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Effect of Repeated Treatment of Pregnant Women with Sulfadoxine-Pyrimethamine and Azithromycin on Preterm Delivery in Malawi: A Randomized Controlled Trial

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Abstract. Preterm delivery, which is associated with infections during pregnancy, is common in sub-Saharan Africa. We enrolled 1,320 pregnant women into a randomized, controlled trial in Malawi to study whether preterm delivery and low birth weight (LBW) incidence can be reduced by intermittent preventive treatment of maternal malaria and reproductive tract infections. The participants received either sulfadoxine-pyrimethamine (SP) twice (controls), monthly SP, or monthly SP and two doses of azithromycin (AZI-SP). The incidence of preterm delivery was 17.9% in controls, 15.4% in the monthly SP group ($P = 0.32$), and 11.8% in AZI-SP group (risk ratio = 0.66, $P = 0.01$). Compared with controls, those in AZI-SP group had a risk ratio of 0.61 ($P = 0.02$) for LBW. Incidence of serious adverse events was low in all groups. In conclusion, the incidence of preterm delivery and LBW can in some conditions be reduced by treating pregnant women with monthly SP and two azithromycin doses.

INTRODUCTION

The incidence of preterm delivery (birth before 37 completed gestation weeks) is estimated to be 6% in Europe, 11% in the United States,[1] and up to 20% in some countries in sub-Saharan Africa.[2–5] In industrialized countries, preterm delivery accounts for 75% of perinatal mortality and a large part of serious neonatal morbidity.[6] Additionally, it is associated with low birth weight (LBW, birth weight less than 2,500 grams) and a variety of more chronic conditions such as impaired lung and eye function, and neurologic and psychological problems.[7–9] In low-income settings, babies born too early have also an increased risk of early growth failure,[10] which further predisposes them to a multitude of adverse, long-term sequelae.[7,11]

Considering the frequency and consequences of preterm delivery, preventive measures are urgently needed. In sub-Saharan Africa, maternal malaria parasitemia and reproductive tract infections (RTIs) are believed to account for a large part of preterm delivery and LBW.[3,4,12–14] Therefore, several countries in Africa offer intermittent preventive treatment (IPT) for malaria with two doses of sulfadoxine-pyrimethamine (SP) to all pregnant women.[15] However, the efficacy of this intervention has been questioned and more frequent dosing and other treatment regimens have been suggested.[16–20] The effect on preterm delivery of antibiotic treatment of RTIs given for unselected pregnant women without screening has only been tested in two trials. A trial in Uganda reported an apparently reduced incidence of preterm delivery and LBW among participants treated with antibiotics, whereas no impact on the incidence of preterm delivery or mean duration of pregnancy was found in a trial in Malawi.[13,21] No trials in sub-Saharan Africa have addressed the impact on preterm deliveries of IPT with a combination of monthly antimalarial drugs and antibiotics against RTIs.

We carried out a randomized, three-arm trial in Malawi to examine the potential to prevent preterm deliveries and LBW through intensified gestational IPT containing antibiotics against malaria and RTIs. The compared interventions included a standard two-dose SP regimen, monthly SP treatment, and monthly SP combined with two doses of azithromycin. The latter antibiotic was chosen because of its known efficacy against many of the common pathogens in female reproductive tract, its potential antimalarial activity, and its ease of use with few expected side effects.[22–27]

MATERIALS AND METHODS

Study design. We undertook a single-center, randomized, partially placebo controlled, outcome assessor–blinded clinical trial in rural Malawi. The study hypothesis was that preterm delivery and many other adverse pregnancy outcomes could be reduced by IPT of pregnant women with monthly SP alone or in combination with two doses of azithromycin. The trial was performed according to Good Clinical Practice guidelines and the ethical standards of Helsinki Declaration. The protocol was reviewed and approved by the College of Medicine Research and Ethics Committee, Malawi and the Ethical Committee of Pirkanmaa Hospital District, Finland. An independent data safety and monitoring board monitored the incidence of suspected serious adverse events (SAEs) and performed two interim analyses for safety and efficacy and one site monitoring visit. Only participants who signed or thumb-printed an informed consent form were enrolled in the study. Key details of the protocol were published at the clinical trial registry of the National Library of Medicine (Bethesda, MD) (http://www.clinicaltrials.gov, trial identification NCT00131235).

