Intermittent Preventive Treatment with Sulfadoxine-Pyrimethamine in Burundi

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April 2010

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This report is made possible by the generous support of the American people through the U.S. Agency for International Development (USAID), under the terms of cooperative agreement number GHN-A-00-07-00002-00. The contents are the responsibility of Management Sciences for Health and do not necessarily reflect the views of USAID or the United States Government.

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Recommended Citation

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Shretta, R., and A. Kwiecien. 2010. *Intermittent Preventive Treatment with Sulfadoxine-Pyrimethamine in Burundi.* Submitted to the U.S. Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.

Key Words

malaria, IPT, Burundi

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ACRONYMS AND ABBREVIATIONS

AL	artemether-lumefantrine
AQ	amodiaquine
AS	artesunate
CQ	chloroquine
CWC	classic weekly chemoprophylaxis
FC	fosmidomycin-clindamycin
ITN	insecticide-treated nets
IPT	intermittent preventive treatment
IPTp	intermittent preventive treatment during pregnancy
MQ	mefloquine
MSH	Management Sciences for Health
P	pyrimethamine
PNILP	Programme National Intégré Lutte contre le Paludisme
SP	sulfadoxine-pyrimethamine
SPS	Strengthening Pharmaceutical Management
WHO	World Health Organization

BACKGROUND

Malaria during pregnancy has been associated with anemia in the mother and impairment of fetal nutrition, which contributes to low birth weight, and is a leading cause of poor infant survival and development in Africa. Each year, more than 30 million African women become pregnant in malaria-endemic areas and are at risk for *Plasmodium falciparum* malaria infection during pregnancy.

Research has shown that intermittent preventive therapy during pregnancy (IPTp) using sulfadoxine-pyrimethamine (SP) significantly reduces placental malaria, low birth weight, and severe maternal anemia (Parise et al. 1998; Rogerson et al. 2000; Schultz et al. 1994; Shulman et al. 1999; Verhoeff et al. 1998). The World Health Organization (WHO) recommends that to attain the greatest program effectiveness with IPTp, all pregnant women should receive a treatment dose of the recommended antimalarial drug at the first regularly scheduled prenatal clinic visit after quickening (first noted movement of the fetus) and during each regularly scheduled visit thereafter. WHO currently recommends an ideal visit schedule of four prenatal clinic visits, one in the first trimester and three after quickening. However, recent reports of SP resistance have questioned its continued efficacy for the prevention of malaria during pregnancy.

In 2005, WHO convened a Technical Expert Group to review the global evidence available for intermittent preventive treatment (IPT) failure and its effectiveness for IPTp. The group concluded the following:

- Even though the IPTp policy was recommended and adopted in 1998 based on limited data, subsequent evidence has confirmed that IPTp is a useful intervention.

- Given the possible detrimental effect that increasing SP resistance would have on the benefits and cost-effectiveness of IPTp with SP, uncertainty exists about how long this intervention with SP will remain useful.

- Currently available SP efficacy data are insufficient to make specific and meaningful changes to current WHO recommendations on IPTp with SP. SP efficacy as currently measured in children cannot be extrapolated directly to the efficacy of IPTp. Therefore, in the absence of new data, the recommendation should be streamlined to state that all countries in stable malaria transmission situations should deploy and scale up the strategy of IPTp with SP until relevant data on its effectiveness under current conditions become available for WHO to review this recommendation. This revision demands

    - The urgent evaluation of the in vivo therapeutic and protective efficacy of SP in asymptomatic pregnant women, and its correlation with molecular markers of SP resistance, and the continuous monitoring of effectiveness of IPTp with SP

    - The urgent and comprehensive evaluation of alternative antimalarials for IPTp to inform the review of WHO recommendations and ensure an evidence-based IPTp strategy

- WHO provide methodological guidelines and protocols for these evaluations

The WHO recommendations were based on a comprehensive evaluation of published literature on past resistance studies and efficacy trials done by ter Kuile, van Eijk, and Filler (2007) and published separately in *JAMA*. The main findings of that paper are summarized in the box.

Summary of ter Kuile, van Eijk, and Filler (2007)

This paper examined the effect of increasing resistance to SP on the efficacy of ITPp in Africa. The investigators performed a comprehensive review of literature published between 1966 and December 2006 to identify potentially relevant IPTp and malaria treatment trials to estimate the degree of SP resistance in the population when it was used for the treatment of uncomplicated malaria compared to IPTp trials in the same geographic location.

Nine trials of IPTp with SP in Africa were identified and matched by year and location with treatment studies of SP among symptomatic children. Seven of the nine trials were judged by the investigators to be of acceptable quality for analysis; two of the nine trials were judged to be of low quality.

