A Randomized, Controlled Trial of Intermittent Preventive Treatment with Sulfadoxine-Pyrimethamine, Amodiaquine, or the Combination in Pregnant Women in Ghana

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Background. The use of sulfadoxine-pyrimethamine (SP) for intermittent preventive treatment in pregnancy (IPTp) is threatened by the spread of resistance to SP. Therefore, we studied the efficacy, safety, and tolerance of amodiaquine (AQ) or the combination of AQ and SP (SPAQ) as possible alternative treatments.

Methods. The study was performed in Ghana from June 2004 through February 2007. Women were individually randomized to receive IPTp with SP ($n = 1328$), AQ ($n = 986$), or SPAQ ($n = 1328$). Incidences of anemia, peripheral anemia, and placental parasitemia at delivery were assessed for paucigravidae, as were the birth weights of their infants. Delivery outcomes and the incidence of adverse events were investigated for all women.

Results. The prevalences of anemia (as defined by a hemoglobin concentration of <11.0 g/dL) at delivery were comparable between the SP and AQ groups and between the SP and SPAQ groups. Similarly, there was no significant difference between the SP and AQ groups or between the SP and SPAQ groups with regard to the incidences of low birth weight (LBW). Women who received AQ or SPAQ were more likely to report adverse events than were those who received SP.

Conclusion. The effects of IPTp with AQ or SPAQ on maternal anemia and LBW were comparable to the effects of IPTp with SP; however, IPTp regimens that contain AQ are unlikely to be useful as an alternative to IPTp with SP in Ghana, because of a high frequency of associated adverse events.

Trial registration. Clinicaltrials.gov identifier: NCT00146783.

Malaria in pregnancy contributes to maternal anemia and low birth weight (LBW) [1]. The World Health Organization (WHO) recommends administration of sulfadoxine-pyrimethamine (SP) as intermittent preventive treatment (IPT) in pregnancy (IPTp) to pregnant women in sub-Saharan Africa. This policy is based on studies performed in the 1990s in Kenya and Malawi, where transmission of malaria is perennial [2]. IPTp has been little investigated in West Africa, where there is a period of very high transmission during the rainy season, followed by a long period of low transmission [3, 4].

In the context of increasing resistance to SP [5–7], alternative drugs are needed for IPTp. Prevention of new infections is probably the main mechanism of action of IPTp [8]. Therefore, an ideal drug should have a long elimination half-life. In addition, it must have an excellent safety profile, ideally should be given as a single dose, and should be well-tolerated, available, affordable, and acceptable [9, 10]. However, information available on the safety of most antimalarial drugs is insufficient to warrant their regular use in pregnant women [11]. Amodiaquine (AQ) is an effective antimalarial [12–14]. It has been safe and effective when used for IPT in infants [15] and for treatment of uncomplicated malaria in pregnant women [16]. The use of AQ during pregnancy recently was reviewed elsewhere [17]. The efficacy and safety of the combination of SP and AQ (SPAQ) for the treatment

Received 1 February 2008; accepted 24 April 2008; electronically published XX August 2008.

Potential conflicts of interest: none reported.

Presented in part: Meeting on Malaria Control in Africa, London, United Kingdom, 7–8 June 2006.

Financial support: The Gates Malaria Partnership, which is funded by the Bill and Melinda Gates Foundation.

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The Journal of Infectious Diseases 2008; 198:xxx

0022-1899/2008/19808-00XX$15.00
DOI: 10.1086/591944

of uncomplicated malaria has been demonstrated in children [18–20] and in pregnant women [16]. However, to our knowledge, no studies of the efficacy and tolerability of AQ or SPAQ as IPTp have been reported to date. Therefore, we undertook a comparative study of the efficacy and safety of AQ and SPAQ used for IPTp.

SUBJECTS AND METHODS

Study site and population. The study was performed from June 2004 to February 2007 in the Kassena-Nankana district of Ghana, where malaria is highly endemic and is characterized by marked seasonal variation [21]. Rates of parasitemia in children <5 years of age ranged from 33% during the season characterized by low transmission to 65% during the season characterized by high transmission in 2001 [22]. The average entomologic inoculation rate is 418 infective bites per person per year [23]. In 2004, the uncorrected parasitological failure rates at day 28 after treatment with SP or AQ in children <5 years of age were 10.3% and 9.6%, respectively [13]. The prevalence of HIV infection among antenatal attendants was 2.8% in 2004 [24]. Pregnant women of 18–32 weeks' gestation who were attending any of the 13 antenatal clinics (ANCs) in the area were invited to join the study.

Enrollment. Women were screened after informed consent was obtained. Inclusion criteria were availability for follow-up during the pregnancy and willingness to comply with study procedures. Women who presented with a body temperature of ⩾37.5°C, had medical conditions requiring hospital admission, or had known allergies to the study drugs were excluded. At enrollment, information on sociodemographic characteristics, obstetric history, and bed net use were collected; gestational age, blood pressure, height, and weight were assessed; and blood samples were obtained by fingerprick to prepare a thick blood film and to determine the hemoglobin concentration.