The primary outcome measure was the incidence of preterm delivery. Secondary outcomes included mean duration of pregnancy, prevalence of maternal laboratory-diagnosed peripheral malaria parasitemia during pregnancy and at delivery; prevalence of LBW; perinatal and neonatal mortality rate; post-natal prevalence of maternal *Trichomonas vaginalis*, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae* infections; and incidence of maternal and newborn SAEs.

Study site and participants. The target population was composed of pregnant women who came to Lungwena Health Center, Mangochi District, southern Malawi during December 2003–October 2006 for antenatal care. Malaria is holoendemic at this rural site and earlier evidence suggested that RTIs would be common among pregnant women.[28,29] Inclusion criteria were gestational age 14–26 weeks by ultrasound assessment, felt movements of the fetus, availability for follow-up,

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and informed consent. Exclusion criteria included severe illness, receipt of azithromycin during the current pregnancy or SP within preceding 28 days, allergy to study drugs, and any previous serious allergic reaction.

Study interventions. Participants in the control group received standard Malawian antenatal care that includes intermittent preventive malaria treatment with SP (three tablets orally, each containing 500 mg of sulfadoxine and 25 mg of pyrimethamine) twice during pregnancy: at enrollment and at a visit between the 28th–34th weeks of gestation. At the same visits, they also received a placebo instead of azithromycin. Participants in the first intervention group (monthly SP) received otherwise the same treatment, but SP was given monthly from enrollment until 37 gestation weeks. Participants in the second intervention group (AZI-SP) received otherwise the same treatment as the monthly SP group, but instead of placebo, they received two doses of active azithromycin (two tablets orally, each containing 500 mg of azithromycin): at enrollment visit and at a visit between 28th–34th weeks of gestation. All participants were given ferrous sulfate (200 mg/day) and folic acid (0.25 mg/day) throughout pregnancy.

Sulfadoxine-pyrimethamine tablets were obtained from Malawi Central Medical Stores that were supplied by Pharmanova (Blantyre, Malawi), Ipca Laboratories Ltd (Mumbai, India), F. Hoffmann-La Roche Ltd. (Basel, Switzerland), and Universal Corporation Kenya Ltd (Kikuyu, Kenya). Active azithromycin and its placebo were manufactured and donated by Pfizer Inc. (New York, NY).

Randomization and enrollment. A researcher not involved in data collection generated a randomization code list. Based on this list, individual code slips containing unique identification numbers, but not group allocation, were sealed in individual opaque randomization envelopes. An individual drug box was pre-packed for each identification number. It contained appropriate study drugs for each planned study visit in opaque drug envelopes labeled with identification number and visit information.

At enrollment visit, research personnel interviewed interested persons about their socioeconomic status and obstetric history, gave pre-test human immunodeficiency virus (HIV) counseling, and performed antenatal examination. The duration of pregnancy was determined by measuring the fetal biparietal diameter and femur length with an ultrasound imager (Aloka SSD-500; Aloka Co. Ltd., Tokyo, Japan, or Hitachi EUB 310; Hitachi, Ltd., Tokyo, Japan). Hadlock tables were used to calculate fetal age. A laboratory assistant with extensive experience assessed from all participants blood hemoglobin concentration (HemoCue AB, Ängelholm, Sweden), peripheral blood malaria parasitemia by using Giemsa-stained thick and thin blood films, and syphilis reactivity (Determine Syphilis TP; Abbott Laboratories, Abbott Park, IL, or VDRL carbon antigen; Biotec Laboratories, Ipswich, UK, and TPHA kit, Lorne Laboratories, Twyford, United Kingdom). HIV testing (Determine; Abbot Laboratories, and Uni-Gold; Trinity Biotech Plc., Bray, Ireland) was optional. Quality assurance for hemoglobin measurement and syphilis confirmation test was performed with controls supplied with the kits. There were no quality control measures for malaria slide readings.

Eligible persons signed or thumb-printed informed consent and picked one randomization envelope with an identification number. A research assistant not involved in outcome assessment gave the corresponding pre-packed study drugs to the participant under direct observation and monitored her for possible adverse reactions.