Thirteen treatment studies in children were identified to match the IPTp studies. Good matching quality (defined as being conducted at a similar time and the same location or within 100 miles of each other) was found for seven of the nine IPTp studies.

Four of the nine trials compared two-dose IPTp with SP to case management or placebo in women during their first or second pregnancy. The IPTp reduced the risk of placental malaria by 52 percent, the risk of low birth weight by 29 percent, and the risk of anemia by 10 percent. The effect did not vary by SP resistance levels (range, 19 percent–26 percent).

Three of the nine trials compared two-dose to monthly IPTp with SP. Among HIV-positive women in their first or second pregnancy, monthly IPTp resulted in less placental malaria and higher birth weight over the range of SP resistance tested (8–39 percent). Among HIV-negative women, monthly dosing demonstrated no conclusive additional effect.

From their review, the authors concluded that "2-dose IPT with sulfadoxine pyrimethamine during pregnancy maintains its efficacy….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 WHO's African Regional Office to issue a statement on the continued use of SP for IPTp." The authors also suggest that "with the emerging spread of high-grade resistance to sulfadoxine-pyrimethamine, high priority must be given to determining safe and affordable alternatives. A series of multicenter trials are planned 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" (ter Kuile, van Eijk, and Filler 2007, 2615).

Therapeutic efficacy studies carried out in Burundi in 2000–01 illustrated a failure rate of 49 percent with SP when used for the treatment of uncomplicated malaria in Burundi. As result, Burundi changed its first-line treatment for malaria from SP to an artemisinin-based combination therapy in late 2003. At the same time, the Ministry of Public Health decided to discontinue IPTp

with SP. Burundi's malaria in pregnancy strategy currently focuses on prevention through increasing ownership and use of long-lasting insecticide-treated nets among pregnant women.

Recent discussions in the country have considered reintroducing a strategy of IPTp; however, differing schools of thought appear to exist regarding the usefulness of SP for IPTp in light of the high levels of drug resistance observed for treatment in 2001. Although many stakeholders felt that IPTp should be reintroduced, a strong lobby of clinicians does not support using SP for IPTp.

The Programme National Intégré Lutte contre le Paludisme (PNILP; National Integrated Malaria Control Program), in collaboration with the Centre Hospitalier Universitaire d'Avicenne in France, has developed a proposal for studying the efficacy of mefloquine (MQ) for IPTp. The proposal, which is currently in draft form, has been sent to partners for comments. The funding for this study will be from the Global Fund to Fight AIDS, Tuberculosis and Malaria. However, findings from the research are not likely to be available for two years after commencement of the study, and concern exists about the significant mortality and morbidity in pregnant women and their newborns that may result from malaria during pregnancy in the interim. This concern has prompted the PNILP to look for alternative mechanisms to prevent the excess mortality in the meantime.

The PNILP and U.S. Agency for International Development/Burundi requested that Management Sciences for Health's Strengthening Pharmaceutical Systems Program (MSH/SPS) conduct a literature search on SP efficacy for IPTp as well as studies on treatment failures conducted since the review by ter Kuile, van Eijk, and Filler (2007) (which looked at published studies through December 2006) to assess whether the same conclusions and recommendations are still likely to be valid.

Purpose of This Literature Review

This paper presents a review of published and gray literature between January 2007 and December 2009 on the relationship between SP efficacy for the treatment of malaria cases and its efficacy for the prevention of malaria in pregnancy. The paper assumes that the review done by ter Kuile, van Eijk, and Filler (2007) was comprehensive and the recommendations based on valid scientific analysis. The purpose of this review is to establish whether new data published after December 2006 are likely to change the recommendations of the earlier report and the WHO (2005).

METHODOLOGY

The authors searched three databases—Medline, PubMed, and Popline—for studies and trials published between January 2007 and December 2009 using the following keywords—

- IPTp and malaria and resistance and efficacy
- IPTp and malaria and efficacy
- Sulfadoxine pyrimethamine and pregnancy and malaria and efficacy
- Sulphadoxine pyrimethamine and pregnancy and malaria and efficacy
- Sulfadoxine pyrimethamine malaria efficacy
- Sulphadoxine pyrimethamine malaria efficacy
- Sulfadoxine pyrimethamine malaria resistance
- Sulphadoxine pyrimethamine malaria resistan
- IPT and sulfadoxine pyrimethamine
- IPT and malaria

Six trials on treatment of uncomplicated malaria with SP and 11 trials of SP efficacy for the prevention of malaria during pregnancy when used as IPTp were identified. Four of the treatment trials could be matched to the six prevention trials. These were matched with each other based on geographical location of the studies using a methodology similar to that used by ter Kuile and colleagues.