Randomization and treatment. Eligible women were individually randomized to receive a single dose of SP (1500 mg of sulfadoxine and 75 mg of pyrimethamine), a full treatment course of AQ (25 mg/kg) or SPAQ given over 3 days. The study drugs and identical placebos were produced and prepacked by Kinapharma in Ghana. The solubility and drug content of each formulation were confirmed by high-pressure liquid chromatography performed at the London School of Hygiene and Tropical Medicine (London, United Kingdom). An independent statistician allocated the drugs to 9 groups that were numbered "1" through "9" (with 3 subgroups per study group). Each woman picked one chip from a bag that contained 9 chips labeled "1" through "9," and she then was assigned to the study group corresponding to that number. Chips were not replaced until all 9 had been selected, after which time the process was repeated. All doses were given under supervision, either at the ANC (on day 0) or at home (on days 1 and 2). Women received up to 3 courses of IPTp, with a minimum interval of 4 weeks between courses. All pregnant women were routinely prescribed iron and folate supplementation.

Adverse events. Women were visited at home 7–10 days after each course of IPTp, to assess the incidence of adverse events attributable to the study drugs. Agranulocytosis and hepatotoxicity were not assessed because of logistical constraints. Women were advised to report at a health facility if they experienced any untoward effect of drugs before or after a home visit.

Observations on the course and outcome of pregnancy. Pregnancy outcomes and the health status of infants after the neonatal period were assessed for all randomized women. Hemoglobin concentration, peripheral and placental parasitemia, and birth weight were assessed only in primigravidae and secundigravidae, because any effect of IPTp is likely to be evident in these women.

The birth weight and gestational age of infants delivered at health facilities, as assessed by a modification of Dubowitz's examination [25], were recorded within 24 h of delivery. The hemoglobin concentration was measured, and a peripheral blood film and a placental blood film were prepared. Women who delivered at home were visited within one week of delivery for the assessment of infant weight, the maternal hemoglobin concentration, and the presence of peripheral blood parasitemia.

Laboratory investigations. Hemoglobin concentrations were determined using a HemoCue photometer (HemoCue). Thick blood films were stained with Giemsa, asexual parasites were counted against 200 WBCs, and parasite density was computed under the assumption of an average WBC count of 8000 cells/μL. All blood slides were read independently by 2 microscopists who were blinded to the treatment codes of the women. Discrepant results were resolved by a third microscopist.

Drug susceptibility study. The efficacy of the drugs in clearing peripheral parasitemia by day 28 after a first course of IPTp among women who had parasitemia at enrollment was assessed using a modified WHO protocol [26]. The sample size for this substudy was calculated to detect a parasite clearance rate of 80% by day 28, at 95% significance and 80% power, under the assumption that the parasitological response would be no less than 78% for SP and 86% for AQ or SPAQ, as observed in children <5 years of age in the area [13]. Allowing for a 15% loss to follow-up on day 28, a total of 615 women were needed for the study. However, this number of women was not attained because of a very low rate of enrollment, as well as logistic constraints. Individuals who consented to participate in this substudy were tested for malaria parasitemia by use of the OptiMAL-IT (Diamed AG) test kit; parasitemia was confirmed by microscopic examination. Blood slides and filter paper samples were obtained from these women on days 14 and 28. Merozoite surface protein 2 gene *(msp2)* polymorphisms were studied in pretreatment and posttreatment samples obtained from women who failed to clear parasitemia by days 14 or 28, to differentiate recrudescences

from new infections by use of the methods described by Snounou et al. [27].

Definitions. Anemia and severe anemia were defined by hemoglobin concentrations of <11.0 g/dL and <7.0 g/dL, respectively. Thirty-nine percent of infants had their weights assessed between days 1 and 7 after delivery. For these infants, birth weight was estimated using adjustment factors obtained from Gambian infants by D'Alessandro et al. [28]. All analyses of birth weight refer to the adjusted birth weights of singleton newborns. Infants weighing <2500 g were classified as having a LBW. LBW infants for whom a Dubowitz's score was obtained were classified as premature if their gestational age was <37 weeks or as having intrauterine growth retardation (IUGR) if the gestational age was ⩾37 weeks. Seasons were defined using data on rainfall measurements in the area: the period from March through June was considered to be the "prerainy season"; July through October, the "rainy season"; and November through February, the "postrainy season."

Statistical analysis. The sample size was calculated to allow detection of an 11% difference in the prevalence of anemia among primigravidae and secundigravidae who received AQ or SPAQ, compared with those who received SP, at 95% significance and 80% power, under the assumption of a 56% prevalence of anemia at delivery in the SP arm, on the basis of a preliminary analysis of the prevalence of anemia at delivery among 288 women. Allowing for a 25% loss to follow-up, 433 primigravidae and secundigravidae were needed in each arm. A larger number of women (1891 women) were eventually enrolled, because of an additional concurrent study that was undertaken to assess the efficacy of the study drugs in a subset of the women who had parasitemia at enrollment. Eligible multigravidae were also enrolled to assess safety end points. Therefore, a total of 3643 women were enrolled in the study.