Follow-up. At follow-up visits (at four-week intervals until 36 completed gestation weeks and weekly thereafter), the research personnel interviewed the participants about health problems and conducted antenatal examination. Hemoglobin concentration was assessed from a finger prick blood sample. At the visit during 28th–34th weeks of gestation, a malaria test was conducted. Post-test counseling was offered to HIV-tested participants and HIV-infected participants received a 200-mg nevirapine tablet for prevention of mother-to-child transmission. The HIV-negative participants received a similar-looking vitamin C tablet. At each visit, the participant took the appropriate pre-packed study drugs and was observed as at enrollment visit.

Upon notification of a delivery, a research assistant visited the delivery site. She interviewed the participant and delivery attendant, examined the newborn, gave him or her 0.6 mL of syrup containing 6 mg of nevirapine or placebo (based on maternal HIV status) and weighed the newborn with a spring scale (at home) or with electronic infant weighing scale (at a health facility). For participants who delivered at a local health facility, the attending nurse measured the hemoglobin concentration and made thick and thin blood films from peripheral, placenta, and cord blood to be examined by the laboratory assistant.

At the post-natal visit one month after delivery, research personnel interviewed the participant about health problems and did a post-natal examination. After a participant's approval, the nurse collected a vaginal swab to detect *Trichomonas vaginalis* (direct microscopy from a wet mount), *C. trachomatis,* and *N. gonorrhoeae* infections (both diagnosed at the University of North Carolina Laboratories in Lilongwe, Malawi, by using the AMPLICOR CT-NG polymerase chain reaction assay; F. Hoffmann-La Roche Ltd.).

Research assistants made a tracing home visit if a participant did not come for her scheduled visit within 14 days of the appointment. At each scheduled and non-scheduled visit, information on suspected adverse events was obtained. All suspected SAEs were reported to the data safety and monitoring board.

Participants with malaria at enrollment or at 28th–34th weeks visit received the normal pre-packed study medication that included SP for all study groups. Laboratory-confirmed malaria at any other point was treated with quinine (300 mg, two tablets orally three times a day for seven days). Participants diagnosed with syphilis were given a 2.4 mU intramuscular injection of benzathine penicillin and their babies received the same drug (50 kU/kg) at the age of 4 weeks. Participants with *Trichomonas* at post-natal visit were immediately treated with metronidazole, 2 grams given orally as a single dose. As soon as *Chlamydia* and gonorrhea results were available to the study nurse, the infected participants were traced. Gonorrhea was treated with ciprofloxacin, 500 mg, and *Chlamydia* infection was treated with azithromycin, 1 gram, each administered as a single oral dose. Participants diagnosed with syphilis, *Trichomonas* infection, *Chlamydia* infection, or gonorrhea were asked to advise their partners to seek treatment from the health center. Participants with severe anemia (hemoglobin < 50 g/L) were referred to the district hospital for treatment according to Malawian national guidelines. Any other disease was treated according to national guidelines.

Statistical analyses. The target sample size of 1,320 participants was based on earlier results from Malawi and Mozambique, which showed an incidence of preterm delivery of approximately 20%.[2–5] Because of a predicted increase in bed net use, we estimated this proportion to be 18% in the control group. Assuming a 10% loss to follow-up, we calculated that a sample size of 440 pregnant women per group would give 80% power at a 5% level of significance to detect a 40% reduction in the rate of preterm delivery (birth before 37 completed gestation weeks). For secondary outcomes, we estimated the chosen sample size to have 80% power at a 5% level of significance to detect a 0.5 gestation week difference in the mean duration of pregnancy and a 7.5% point reduction in the incidence of LBW (birth weight less than 2,500 grams).

Statistical analysis was carried out by using Stata 9.2 (StataCorp, College Station, TX) according to a statistical analysis plan written before the code was opened. We based the analysis on the principle of intention-to-treat. Data on birth weight was considered missing if it was collected more than two days after delivery.

We estimated risk ratio (RR) and risk difference for comparison of binary end-points at a single time point. To prevent inflated type I errors caused by multiple comparisons, we began hypothesis testing with global null hypotheses of all three groups being identical before doing pairwise comparisons. We tested the global null hypotheses either with Fisher's exact test (for binary end-points) or analysis of variance (quantitative end points), and the two-group hypotheses with Fisher's exact test (for binary end points) or Student's *t*-test (quantitative end-points). We performed tests for interaction between interventions and number of previous pregnancies (categorized as none, one, and two or more), maternal HIV status, and bed net use at enrollment by using the likelihood ratio test, and performed analyses stratified by the same variables for the primary outcome. The proportion of women with none or one previous pregnancy and with peripheral blood malaria parasitemia at enrollment was higher in the control group than in the intervention groups. As sensitivity analyses, we adjusted for these two covariates as categorical variables by generalized linear models and compared the adjusted and main analyses.