Table 1 summarizes the main findings of the 11 trials of SP efficacy for the prevention of malaria during pregnancy when used as IPTp. Table 2 presents data from the six trials on treatment of uncomplicated malaria with SP. Table 3 presents the main data from matching the SP efficacy trials in pregnant women to the trials on treatment of uncomplicated malaria with SP. The MSH authors calculated the relative risk[1] for the studies where this figure was not available to obtain a consistent parameter for comparison across the studies.[2]

The following formula was used—

Relative risk = (a / (a + b)) / (c / (c + d))

a = Number of positive outcomes in SP IPTp group
b = Number with negative outcomes in SP IPTp group
c = Number of positive outcomes in comparator
d = Number of positive outcomes in comparator

No other statistical analysis or modeling was performed to analyze the statistical significance of the findings. The purpose of this analysis is to provide a snapshot of new studies to determine whether more sophisticated modeling may be required or if these new studies are likely to

[1] *Relative risk* is the ratio of the chance of a disease developing among members of a population exposed to a factor compared with a similar population not exposed to the factor.
[2] Website for relative risk calculator: http://www.medcalc.be/calc/relative_risk.php.

change previous recommendations to assist the Burundi malaria program in the decision-making process.

DATA ANALYSIS

Table 1. Published Studies of SP Efficacy in Pregnancy

Study Information			Evaluable Participant Analysis			
Author, Year, Title	**Study Objective**	**Geographic Location and Time Frame**	**SP IPTp Endpoint Number of Events/Total Participants Percentage**	**Comparator(s) Endpoint Number of Events/Total Participants Percentage**	**Relative Risk (95% Confidence Interval) (MSH Calculated)**	**Risk as Author Presented**
Diallo et al. 2007 Randomized Clinical Trial of Two Malaria Prophylaxis Regimens for Pregnant Women in Faladie, Mali	To compare the efficacy of two regimens using chloroquine (CQ) or SP during pregnancy and delivery in a village located in an endemic area of Mali	Faladié (District of Kati) located 80 kilometers from Bamako, Mali June 2003–May 2004	*SP* Maternal malaria 14/133 10.5% Anemia 23/133 17.2%	*CQ* Maternal malaria 34/136 25% Anemia 35/136 25.7%	1.1930 (1.0653 to 1.3360) 1.0653 to 1.3360 (0.9820 to 1.2630)	CQ 43.3% SP 79.1% CQ 57.5% SP 74.8% Change in rate of endpoint from enrollment to delivery

Study Information			Evaluable Participant Analysis			
Author, Year, Title	**Study Objective**	**Geographic Location and Time Frame**	**SP IPTp Endpoint Number of Events/Total Participants Percentage**	**Comparator(s) Endpoint Number of Events/Total Participants Percentage**	**Relative Risk (95% Confidence Interval) (MSH Calculated)**	**Risk as Author Presented**
Hommerich et al. 2007 Decline of Placental Malaria in Southern Ghana after the Implementation of Intermittent Preventive Treatment in Pregnancy	Comparison of parasitological and clinical parameters among women delivering at the Presbyterian Mission Hospital in Agogo, southern Ghana, before (2000) and after (2006) implementation of IPTp	Agogo, southern Ghana Recruited between April and June 2006	*Year 2006* Low birth weight 28/225 12.4% Maternal anemia 53/226 23.5% Placental malaria[3] 72/226 31.9% Breakdown by number of doses 0 doses Low birth weight 8/52; 15.4% Anemia 21/53; 39.6% Placental malaria 26/53; 49.1% 1 dose Low birth weight 6/60; 10% Anemia	*Year 2000 (baseline)* Low birth weight 38/197 19.3% Maternal anemia 65/197 33.0% Placental malaria 101/197 51.3%	1.0848 (0.9972 to 1.1801) 1.1424 (1.0115 to 1.2903) 1.4434 (0.2147 to 1.7152)	0.055 (0.31–0.96) 0.82 (0.39–1.72) 0.41 (0.25–0.68) Calculated as adjusted odds ratio

[3] Placental malaria measured by polymerase chain reaction.