Among women for whom data on outcome measurements were available, analysis was performed on an intent-to-treat basis. Differences in proportions were tested using the χ^2 test or Fisher's exact test, when appropriate. Multivariate regression analysis was used to investigate the effect of selected risk factors on anemia, parasitemia, and birth weight. Risk factors for which $P \leqslant .1$ were included in the final regression models used to assess the effect of the study drugs. All comparisons with AQ were restricted to the period before the data safety and monitoring board (DSMB) discontinued allocation to the AQ arm. Comparisons between SP and SPAQ groups covered the entire duration of the study.

Ethical considerations. The institutional review boards of the Ghana Health Service, the Navrongo Health Research Centre, and the London School of Hygiene and Tropical Medicine approved the study protocol.

RESULTS

Overall, 3643 of the 4998 women who underwent screening to participate in the study were enrolled and randomized to receive SP ($n = 1329$), AQ ($n = 986$), or SPAQ ($n = 1328$). One woman was excluded after randomization because her gestation was >32 weeks. A total of 1891 (52%) of 3642 women were primigravidae or secundigravidae (figure 1). The distribution of patient characteristics at baseline was similar between the study groups (table 1). After an interim analysis, the DSMB stopped enrollment of women into the AQ arm. Follow-up rates for the primary outcome of anemia in the 3 study groups were as follows: for the SP group, 64%; for the AQ group, 55%; and for the SPAQ group, 63%. Prevalences of anemia and parasitemia at baseline did not differ significantly between women with or without data missing (78% vs. 80% [$P = .4$] and 57% vs. 60% [$P = .2$], respectively).

Influence of IPTp on anemia, parasitemia, and birth weight. There was an overall reduction in the prevalences of anemia and parasitemia at delivery, compared with the prevalences noted at enrollment (56% vs. 79% [$P < .001$] and 21% vs. 58%, [$P < .001$], respectively). There also was an overall increase in the mean (±SD) hemoglobin concentration at delivery, compared with that noted at enrollment (10.7 ± 1.8 g/dL [95% confidence interval {CI}, 10.6–10.8 g/dL] vs. 9.9 ± 1.4 g/dL [95% CI, 9.8–10.0 g/dL]) ($P < .001$). These beneficial effects were evident within each treatment arm, and there was no statistically significant difference in the effects between the 3 arms (table 2). Women in the SPAQ arm experienced a reduction in the risk of severe anemia, compared with women in the SP arm, but this difference was just not statistically significant. Prevalences of peripheral and placental parasitemia at delivery were moderately high in each group and did not differ significantly in the AQ or SPAQ groups, compared with the SP group (table 2). The mean birth weight of infants in the AQ and SPAQ groups did not differ significantly from that of infants in the SP group (table 2). The prevalence of peripheral parasitemia varied by season. At enrollment, rates of parasitemia were 42%, 64%, and 71% during the prerainy, rainy, and postrainy seasons, respectively. There were no significant differences in the effect of IPTp when analysis was stratified by season of enrollment (table 3). Twenty-two percent of 1133 singleton newborns had a LBW, and 86% of LBW infants (126 of 146 infants) who had their gestational age assessed were classified as having IUGR-LBW. The proportions of IUGR-LBW infants were comparable between the study groups.

Fifty-four percent of women received 1 course of IPTp, 36% received 2 courses, and 11% received 3 courses (table 4). The mean interval between courses was 5 weeks. The influence of IPTp did not differ between women who received <2 or ⩾2 courses of IPTp (data not shown). There was no statistically significant difference in the risk of anemia (risk ratio [RR], 0.99 [95% CI, 0.85–1.16]; $P = .9$), peripheral parasitemia (RR, 1.16 [95% CI, 0.90–1.49]; $P = .3$), or placental parasitemia (RR, 1.06 [95% CI, 0.80–1.40]; $P = .7$) between women with or without access to a bed net.