We included in the analyses 48 persons who participated in the trial twice with consecutive pregnancies and seven inadvertently enrolled women with twin pregnancies. Sensitivity analyses using the robust standard error to enable clustering of preterm delivery (pregnancy as unit of analysis) and LBW (infants as unit of analysis) within participants showed similar results to the main analyses.[30]

RESULTS

Of the 3,358 pregnant women whom we invited to participate in the study, 1,320 were randomized into the three intervention groups: control, monthly SP, and AZI-SP (Figure 1). At enrollment, the three groups were comparable, except for small differences in the number of previous pregnancies and prevalence of malaria parasitemia (Table 1). The enrolled

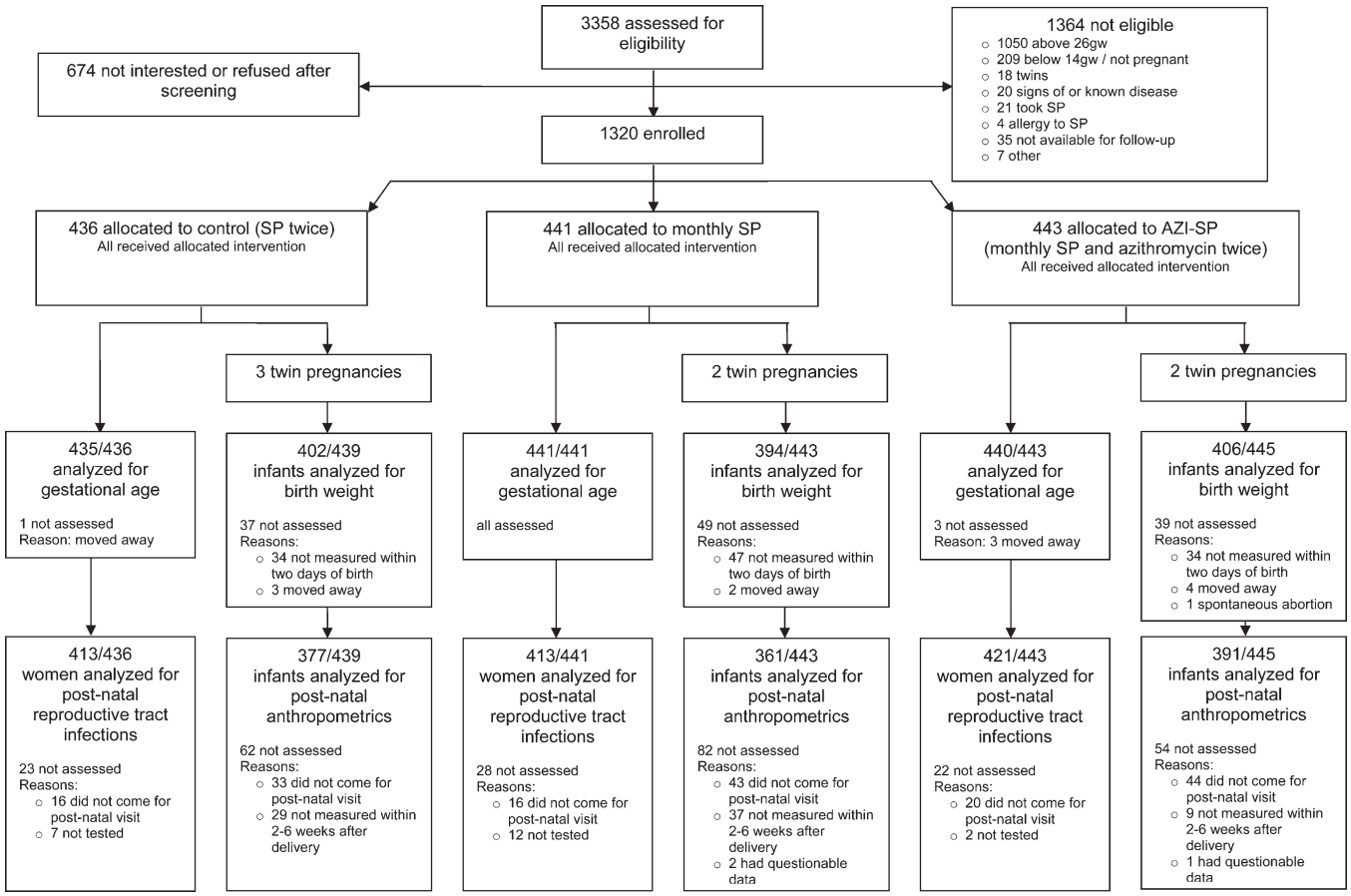

FIGURE 1. Participant flow in the study in Malawi in CONSORT recommended format.[44]

TABLE 1
Baseline characteristics of participants at study enrollment, Malawi*

Characteristic	Control (SP twice)	Monthly SP	AZI-SP
No. enrolled women	436	441	443
Mean (SD) age (years)	25 (7)	25 (7)	25 (6)
Mean (SD) height (cm)	155.0 (5.5)	154.8 (5.4)	155.3 (5.6)
Mean (SD) BMI (kg/m^2)	21.7 (2.2)	21.8 (2.1)	21.9 (2.1)
Mean (SD) gestational age at enrollment (weeks)	20.3 (3.0)	20.0 (3.2)	20.0 (3.0)
No. (%) previous pregnancies			
0	110/436 (25.2)	107/441 (24.3)	89/443 (20.1)
1	86/436 (19.7)	78/441 (17.7)	82/443 (18.5)
≥ 2	240/436 (55.1)	256/441 (58.1)	272/443 (61.4)
Maternal HIV status (%)			
Positive	48/436 (11.0)	64/441 (14.5)	49/443 (11.1)
Negative	348/436 (79.8)	336/441 (76.2)	349/443 (78.8)
Unknown	40/436 (9.2)	41/441 (9.3)	45/443 (10.2)
Maternal syphilis status (%)			