Study Information			Evaluable Participant Analysis			
Author, Year, Title	**Study Objective**	**Geographic Location and Time Frame**	**SP IPTp Endpoint Number of Events/Total Participants Percentage**	**Comparator(s) Endpoint Number of Events/Total Participants Percentage**	**Relative Risk (95% Confidence Interval) (MSH Calculated)**	**Risk as Author Presented**
			10/60; 16.7% Placental malaria 13/60; 21.7% 2 doses Low birth weight 9/59; 15.3% Anemia 16/59; 27.1% Placental malaria 19/59; 32.2% 3 doses Low birth weight 5/54; 9.3% Anemia 6/55; 11.1% Placental malaria 14/55; 25.9%			
Tagbor et al. 2007 Comparison of the Therapeutic Efficacy of Chloroquine and Sulphadoxine-Pyremethamine in Children and Pregnant Women	To compare the parasitological failure rates of children under five and pregnant women with parasitemia treated with CQ or SP	Nkoranza, Ghana March 2003–September 2004	*SP* Parasitological failure Day 14 10/212 4.76% *SP* Parasitological failure Day 28 34/208 16.35%	*CQ* Parasitological failure Day 14 15/212 7.08% *CQ* Parasitological failure Day 28 62/208 29.81%	1.0254 (0.9776 to 1.0755) 1.1918 (1.0708 to 1.3264)	Author calculated relative risk comparing children and pregnancy rather than comparing the two treatments

Study Information			Evaluable Participant Analysis			
Author, Year, Title	**Study Objective**	**Geographic Location and Time Frame**	**SP IPTp Endpoint Number of Events/Total Participants Percentage**	**Comparator(s) Endpoint Number of Events/Total Participants Percentage**	**Relative Risk (95% Confidence Interval) (MSH Calculated)**	**Risk as Author Presented**
ter Kuile, Eijk and Filler 2007	**See summary in box**					
Tukur et al. 2007 A Comparison of Sulfadoxine-Pyrimethamine with Chloroquine and Pyrimethamine for Prevention of Malaria in Pregnant Nigerian Women	To prove the hypothesis that SP would be more effective than CQ + pyrimethamine (P) in preventing malaria in pregnancy among Nigerian women	Jos, Nigeria April–December 2002	*SP* Peripheral parasitemia 0/179 0.0% Anemia 2/173 1.2 %	*CQ+P* Peripheral parasitemia 11/177 78.3% Anemia 9/180 5.0%	1.0661 (1.0249 to 1.1089) 1.0405 (1.0025 to 1.0799)	0 (0.0–0.38) 0.36 (0.10–1.3) Calculated as risk ratio
Asa et al. 2008 Efficacy of Intermittent Preventive Treatment of Malaria with Sulphadoxine-Pyrimethamine in Preventing Anaemia in Pregnancy among Nigerian Women	To evaluate the efficacy of IPT of malaria using SP in the prevention of anemia in women of low parity in a low socioeconomic, malaria-endemic setting	Enuwa in Ile-Ife, Osun State, Nigeria Must purchase article for more info. Study date not available.	*SP* Anemia 33/146 22.6%	*CQ* Anemia 52/140 37.1%	1.2313 (1.0550 to 1.4372)	0.5 (0.290.85) Calculated as odds ratio

Study Information			Evaluable Participant Analysis			
Author, Year, Title	**Study Objective**	**Geographic Location and Time Frame**	**SP IPTp Endpoint Number of Events/Total Participants Percentage**	**Comparator(s) Endpoint Number of Events/Total Participants Percentage**	**Relative Risk (95% Confidence Interval) (MSH Calculated)**	**Risk as Author Presented**
Clerk et al. 2008 A Randomized, Controlled Trial of Intermittent Preventive Treatment with Sulfadoxine-Pyrimethamine, Amodiaquine, or the Combination in Pregnant Women in Ghana	To study the efficacy, safety, and tolerance of amodiaquine (AQ) or the combination of AQ and SP (SPAQ) as possible alternative treatments to SP	Kassena-Nankana district of Ghana June 2004–February 2007	*SP vs. AQ* Anemia 167/292 58.2%	*AQ* Anemia 170/276 61.6%	*SP vs. AQ* 1.1146 (0.9128 to 1.3611)	1.05 (0.85–1.30)
			Peripheral parasitemia 60/316 19.0%	Peripheral parasitemia 59/301 19.6%	1.0076 (0.9328 to 1.0885)	0.92 (0.57–1.48)
			Placental parasitemia 82/202 28.7%	Placental parasitemia 38/183 20.8%	0.7794 (0.6836 to 0.8885)	0.74 (0.46–1.17)
			Low birth weight 68/286 23.8%	Low birth weight 52/270 19.3%	0.9441 (0.8653 to 1.0300)	0.83 (0.58–1.19)
			SP vs. SPAQ Anemia 256/445 56.6%	*SPAQ* Anemia 228/438 52.1%	*SPAQ* 0.8858 (0.7658 to 1.0247)	0.92 (0.77–1.10)
			Peripheral parasitemia 106/470 22.6%	Peripheral parasitemia 99/463 21.4%	0.9851 (0.9203 to 1.0545)	0.83 (0.59–1.16)
			Placental parasitemia 74/326 22.8%	Placental parasitemia 85/308 27.6%	1.0676 (0.9751 to 1.1689)	1.07 (0.78–1.48)