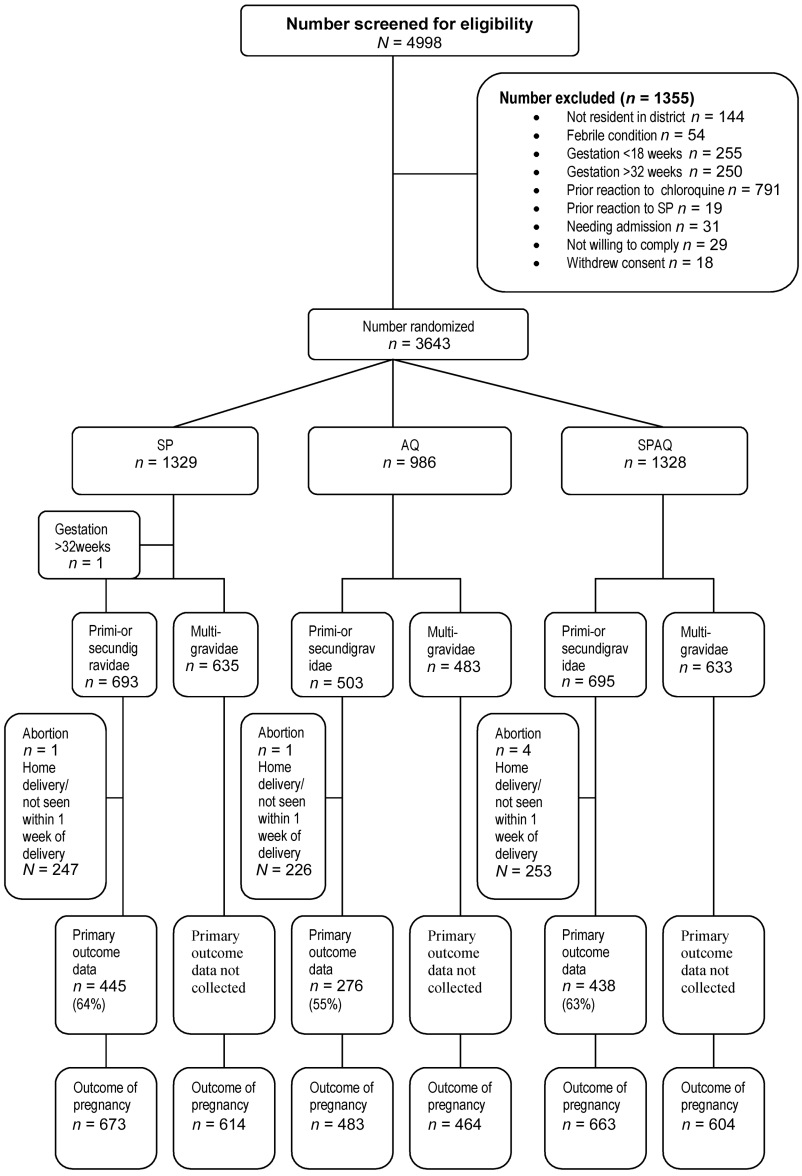

Figure 1. Trial profile. AQ, amodiaquine; SP, sulfadoxine-pyrimethamine; SPAQ, combination of SP and AQ.

Delivery during the rainy or postrainy season was associated with an increased risk of peripheral parasitemia (RR in the rainy season, 1.91 [95% CI, 1.27–2.86]; $P = .002$) (RR in the postrainy season, 1.47 [95% CI, 0.93–2.32]; $P = .1$). A similar observation was made for the risk of placental parasitemia (RR in the rainy season, 2.79 [95% CI, 1.85–4.21; $P < .001$) (RR in the postrainy season, 1.83 [95% CI, 1.15–2.91]; $P = .01$). The effect of season on the prevalence of anemia or LBW was not as marked. However, women were more likely to have anemia if they delivered during the rainy season (RR, 1.24 [95% CI, 1.03–1.49]; $P = .02$). Delivery during the rainy season was associated with an increased risk of LBW on univariate analysis only (RR, 1.43 [95% CI, 1.05–1.93]; $P = .02$).

Drug susceptibility. Follow-up of 248 women occurred on days 14 and 28 after treatment. A total of 139 (56%) of these 248 women were included on the basis of detection of parasitemia by use of the OptiMAL-IT test, and the remainder were included on the basis of detection by microscopy only, because of poor performance of the OptiMAL-IT test. The OptiMAL-IT test had a sensitivity of 28.2% (95% CI, 24.1%–32.6%) and a specificity of 96.1% (95% CI, 93.4%–97.9%) in detecting *Plasmodium falciparum* parasitemia, compared with microscopy. Blood samples were available for 225 (91%) and 229 (92%) of the 248 women on days 14 and 28 after treatment, respectively. After *msp2* genotyping, the corrected parasitological failure rates for SP, AQ, and SPAQ were 6.1% (5 of 82 women), 0% (0 of 37 women), and 3.2% (3 of 93 women) by day 14 and 8.0% (7 of 87 women), 0% (0 of 39 women), and 0% (0 of 97 women) by day 28, respectively.

Adverse events. Data on the incidence of adverse events were available for 3433 (94%) of all 3642 randomized women

Table 1. Characteristics of primigravidae and secundigravidae at study enrollment, by treatment group.