Positive	18/436 (4.1)	27/441 (6.1)	21/443 (4.7)
Negative	415/436 (95.2)	408/441 (92.5)	419/443 (94.6)
Unknown	3/436 (0.7)	6/441 (1.4)	3/443 (0.7)
Mean (SD) blood Hb concentration (g/L)	110 (19)	111 (17)	110 (20)
Maternal anemia status (%)			
Mild or moderate (Hb < 110 g/L)	215/436 (49.3)	205/441 (46.5)	215/443 (48.5)
Moderate (Hb < 80 g/L)	22/436 (5.1)	11/441 (2.5)	30/443 (6.8)
Proportion with microscopic peripheral blood malaria parasitemia (%)	49/435 (11.3)	41/441 (9.3)	27/443 (6.1)
Proportion of literate participants (%)	116/436 (26.6)	129/441 (29.3)	139/443 (31.4)
Mean (SD) years of schooling completed	2.1 (2.7)	2.1 (2.6)	2.4 (2.8)
Proportion of those owning a bed net (%)	320/436 (73.4)	318/441 (72.1)	330/443 (74.5)
Proportion who used bed net during previous night (%)	268/436 (61.5)	262/441 (59.4)	267/443 (60.3)
Proportion with previous delivery complication (%)	118/436 (27.1)	116/441 (26.3)	118/443 (26.6)
No. (%) twin pregnancies in this study	3 (0.7)	2 (0.5)	2 (0.5)

* SP = sulfadoxine-pyrimethamine; AZI = azithromycin; BMI = body mass index; HIV = human immunodeficiency virus; Hb = hemoglobin.

women and those not enrolled had approximately the same mean age (25 versus 26 years) and number of previous pregnancies (2.3 versus 2.5).

The mean (standard deviation, SD) number of scheduled SP treatments received was 2.0 (0.2) in the control group, 4.0 (1.0) in the monthly SP group, and 4.0 (0.9) in the AZI-SP group. Women in the AZI-SP group received a mean (SD) of 2.0 (0.2) azithromycin doses. Follow-up data were obtained from 99.7% of the participants for length of gestation, and from approximately 90% for birth weights within two days of delivery (Figure 1).