Study Information			Evaluable Participant Analysis			
Author, Year, Title	**Study Objective**	**Geographic Location and Time Frame**	**SP IPTp Endpoint Number of Events/Total Participants Percentage**	**Comparator(s) Endpoint Number of Events/Total Participants Percentage**	**Relative Risk (95% Confidence Interval) (MSH Calculated)**	**Risk as Author Presented**
			Low birth weight 105 /438 24.0%	Low birth weight 96/425 22.6%	0.9821 (0.9125 to 1.0570)	0.96 (0.73–1.27) Calculated as risk ratio
Menéndez et al. 2008 A Randomized Placebo-Controlled Trial of Intermittent Preventive Treatment in Pregnant Women in the Context of Insecticide Treated Nets Delivered through the Antenatal Clinic	A double-blind, individually randomized, placebo-controlled trial to estimate the additive protective effect of two-dose IPTp with SP to that of insecticide-treated nets (ITNs) on low birth weight prevalence	Maputo, Mozambique Manhiça District, southern Mozambique August 2003–April 2005	*SP and ITNs* Low birth weight 59/496 11.9%	*Placebo and ITNs* Low birth weight 58/494 11.7%	0. 0.9983 (0.9537 to 1.0448)	0.99 (0.70–1.39) Relative risk
Ouédraogo et al. 2008 Comparative Impact of Three Malaria Preventive Regimens during Pregnancy on Maternal Anemia Due to Malaria in Burkina Faso	To compare the efficacy of three regimens of malaria prevention during pregnancy for the reduction of anemia between the first and third prenatal consultations	Need to purchase article for more information	*SP* Maternal anemia The hemoglobin gain was more significant with the IPT using SP compared to the other treatment arms.	*Weekly CQ* *3-dose CQ* Maternal anemia In the two CQ arms, there was no significant reduction either at second prenatal consultation (p=0.72) or third prenatal consultation.	Not available	Not available

Study Information			Evaluable Participant Analysis			
Author, Year, Title	**Study Objective**	**Geographic Location and Time Frame**	**SP IPTp Endpoint Number of Events/Total Participants Percentage**	**Comparator(s) Endpoint Number of Events/Total Participants Percentage**	**Relative Risk (95% Confidence Interval) (MSH Calculated)**	**Risk as Author Presented**
Briand et al. 2009 Intermittent Treatment for the Prevention of Malaria during Pregnancy in Benin: A Randomized, Open-Label Equivalence Trial Comparing Sulfadoxine-Pyrimethamine with Mefloquine	An equivalent study designed to test the hypothesis that MQ is as efficacious as SP to prevent malaria in pregnancy and that it could replace SP when resistance of *Plasmodium falciparum* becomes too elevated	Ouidah, 40 kilometers from Cotonou, Benin July 2005–April 2008	*SP* Low birth weight 72/730 9.8%	*MQ* Low birth weight 59/735 8.2%	0.98 (0.9491 to 1.0120)	−1.8% (−4.8% to 1.1%) Author calculated as percentage difference between low birth weights in treatment groups.
Gies et al. 2009 Individual Efficacy of Intermittent Preventive Treatment with Sulfadoxine-Pyrimethamine in Primi- and Secundigravidae in Rural Burkina Faso: Impact on Parasitaemia, Anaemia and Birth Weight	To assess the efficacy at individual level of ITPp with SP (IPTp-SP) in primi- and secundigravidae in rural Burkina Faso	Boromo Health District, western Burkina Faso September 2004–October 2006	*≥ 2 doses* Placental parasitemia at delivery 62/617 10.0% Anemia at delivery 146/540 27.0% Low birth weight 104/812 12.8%	*0 doses* Placental parasitemia at delivery 5/9 55.6% Anemia at delivery 7/12 58.3% Low birth weight 19/52 36.5% *1 dose*	2.9234 (1.2929 to 6.6100) 1.7511 (0.8948 to 3.4270) 1.3739 (1.1160 to 1.6915) *1 dose*	0 doses Data for 0 doses combined with 1 dose for anemia and parasitemia