Characteristic	SP (n = 693)	AQ[a] (n = 503)	SPAQ (n = 695)	All (n = 1891)
Age, years				
<20	240 (34.6)	152 (30.2)	220 (31.7)	612 (32.4)
20–24	327 (47.2)	240 (47.7)	331 (47.6)	898 (47.5)
25–29	109 (15.7)	96 (19.1)	128 (18.4)	333 (17.6)
⩾30	17 (2.4)	15 (3.0)	16 (2.3)	48 (2.5)
Mean ± SD	21.1 ± 3.5	21.6 ± 3.5	21.4 ± 3.5	21.3 ± 3.5
Median (IQR)	20.0 (19–23)	20.0 (19–24)	20.0 (19–24)	20.0 (19–24)
No formal education	443 (63.9)	333 (66.2)	447 (64.3)	1223 (64.7)
Bed net use				
Own/share a net	254 (36.7)	187 (37.2)	246 (35.4)	687 (36.3)
Net was treated	180 (26.0)	113 (22.5)	161 (23.2)	454 (24.0)
Slept under net last night	170 (24.5)	138 (27.4)	161 (23.2)	469 (24.8)
Gestation				
2nd trimester	523 (75.5)	375 (74.6)	519 (74.7)	1417 (74.9)
3rd trimester	170 (24.5)	128 (25.4)	176 (25.3)	474 (25.1)
Mean ± SD, weeks	24.0 ± 3.9	24.0 ± 4.0	23.9 ± 3.9	23.9 ± 3.9
Body weight, mean ± SD, kg	56.9 ± 8.5	56.4 ± 8.2	56.0 ± 6.8	56.4 ± 7.8
Height, mean ± SD, cm	158.9 ± 6.5	159.2 ± 6.0	159.0 ± 6.4	159.0 ± 6.3
Hemoglobin level, g/dL				
<7.0	17 (2.5)	22 (4.4)	16 (2.3)	55 (2.9)
7.0–10.9	536 (77.3)	394 (78.3)	506 (72.8)	1436 (75.9)
⩾11.0	140 (20.2)	87 (17.3)	173 (24.9)	400 (21.2)
Mean ± SD	9.8 ± 1.4	9.6 ± 1.4	9.9 ± 1.4	9.8 ± 1.4
Median (IQR)	9.9 (8.9–10.8)	9.8 (8.6–10.6)	10.0 (9.0–10.9)	9.9 (8.9–10.8)
Peripheral parasitemia[b]	405 (58.5)	286 (53.3)	423 (61.0)	1096 (58.0)
GMPD (95% CI)	1217 (1025–1443)	1642 (1354–1992)	1275 (1080–1506)	1333 (1205–1476)

NOTE. Data are the no. (%) of women with the characteristic, unless otherwise indicated. AQ, amodiaquine; CI, confidence interval; GMPD, geometric mean parasite density per microliter; IQR, interquartile range; SP, sulfadoxine-pyrimethamine; SPAQ, combination of SP and AQ.

[a] Enrollment into the AQ arm was terminated by the data safety and monitoring board.

[b] One slide each from the SP and SPAQ arms was of poor quality and could not be read.

who received the first course of IPTp, 1410 (83%) of 1692 women who received a second course, and for 301 (80%) of 374 women who received a third course. After receipt of a first course, women who received AQ or SPAQ were more likely to report an adverse event than were those who received SP (RR, 2.00 [95% CI, 1.76–2.26] [$P < .001$] vs. 1.88 [95% CI, 1.70–2.07] [$P < .001$], respectively) (table 5). The symptoms reported more frequently by women who received AQ or SPAQ were bodily pains and weakness, dizziness, vomiting, and nausea. Symptoms were usually mild. A similar pattern was observed after the second and third courses of IPTp, although the incidences were lower. No severe cutaneous adverse drug event was observed. Because of adverse events, 74 (2.0%) of the 3642 women did not complete the 3-day regimen of the first course of IPTp. However, no woman was withdrawn from the study because of an adverse event. The rates of hospitalization did not differ between study groups.

Delivery outcomes. Follow-up of 3501 (96%) of the women studied occurred 1 month after delivery. The incidences of abortions, stillbirths, neonatal jaundice, and neonatal death did not differ between treatment groups (table 6). A total of 83% of all neonatal deaths were perinatal deaths. There was one maternal death. This woman who died was in the AQ group; she had a normal delivery at the district hospital but died of septicemia 5 days later.

DISCUSSION

Because it was not justifiable to include a control group in the present study, we were unable to prove that the primigravidae and secundigravidae in our trial benefitted from receiving IPTp. However, the observation of substantially lower prevalences of parasitemia and anemia on delivery than at enrollment is consistent with this being the case. Previous research conducted in the study area in 1994–1995 documented a mean birth weight of 2525 g and third-trimester prevalences of anemia (hemoglobin concentration, <10.0 g/dL) and peripheral parasitemia of 78% and 63%, respectively, among paucigravidae who did not use a

Table 2. Comparison of the effect of intermittent preventive treatment in pregnancy with sulfadoxine-pyrimethamine (SP), amodiaquine (AQ), or the combination of SP and AQ (SPAQ) on the prevalences of anemia and parasitemia at the time of delivery and on the birth weight of infants of primigravidae and secundigravidae.