The overall proportion of preterm delivery was 15.1%. Compared with the controls, participants in the monthly SP group had an RR (95% CI) 0.86 (0.64 to 1.16, $P = 0.32$) and an absolute risk reduction of 2.5% (–2.4 to 7.4%) for preterm delivery (Table 2). For women in the AZI-SP group, the corresponding RR was 0.66 (0.48 to 0.91, $P = 0.01$) and risk reduction was 6.1% (1.4 to 10.8%). Analyses adjusting for number of previous pregnancies and malaria at enrollment gave similar results.

The mean (SD) duration of pregnancy was 38.4 (2.2) weeks in the control group, 38.5 (2.4) weeks in the monthly SP group, and 38.8 (2.1) weeks in the AZI-SP group ($P = 0.03$). Compared with the controls, the participants in the monthly SP group delivered on average (95% CI) 0.2 (–0.1 to 0.5, $P = 0.25$) gestation weeks later and those in the AZI-SP group delivered 0.4 (0.1 to 0.7, $P < 0.01$) gestation weeks later. The differences in gestational duration between the three groups concentrated in the lower half of the distribution (Table 3). A cumulative frequency plot demonstrates that more deliveries started to occur at 30–33 gestation weeks in the control and the monthly SP groups, but only after 35 gestation weeks in the AZI-SP group ($P = 0.03$, by log-rank test) (Figure 2). Compared with controls, those in the AZI-SP group had an RR of 0.48 (95% CI) (0.26 to 0.89, $P = 0.02$) for delivery before 35 completed gestation weeks (Table 2).

There was no statistically proven interaction on the incidence of preterm delivery between intervention group and either number of previous pregnancies ($P = 0.25$), maternal HIV status ($P = 0.18$), or bed net use at enrollment ($P = 0.24$). Stratified analyses suggested that monthly SP treatment was associated with a reduced incidence of preterm delivery mainly among women who were primigravida, HIV-infected,

TABLE 2
Incidence of preterm delivery, very preterm delivery, and low birth weight with different definitions by study group, Malawi*

Outcome	No. with adverse outcome/total no. with known outcome data (%)				Comparison between monthly SP and control group		Comparison between AZI-SP and control group	
	Control	Monthly SP	AZI-SP	*P*	Risk ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*
Preterm delivery (< 37 gw), unadjusted	78/435 (17.9)	68/441 (15.4)	52/440 (11.8)	0.04	0.86 (0.64–1.16)	0.32	0.66 (0.48–0.91)	0.01
Preterm delivery (< 37 gw), adjusted analysis†					0.89 (0.66–1.19)	0.42	0.70 (0.51–0.97)	0.03
Very preterm delivery (< 35 gw), unadjusted	29/435 (6.7)	30/441 (6.8)	14/440 (3.2)	0.02	1.02 (0.62–1.67)	1.00	0.48 (0.26–0.89)	0.02
Birth weight < 2,500 g, unadjusted	52/402 (12.9)	36/394 (9.1)	32/406 (7.9)	0.05	0.71 (0.47–1.06)	0.09	0.61 (0.40–0.93)	0.02
Birth weight < 2,500 g, adjusted analysis†					0.72 (0.49–1.07)	0.11	0.64 (0.43–0.97)	0.04

* SP = sulfadoxine-pyrimethamine; AZI = azithromycin; CI = confidence interval; gw = gestation weeks.
† Adjusted for no. of previous pregnancies (categorized as none, one, and two or more) and malaria at enrollment.

TABLE 3
Duration of pregnancy by percentile, by study group, Malawi*

Percentile	Duration of pregnancy by study group, weeks				Comparison between monthly SP and control group		Comparison between AZI-SP and control group	
	Control	Monthly SP	AZI-SP	*P*	Mean risk difference (95% CI)	*P*	Mean risk difference (95% CI)	*P*
3	33.4	32.4	34.8	0.56	−0.9 (−4.9 to 3.2)	0.68	1.3 (−2.7 to 5.4)	0.52
10	35.8	36.1	36.7	0.06	0.3 (−0.5 to 1.1)	0.43	0.9 (0.1 to 1.7)	0.02
25	37.4	37.9	37.9	< 0.01	0.4 (0.1 to 0.7)	< 0.01	0.5 (0.2 to 0.8)	< 0.01
50	38.6	38.9	39.0	< 0.01	0.3 (0.1 to 0.5)	0.01	0.4 (0.2 to 0.6)	< 0.01
75	39.7	39.9	39.9	0.21	0.2 (−0.1 to 0.5)	0.13	0.2 (−0.1 to 0.5)	0.12
90	40.7	40.7	40.8	0.72	0.01 (−0.4 to 0.4)	0.97	0.1 (−0.2 to 0.5)	0.47
97	41.6	41.7	41.6	0.93	0.2 (−0.6 to 0.9)	0.70	0.1 (−0.7 to 0.8)	0.88