Study Information			Evaluable Participant Analysis			
Author, Year, Title	**Study Objective**	**Geographic Location and Time Frame**	**SP IPTp Endpoint Number of Events/Total Participants Percentage**	**Comparator(s) Endpoint Number of Events/Total Participants Percentage**	**Relative Risk (95% Confidence Interval) (MSH Calculated)**	**Risk as Author Presented**
				Placental parasitemia at delivery 91/260 35% Anemia at delivery 92/240 38.3% Low birth weight 100/408 24.5%	1.3839 (1.2610 to 1.5188) 2.2834 (2.0246 to 2.5753) 1.1832 (1.0576 to 1.3237)	0.04 (0.003–0.60) 0.31 (0.18–0.52) 0.11 (0.07–0.17) Adjusted odds ratio
Tiono et al. 2009 Placental Malaria and Low Birth Weight in Pregnant Women Living in a Rural Area of Burkina Faso Following the Use of Three Preventive Treatment Regimens	To compare the efficacy of two IPT regimens, using chloroquine (CQ) or SP, with the classic weekly chemoprophylaxis regimen (CWC) using CQ in reducing the adverse outcomes of malaria infection, for the mother and the fetus	Bousse, a district located about 50 kilometers northwest of Ouagadougou, Burkina Faso September–December 2003	*SP* Placental malaria 15/141 10.6% Low birth weight 16/137 11.6%	*CWC/CQ* Placental malaria 26/137 18.8% Low birth weight 32/134 23.9% *IPT/CQ* Placental malaria 23/145 15.9% Low birth weight 22/138	1.1029 (0.9989 to 1.2178) 1.1603 (1.0366 to 1.2987) 1.0621 (0.9699 to 1.1630) 1.0507 (0.9557 to 1.1552)	0.44 (0.22–0.90) 0.38 (0.19–0.72) Not statistically significant Not statistically significant

Study Information			Evaluable Participant Analysis			
Author, Year, Title	**Study Objective**	**Geographic Location and Time Frame**	**SP IPTp Endpoint Number of Events/Total Participants Percentage**	**Comparator(s) Endpoint Number of Events/Total Participants Percentage**	**Relative Risk (95% Confidence Interval) (MSH Calculated)**	**Risk as Author Presented**
				15.6%		Calculated as odds ratio

Table 2. Published Studies of SP Efficacy in Nonpregnant Population

Study Information			Evaluable Participant Analysis			
Author and Publication Year	**Title**	**Geographic Location Time Frame Study Population**	**SP Treatment Day Number of Treatment Failures/Total Participants %**	**Comparator Treatment Day Number of Treatment Failures/Total Participants %**	**Relative Risk (95% Confidence Interval) MSH Calculated**	**Risk as Author Presented**
Zongo et al. 2005	Amodiaquine, Sulfadoxine-Pyrimethamine, and Combination Therapy for Uncomplicated Falciparum Malaria: A Randomized Controlled Trial from Burkina Faso	Bobo-Dioulasso, Burkina Faso Time frame not provided 6 months of age or older	*SP* Day 28 24/264 9.1%	*AQ* Day 28 37/208 17.9% *AQ+SP* Day 28 12/285 4.2%	*AQ* 1.1058 (1.0271 to 1.1905) *AQ+SP* 0.9491 (0.9071 to 0.9930)	8.8% (3.1–14.4%) 4.9% (0.7–9.1%) Calculated as risk difference
Oyakhirome et al. 2007	Randomized Controlled Trial of Fosmidomycin-Clindamycin versus Sulfadoxine-Pyrimethamine in the Treatment of *Plasmodium falciparum* Malaria	July 2005–March 2006 Lambaréné, Gabon 3 to 14 years of age	*SP* Day 28 3/49 6%	*Fosmidomycin-clindamycin (FC)* Day 28 3/49 6%	1.0000 (0.9038 to 1.1064)	FC 94 (83–98) SP 94 (83–98) Cure rates (%) Not compared to each other by risk

Study Information			Evaluable Participant Analysis			
Author and Publication Year	**Title**	**Geographic Location Time Frame Study Population**	**SP Treatment Day Number of Treatment Failures/Total Participants %**	**Comparator Treatment Day Number of Treatment Failures/Total Participants %**	**Relative Risk (95% Confidence Interval) MSH Calculated**	**Risk as Author Presented**
Tagbor et al. 2007	Comparison of the Therapeutic Efficacy of Chloroquine and Sulphadoxine-Pyremethamine in Children and Pregnant Women	Nkoranza, Ghana August 2003–September 2004 6 months to 5 years	*SP* Day 14 45/93 48.39% Day 28 55/94 58.51%	*CQ* Day 14 23/92 25% Day 28 32/88 36.36%	*CQ* Day 14 0.6882 (0.9120 to 1.6968) Day 28 0.6520 (0.4891 to 0.8690)	Author calculated relative risk comparing children and pregnancy rather than comparing the two treatments.
Allen et al. 2009	Efficacy of Sulphadoxine-Pyrimethamine with or without Artesunate for the Treatment of Uncomplicated *Plasmodium falciparum* Malaria in Southern Mozambique: A Randomized Controlled Trial	Southern Mozambique Catuane and Namaacha (2003), thereafter Boane and Magude (2004–2005) Over 1 year old; average age was 11 years	*SP* Reinfection by Day 42 18/174 10.3%	*Artesunate (AS)/SP* Reinfection by Day 42 9/182 4.9%	0.9409 (0.8865 to 0.9986)	. 0.2 (0.1–0.6) Calculated as hazard ratio: AS/SP vs. SP