Outcome	All women	Effect of AQ vs. SP[a]				Effect of SPAQ vs. SP			
		SP	AQ	RR[b] or difference in means (95% CI)	*P*	SP	SPAQ	RR[b] or difference in means (95% CI)	*P*
Hemoglobin level, g/dL[c]									
<7.0	2.9	4.8	4.0	0.83 (0.38–1.83)	.6	3.6	1.6	0.44 (0.18–1.07)	.07
<11.0	56.1	58.2	61.6	1.05 (0.85–1.30)	.6	56.6	52.1	0.92 (0.77–1.10)	.4
Mean ± SD	10.7 ± 1.8	10.5 ± 1.8	10.4 ± 1.8	0.09[d] (−0.21 to 0.39)	.5	10.6 ± 1.8	10.8 ± 1.8	−0.18[d] (−0.42 to 0.06)	.1
Parasitemia									
Peripheral[e]	21.4	19.0	19.6	0.92 (0.57–1.48)	.7	22.6	21.4	0.83 (0.59–1.16)	.3
Placental[f]	26.6	28.7	20.8	0.74 (0.46–1.17)	.2	28.8	27.6	1.07 (0.78–1.48)	.7
Birth weight,[g] mean ± SD, g	2790 ± 452	2793 ± 483	2786 ± 421	7[d] (−69 to 82)	.6	2782 ± 470	2801 ± 453	−19[d] (−81 to 42)	.8
LBW	22.3	23.8	19.3	0.83 (0.58–1.19)	.3	24.0	22.6	0.96 (0.73–1.27)	.8

NOTE. Data are the percentage of women assessed at delivery, unless otherwise indicated. CI, confidence interval; LBW, low birth weight; RR, risk ratio.

[a] Comparison was restricted to women enrolled before the data safety and monitoring board discontinued enrollment into the AQ arm.

[b] RRs for hemoglobin concentrations were adjusted for age, parasite density at enrollment, and season of delivery. RRs for peripheral parasitemia were adjusted for season of delivery, placental parasitemia, and place of delivery. RRs for placental parasitemia were adjusted for peripheral parasitemia at enrollment and at delivery, season of delivery, and place of delivery. RRs for birth weight were adjusted for gravidity, maternal weight, and place of delivery.

[c] For comparisons of SP and AQ, the SP arm included 292 women, and the AQ arm included 276 women. For comparisons of SP vs. SPAQ, the SP arm included 445 women, and the SPAQ arm included 438 women.

[d] The difference in means, 95% CI, and *P* value of the difference in means are presented.

[e] For comparisons of SP and AQ, the SP arm included 316 women, and the AQ arm included 301 women. For comparisons of SP and SPAQ, the SP arm included 470 women, and the SPAQ arm included 463 women.

[f] For comparisons of SP and AQ, the SP arm included 202 women, and the AQ arm included 183 women. For comparisons of SP and SPAQ, the SP arm included 326 women, and the SPAQ arm included 308 women.

[g] For comparisons of SP and AQ, the SP arm included 286 women, and the AQ arm included 270 women. For comparisons of SP and SPAQ, the SP arm included 438 women, and the AQ arm included 425 women.

Table 3. Comparison of the effect of intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP), amodiaquine (AQ), or the combination of SP and AQ (SPAQ) on anemia, parasitemia, and birth weight among primigravidae and secundigravidae, according to the season of administration of the first dose of IPTp.

Outcome, season	AQ vs. SP[a]		SPAQ vs. SP	
	RR[b] (95% CI)	*P*	RR[b] (95% CI)	*P*
Anemia[c]				
Prerainy[d]	1.06 (0.76–1.48)	0.7	0.96 (0.73–1.26)	0.8
Rainy[e]	1.07 (0.76–1.49)	0.7	0.79 (0.56–1.11)	0.2
Postrainy[f]	0.99 (0.60–1.64)	0.9	0.92 (0.66–1.29)	0.6
Parasitemia				
Peripheral				
Prerainy	0.77 (0.39–1.53)	0.5	0.73 (0.44–1.20)	0.2
Rainy	1.06 (0.52–2.14)	0.9	0.96 (0.51–1.82)	0.9
Postrainy	0.73 (0.07–8.07)	0.8	0.92 (0.47–1.81)	0.8
Placental				
Prerainy	0.62 (0.30–1.27)	0.2	1.11 (0.71–1.74)	0.6
Rainy	0.65 (0.30–1.40)	0.3	1.05 (0.56–1.95)	0.9
Postrainy	1.02 (0.33–3.14)	0.9	0.74 (0.36–1.53)	0.4
Birth weight				
Prerainy	0.99 (0.55–1.81)	0.9	1.03 (0.66–1.60)	0.9
Rainy	0.95 (0.55–1.63)	0.9	0.97 (0.59–1.59)	0.9
Postrainy	0.43 (0.17–1.10)	0.1	0.90 (0.54–1.52)	0.7

NOTE. CI, confidence interval; RR, risk ratio.

