaquine and sulfadoxine-pyrimethamine as first-line treatment of falciparum malaria in Kenya. *Trans R Soc Trop Med Hyg.* 1999;93: 185-188.
  20. Omar SA, Bakari A, Owiti A, Adagu IS, Warhurst DC. Co-trimoxazole compared with sulfadoxine-pyrimethamine in the treatment of uncomplicated malaria in Kenyan children. *Trans R Soc Trop Med Hyg.* 2001;95:657-660.
  21. Shulman CE, Dorman EK, Cutts F, et al. Intermittent sulphadoxine-pyrimethamine to prevent severe anaemia secondary to malaria in pregnancy: a randomized placebo-controlled trial. *Lancet.* 1999;353: 632-636.
  22. Adjuik M, Babiker A, Garner P, Olliaro P, Taylor W, White N. Artesunate combinations for treatment of malaria: meta-analysis. *Lancet.* 2004;363:9-17.
  23. Amukoye E, Winstanley PA, Watkins WM, et al. Chlorproguanil-dapsone: effective treatment for uncomplicated falciparum malaria. *Antimicrob Agents Chemother.* 1997;41:2261-2264.
  24. Njagi JK. *The Effects of Sulfadoxine-Pyrimethamine Intermittent Treatment and Pyrethroid Impregnated Bed Nets on Malaria Morbidity in Pregnancy and Birth Weight in Bondo District, Kenya* [dissertation]. Nairobi, Kenya, and Copenhagen, Denmark: University of Nairobi and Danish Bilharziasis Laboratory; 2002.
  25. Njagi JK, Magnussen P, Estambale B, Ouma J, Mugo B. Prevention of anaemia in pregnancy using insecticide-treated bednets and sulfadoxine-pyrimethamine in a highly malarious area of Kenya: a randomized controlled trial. *Trans R Soc Trop Med Hyg.* 2003;97:277-282.
  26. Obonyo CO, Ochieng F, Taylor WR, et al. Artesunate plus sulfadoxine-pyrimethamine for uncomplicated malaria in Kenyan children: a randomized, double-blind, placebo-controlled trial. *Trans R Soc Trop Med Hyg.* 2003;97:585-591.
  27. Challis K, Osman NB, Cotiro M, Nordahl G, Dgedge M, Bergstrom S. Impact of a double dose of sulphadoxine-pyrimethamine to reduce prevalence of pregnancy malaria in southern Mozambique. *Trop Med Int Health.* 2004;9:1066-1073.
  28. Abacassamo F, Enosse S, Aponte JJ, et al. Efficacy of chloroquine, amodiaquine, sulphadoxine-pyrimethamine and combination therapy with artesunate in Mozambican children with non-complicated malaria. *Trop Med Int Health.* 2004;9:200-208.
  29. Kayentao K, Kodio M, Newman RD, et al. Comparison of intermittent preventive treatment with chemoprophylaxis for the prevention of malaria during pregnancy in Mali. *J Infect Dis.* 2005;191:109-116.
  30. Mbaye A, Richardson K, Balajo B, et al. A randomized, placebo-controlled trial of intermittent preventive treatment with sulphadoxine-pyrimethamine in Gambian multigravidae. *Trop Med Int Health.* 2006;11:992-1002.
  31. Dunyo S, Ord R, Hallett R, et al. Randomised trial of chloroquine/sulphadoxine-pyrimethamine in Gambian children with malaria: impact against multidrug-resistant *P. falciparum*. *PLoS Clin Trials.* 2006; 1:e14.
  32. Filler SJ, Kazembe P, Thigpen M, et al. Randomized trial of 2-dose versus monthly sulfadoxine-pyrimethamine intermittent preventive treatment for malaria in HIV-positive and HIV-negative pregnant women in Malawi. *J Infect Dis.* 2006;194:286-293.
  33. Plowe CV, Kublin JG, Dzinjalimala FK, et al. Sustained clinical efficacy of sulfadoxine-pyrimethamine for uncomplicated falciparum malaria in Malawi after 10 years as first line treatment: five year prospective study. *BMJ.* 2004;328:545.
  34. National Malaria Control Center/Central Board of Health. *Preliminary Findings of in Vivo Antimalarial Drug Efficacy Studies in Zambia*. Lusaka, Zambia: National Malaria Control Center, Central Board of Health; 2002.
  35. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA.* 1996;276:637-639.
  36. Plowe CV, Doumbo OK, Djimde A, et al. Chloroquine treatment of uncomplicated *Plasmodium falciparum* malaria in Mali: parasitologic resistance versus therapeutic efficacy. *Am J Trop Med Hyg.* 2001; 64:242-246.
  37. Boland PB, Kazembe PN, Oloo AJ, Himonga B, Barat LM, Ruebush TK. Chloroquine in Africa: critical assessment and recommendations for monitoring and evaluating chloroquine therapy efficacy in sub-Saharan Africa. *Trop Med Int Health.* 1998;3:543-552.
  38. Meshnick SR, Mwapasa V, Rogerson SJ. Protecting pregnant women from malaria in areas of high HIV infection prevalence. *J Infect Dis.* 2006;194:273-275.
  39. Worrall E, Morel C, Yeung S, et al. The economics of malaria in pregnancy—a review of the evidence and research priorities. *Lancet Infect Dis.* 2007;7:156-168.
  40. Global Fund Web site. Fighting malaria. <http://www.theglobalfund.org/en/about/malaria/>. Accessed March 23, 2007.
  41. US Agency for International Development. President's malaria initiative. <http://www.usaid.gov/press/factsheets/2006/fs060608.html>. Accessed March 23, 2007.
  42. World Bank. *Rolling Bank Malaria: The World Bank Global Strategy and Booster Program*. Washington, DC: International Bank for Reconstruction and Development; 2005.
  43. World Health Organization. Recommendations on the use of sulfadoxine-pyrimethamine for intermittent preventive treatment during pregnancy in areas of moderate to high resistance to sulfadoxine-pyrimethamine in the African region [October 2005]. [http://afro.who.int/malaria/publications/who\\_sp\\_statement.pdf](http://afro.who.int/malaria/publications/who_sp_statement.pdf). Accessibility verified May 23, 2007.
  44. Hastings MD, Bates SJ, Blackstone EA, Monks SM, Mutabingwa TK, Sibley CH. Highly pyrimethamine-resistant alleles of dihydrofolate reductase in isolates of *Plasmodium falciparum* from Tanzania. *Trans R Soc Trop Med Hyg.* 2002;96:674-676.
  45. Alker AP, Mwapasa V, Purfield A, et al. Mutations associated with sulfadoxine-pyrimethamine and chlorproguanil resistance in *Plasmodium falciparum* isolates from Blantyre, Malawi. *Antimicrob Agents Chemother.* 2005;49:3919-3921.
  46. Färnert A, Tengstam K, Palme IB, et al. Polyclonal *Plasmodium falciparum* malaria in travelers and selection of antifolate mutations after proguanil prophylaxis. *Am J Trop Med Hyg.* 2002;66:487-491.
  47. Staedke SG, Sendagire H, Lamola S, Kanya MR, Dorsey G, Rosenthal PJ. Relationship between age, molecular markers, and response to sulphadoxine-pyrimethamine treatment in Kampala, Uganda. *Trop Med Int Health.* 2004;9:624-629.