Study Information			Evaluable Participant Analysis			
Author and Publication Year	**Title**	**Geographic Location Time Frame Study Population**	**SP Treatment Day Number of Treatment Failures/Total Participants %**	**Comparator Treatment Day Number of Treatment Failures/Total Participants %**	**Relative Risk (95% Confidence Interval) MSH Calculated**	**Risk as Author Presented**
Faucher et al. 2009	Comparison of Sulfadoxine-Pyrimethamine, Unsupervised Artemether-Lumefantrine, and Unsupervised Artesunate-Amodiaquine Fixed-Dose Formulation for Uncomplicated *Plasmodium falciparum* Malaria in Benin: A Randomized Effectiveness Noninferiority Trial	Allada and Sekou, southern Benin May–November 2007 Children 6–60 months of age	*SP* Day 28 36/46 78.2% Day 42 38/44 86.4%	*Artemether-lumefantrine (AL)* Day 28 10/83 12.0% Day 42 18/81 22.2% *AS/AQ* Day 28 21/88 23.9% Day 42 33/86 38.4%	*AL* Day 28 0.2472 (0.1420 to 0.4302) Day 42 0.1753 (0.0826 to 0.3722) *AS/AQ* Day 28 0.2855 (0.1630 to 0.5002) Day 42 0.2213 (0.1033 to 0.4741)	 26.3 (10.0–68.8) 22.2 (8.1–60.7) 11.5 (4.9–27.0) 10.2 (3.9–26.7) Calculated as odds ratio

Study Information			Evaluable Participant Analysis			
Author and Publication Year	**Title**	**Geographic Location Time Frame Study Population**	**SP Treatment Day Number of Treatment Failures/Total Participants %**	**Comparator Treatment Day Number of Treatment Failures/Total Participants %**	**Relative Risk (95% Confidence Interval) MSH Calculated**	**Risk as Author Presented**
Tekete et al. 2009	Efficacy of Chloroquine, Amodiaquine and Sulphadoxine-Pyrimethamine for the Treatment of Uncomplicated Falciparum Malaria: Revisiting Molecular Markers in an Area of Emerging AQ and SP Resistance in Mali	Kolle, Mali August 2002–January 2003 July 2003–January 2004 Between 6 and 59 months of age	*SP* Day 14 8/116 6.9% Day 28 15/115 13.1%	*CQ* Day 14 89/202 44.1% Day 28 169/202 83.7% *AQ* Day 14 11/108 10.2% Day 28 42/108 38.1%	*CQ* Day 14 1.6643 (1.4585 to 1.8992) Day 28 5.3228 (3.8651 to 7.3302) *AQ* Day 14 1.0366 (0.9564 to 1.1236) Day 28 1.4229 (1.2050 to 1.6803)	Not calculated. Author calculated early treatment failure, late clinical failure, late parasitological failure, and adequate clinical and parasitological response.

Table 3. Matched Treatment Studies among Symptomatic Children[4]

					Quality of Trial Match			
SP Efficacy Trial	**Trial Population**	**SP Treatment Day % Failure**	**SP IPTp Trial**	**Endpoint Treatment Failure %**	**Difference in Study Period**	**Location**	**Overall**	**Comments**
Tagbor et al. 2007	6 months to 5 years	Day 14 48.39% Day 28 58.51%	Tagbor et al. 2007	*SP* Day 28 Parasitological failure 4.76% Day 28 Parasitological failure 16.35%	Overlap	Overlap	Good	Matched by author The high levels of SP resistance for treatment do not seem to translate to SP failure for IPTp.
Tagbor et al. 2007	6 months to 5 years	Day 14 48.39% Day 28 58.51%	Clerk et al. 2008	*SP vs. AQ* Anemia 58.2% Peripheral parasitemia 19.0% Placental parasitemia 28.7% Low birth weight 23.8% *SP vs. SPAQ* Anemia 56.6%	Overlap	< 100 miles	Moderate	The high levels of SP resistance appear to correlate with less efficacy for preventing anemia on pregnant women. Placental parasitemia and low birth weight appear to be prevented in more than 75 percent of neonates.