[a] Comparison was restricted to women enrolled before the data safety and monitoring board discontinued enrollment into the AQ arm.

[b] RRs for hemoglobin levels were adjusted for age, parasite density at enrollment, and season of delivery. RRs for peripheral parasitemia were adjusted for season of delivery, placental parasitemia, and place of delivery. RRs for placental parasitemia were adjusted for peripheral parasitemia at enrollment and at delivery, season of delivery, and place of delivery. RRs for birth weight were adjusted for gravidity, maternal weight, and place of delivery.

[c] As defined by a hemoglobin level of <11.0 g/dL.

[d] March through June.

[e] July through October.

[f] November through February.

bed net [29]. The mean birth weight of infants in all groups of women in the current trial was substantially higher than that recorded in this previous study, and the prevalence of anemia was lower. Our findings are consistent with those of other studies that have demonstrated that IPTp is associated with higher mean hemoglobin concentrations and lower prevalences of anemia and parasitemia at delivery, compared with findings at enrollment [3, 30–32].

The efficacy of a drug used for IPTp will be influenced by the pharmacokinetics and the susceptibility of the parasite. Findings in Kenya indicate that pregnancy modifies the disposition of SP [33]. However, there are no pharmacokinetic data on the use of AQ in pregnancy [8, 34]. With the possible exception of an effect on severe anemia, we were unable to show that SPAQ was any more effective for IPTp than was SP or AQ used alone. This finding may be associated with the fact that SP is still reasonably effective in the study area. The drug susceptibility study results must be interpreted with caution because of the small sample size. However, these findings are compatible with results obtained for children in the area [13]. Drug efficacy is likely to be higher in asymptomatic pregnant women than in symptomatic children [35, 36]. It is possible that SPAQ might be more effective than SP alone in areas with a higher prevalence of resistance to SP than is currently found in northern Ghana. It is also possible that different results could be obtained in areas with a higher prevalence of HIV infection than northern Ghana, because HIV-infected women require >2 courses of IPTp [37, 38].

We did not detect any significant differences in the effect of IPTp, depending on the season of administration of the first dose. This may be because of the small numbers involved in the subgroup analyses. However, considering the high seasonality of malaria transmission and the observed association between the increased risk of peripheral and placental parasitemia during the rainy and postrainy season, it may be worthwhile to consider the restriction of IPTp to this period of maximum transmission.

Adverse events after IPTp were frequent, especially in the AQ and SPAQ groups, and they led to the premature discontinuation of the AQ arm. The DSMB recommended discontinuing recruitment into the AQ arm, but not into the SPAQ arm, because the incidence of side effects in each of these groups was higher than that in the SP arm; however, there was some evidence for a counterbalancing improvement in the prevalence of anemia in the SPAQ group. A secondary reason was to increase

Table 4. Distribution of courses of intermittent preventive treatment in pregnancy (IPTp) received by primigravidae and secundigravidae.

Course(s) received	SP[a] (*n* = 490)	AQ (*n* = 503)	*P* for SP vs. AQ	SP (*n* = 693)	SPAQ (*n* = 695)	*P* for SP vs. SPAQ	AQ (*n* = 503)	SPAQ[a] (*n* = 485)	*P* for AQ vs. SPAQ
1	37.8	57.1	<.001	44.0	61.4	<.001	57.1	58.1	.7
2	42.2	33.2	.003	39.8	33.2	.01	33.2	36.7	.2
3	20.0	9.7	<.001	16.2	5.3	<.001	9.7	5.2	.006

NOTE. Data are the percentage of women receiving a course of a drug, unless otherwise indicated. AQ, amodiaquine; SP, sulfadoxine-pyrimethamine; SPAQ, combination of SP and AQ.

[a] Comparisons with AQ were restricted to the no. of women enrolled before the AQ arm was discontinued.

Table 5. The incidence of adverse events among all randomized women 7–10 days after receipt of a first course of intermittent preventive treatment in pregnancy.

Adverse event	SP[a] (n = 904)	AQ (n = 916)	P for SP vs. AQ	SP (n = 1275)	SPAQ (n = 1242)	P for SP vs. SPAQ	AQ (n = 916)	SPAQ[a] (n = 905)	P for AQ vs. SPAQ
Any	41.3	82.8	<.001	47.8	89.9	<.001	82.8	89.0	<.001
BWP	19.2	62.8	<.001	26.4	65.9	<.001	62.8	62.0	.7
Dizziness	12.8	52.9	<.001	20.2	56.0	<.001	52.9	53.4	.8
Vomiting	9.0	31.8	<.001	15.4	51.8	<.001	31.8	51.5	<.001
Nausea	11.2	24.9	<.001	15.6	35.9	<.001	24.9	34.2	<.001
Abdominal pain	4.8	10.9	<.001	7.3	11.0	.001	10.9	10.3	.7
Diarrhea	5.3	10.3	.0001	6.3	15.5	<.001	10.3	15.0	.002
Body itch	7.0	7.5	.6	6.9	8.1	.2	7.5	9.1	.2
Body rash	0.7	0.1	.06	1.0	1.2	.7	0.1	1.1	.006
Sores/blisters or peeling[b]	0.3	0.2	.6	0.3	0.6	.3	0.2	0.2	.9

NOTE. Data are the percentage of women reporting an adverse event, unless otherwise indicated. AQ, amodiaquine; BWP, bodily weakness and pains; SP, sulfadoxine-pyrimethamine; SPAQ, combination of SP and AQ.

[a] Comparisons with AQ are restricted to the no. of women enrolled before the AQ arm was discontinued.

[b] Of skin/buccal mucosa.

the power of the study by recruiting into the remaining 2 arms, to establish whether SPAQ had any greater influence than SP alone.

The most frequently reported symptoms were bodily pains and weakness, dizziness, vomiting, and nausea. Similar observations were made by Tagbor et al. [16]. SPAQ was poorly tolerated among nonpregnant adults in Rwanda [39]. Our observation of a decrease in the incidence of adverse events occurring with subsequent courses of IPTp suggests that the expectation of an adverse event after IPTp, engendered by discussions in the community, may have contributed to the high incidence of adverse events associated with the first course of IPTp. Symptoms generally attributed to IPTp were mild, and the incidence of nonadherence to treatment was only 2%. The rate of nonadherence might be higher under programmatic conditions with no supervision of treatment. The proportions of women who received ⩾2 courses were lower in the AQ and SPAQ groups than in the SP group, suggesting that the adverse events experienced with AQ or SPAQ deterred women from receiving additional courses. Thus, the increased frequency of adverse events associated with AQ and SPAQ may limit their use for IPTp. Also, the 3-day schedule of AQ-based regimens is likely to result in poor adherence, because all doses may not be supervised.

The neonatal mortality rate (44 deaths per 1000 live births) was high, compared with rates obtained in the district between 1996 and 2002, although the latter rates may have been underestimated, because data on stillbirths were not available for those analyses [40]. The rates of abortions, stillbirths, congenital abnormalities, and neonatal deaths were comparable between the treatment groups, as was the incidence of neonatal jaundice.

Despite intensive efforts, the loss to follow-up was high. Migration and delivery at home were the main reasons for missing data. However, the rates of loss to follow-up were comparable between study groups, and the prevalences of anemia and parasitemia at baseline were not statistically different among women lost to follow-up and women with adequate follow-up. Women

Table 6. Pregnancy outcomes among all study participants, by treatment group.

Outcome	SP (n = 1287)	AQ (n = 947)	SPAQ (n = 1267)	All (n = 3501)
Abortion	1 (0.1)	3 (0.3)	4 (0.3)	8 (0.2)
Stillbirth	11 (0.9)	8 (0.8)	8 (0.6)	27 (0.7)
Congenital abnormality[a]	3 (0.2)	3 (0.3)	4 (0.3)	10 (0.3)
History of jaundice	64 (5.0)	42 (4.4)	66 (5.2)	172 (4.9)
Neonatal death	56 (4.4)	46 (4.9)	53 (4.2)	155 (4.4)

NOTE. Data are the no. (%) of women with the outcome. AQ, amodiaquine; SP, sulfadoxine-pyrimethamine; SPAQ, combination of SP and AQ.

[a] These were cases of polydactyly, except for 1 infant in the AQ arm who had hydrocephalus and was a stillbirth.

lost to follow-up were more likely to be primigravidae and younger, and this may have led to underestimation of the prevalence of outcome measurements. The hemoglobin concentration decreases during the first 4 days of the puerperium and then progressively increases to stabilize toward the end of the puerperium [41, 42]. In the present study, 18% of assessments of the hemoglobin concentration were performed on the day of delivery; 52%, between days 1 and 4 after delivery; and 30%, between days 5 and 7 after delivery. However, the proportion of women in each drug treatment group was comparable for each day of assessment.

The use of either AQ alone or its combination with SP has been shown to be an option for the treatment of malaria in pregnancy. However, the present study shows that, even though AQ and SPAQ are as efficacious as SP for IPTp in an area where there is a relatively low level of resistance to these 2 drugs, the high incidence of adverse events associated with the administration of AQ or SPAQ limits the suitability of these treatments for IPTp.

Acknowledgments

We thank the women who participated in this study and acknowledge the support received from the Navrongo Health Research Centre, the District Health Management Team, and the staff of the health facilities within the Kassena-Nankana district. We also thank Abdul-Hamid Wahab, Kalifa Bugri, Harparkash Kaur, Rosalynn Ord, and all field staff who in diverse ways contributed to the conduct of the trial. We acknowledge the roles played by John Williams, the local safety monitor, and members of the data safety monitoring board (J. Whitworth, M. Quigley, and K. Yeboah-Antwi).

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