[4] 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 two matching studies overlapped with the IPT study period

					Quality of Trial Match			
SP Efficacy Trial	**Trial Population**	**SP Treatment Day % Failure**	**SP IPTp Trial**	**Endpoint Treatment Failure %**	**Difference in Study Period**	**Location**	**Overall**	**Comments**
				Peripheral parasitemia 22.6% Placental parasitemia 22.8% Low birth weight 24.0%				
Tagbor et al. 2007	6 months to 5 years	Day 14 48.39% Day 28 58.51%	Hommerich et al. 2007	Low birth weight 12.4% Maternal anemia 23.5% Placental malaria 31.9%	< 2 years	< 100 miles	Moderate	SP still has a protective efficacy greater than 75 percent for preventing material anemia and greater than 85 percent for preventing low birth weight in neonates.
Faucher et al. 2009	Children ages 6–60 months	Day 28 78.2% Day 42 86.4%	Briand et al. 2009	Low birth weight 9.8%	Overlap	Overlap	Good	Despite high rates of SP resistance when used for treatment, SP still has a protective efficacy of over 90 percent for preventing low birth weight in neonates.

					Quality of Trial Match			
SP Efficacy Trial	**Trial Population**	**SP Treatment Day % Failure**	**SP IPTp Trial**	**Endpoint Treatment Failure %**	**Difference in Study Period**	**Location**	**Overall**	**Comments**
Allen et al. 2009	Over 1 year	Day 42 10.3%	Menéndez et al. 2008	Low birth weight 11.9%	Overlap	Overlap	Good	SP resistance for treatment in this study had not reached critical levels. SP also still has a protective efficacy of almost 90 percent for preventing low birth weight in neonates.
Tekete et al. 2009	Between 6 and 59 months	Day 14 6.9% Day 28 13.1%	Diallo et al. 2007	Maternal malaria 10.5% Anemia 17.2%	Overlap	Overlap	Good	SP resistance for treatment in this study had not reached critical levels. SP also still has a protective efficacy of over 80 percent for preventing low birth weight in neonates and more than 70 percent for preventing material anemia.

CONCLUSIONS AND RECOMMENDATIONS

The literature review identified six trials on treatment of uncomplicated malaria with SP and 11 trials of SP efficacy for the prevention of malaria during pregnancy when used as IPTp since December 2006. Four of the treatment trials could be matched to the six prevention trials. These were matched with each other based on geographical location of the studies (table 3). Of these, one (Tagbor et al. 2007) had already been matched by the investigators of the study.

Tagbor et al. (2007) conclude that although SP failure rates for the treatment of uncomplicated malaria were 48.39 percent on day 14 and 58.21 percent on day 28, when SP was used for the prevention of malaria during pregnancy, SP failure rates were 4.76 percent and 16.35 percent, respectively. This, the high levels of resistance did not correlate with the same levels of SP failure rates when it was used to prevent malaria during pregnancy.

Tagbor et al. (2007) was matched by the authors of this review with Hommerich et al. (2007). The two studies were conducted within two years of each other and within a 100-mile geographical radius in Burkina Faso. SP still showed a protective efficacy greater than 75 percent for preventing material anemia and greater than 85 percent for preventing low birth weight in neonates despite treatment failures of greater than 50 percent.

Faucher et al. (2009) was matched with Briand et al. (2009). Both studies overlapped well in terms of time frame as well as geographical proximity in Benin. Faucher et al. (2009) recorded treatment failures of 78.2 percent on day 28 and 86.4 percent on day 42. However, SP failure rates when used for the prevention of malaria during pregnancy were only 9.8 percent (Briand et al.).

Allen et al. (2009) recorded treatment failures of 10.3% in Mozambique. These failure rates had not reached the critical rates observed in other countries. This was matched with a study on SP efficiacy for preventing malaria in pregnancy conducted by Menendez et al (2008) which indicted low birth weight rates of 11.9%.

The matched studies indicate that in areas of high SP resistance when used for the treatment of uncomplicated malaria in children, although SP efficacy for the prevention of malaria during pregnancy may have also declined, SP remains efficacious for the prevention of placental malaria, maternal anemia, and low birth weight in 70–90 percent of pregnant women. These findings suggest that the WHO recommendations of 2005 and previous expert recommendations (ter Kuile, van Eijk, and Filler 2007) may still be valid.

In the absence of suitable alternatives to SP for IPTp, this report recommends that the use of SP for IPTp in Burundi be reconsidered. The risks of significant mortality and morbidity from malaria during pregnancy should be weighed against the use of SP, whose efficacy may be waning. Policy makers should consider that SP may potentially be at least 70 percent efficacious for the prevention of placental malaria, maternal anemia, and low birth weight in pregnant women in Burundi. In the meantime, SP efficacy in pregnancy should continue to be monitored, and alternatives for its replacement should be tested.

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