* SP = sulfadoxine-pyrimethamine; AZI = azithromycin; CI = confidence interval.

or did not use a bed net at enrollment (Table 4). In the AZI-SP group, the differences between those with and those without these risk factors were smaller. However, most of these subgroup results were statistically insignificant.

The overall proportion of recorded LBW < 2,500 grams was 10.0%. Compared with the controls, babies in the AZI-SP group had a RR of 0.61 (95% CI) (0.40 to 0.93, $P = 0.02$) and absolute risk reduction of 5.1% (95% CI) (0.9 to 9.3%) for LBW, whereas babies in the monthly SP group did not differ significantly from the controls (Table 2). Analyses adjusting for baseline malaria and number of previous pregnancies gave similar results.

The overall proportion of maternal peripheral blood malaria parasitemia was 3.0% at approximately 32 gestation weeks and 2.9% at delivery (Table 5). Compared with the controls, participants in the monthly SP and AZI-SP groups had a lower prevalence of peripheral malaria parasitemia at 32 gestation weeks (RR = 0.45 and 0.34, respectively) and at delivery (RR = 0.40 and 0.35, respectively), but only the 32-week results reached statistical significance. For placental malaria, the inter-group differences were smaller (RR = 0.84 and 0.72, respectively, $P > 0.05$).

At post-natal visit, the prevalence of maternal vaginal *Trichomonas* infection was 14.3% whereas *C. trachomatis* and *N. gonorrhoeae* infections were uncommon. Compared with the controls, women in the AZI-SP group had a lower prevalence (RR = 0.65, $P = 0.02$) of *T. vaginalis* infection (Table 5).

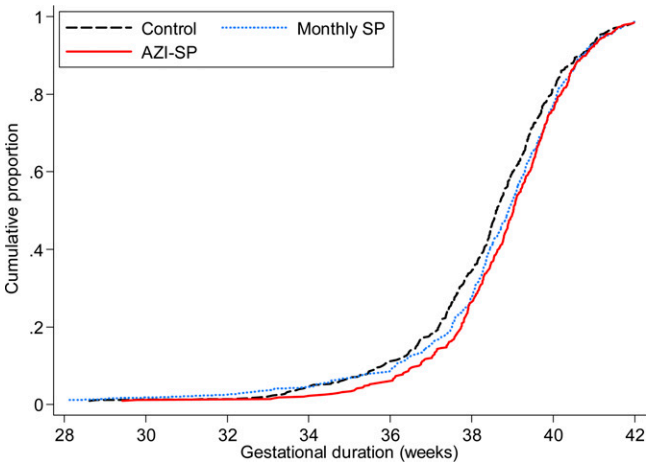

FIGURE 2. Cumulative frequency plot showing timing (gestational weeks) of deliveries in each group, Malawi. This figure appears in color at www.ajtmh.org.

During maternal follow-up, the mean (SD) number of non-scheduled outpatient visits to the research health center was 0.5 (0.8) in the control group, 0.6 (0.9) in the monthly SP group, and 0.4 (0.7) in the AZI-SP group ($P < 0.01$). The mean (SD) number of quinine doses given at these visits was 0.03 (0.18) for the control group, 0.02 (0.16) for the monthly SP group, and 0.01 (0.09) for the AZI-SP group ($P = 0.10$). Against the agreed practice, some SP doses were also given at the non-scheduled visits, but the number of these was small (mean = 0.008 doses), and there were no differences between the groups. Syphilis treatment during pregnancy was given to 19, 25, and 22 participants in the control, monthly SP and AZI-SP groups, respectively.

The overall perinatal mortality rate was 64/1,000 births and the neonatal mortality rate was 25/1,000 live births, and there were no major differences between the groups ($P = 0.99$ for perinatal deaths and $P = 0.32$ for neonatal deaths). We recorded 125 SAEs for infants (89 abortions, stillbirths, and infant deaths, 28 hospitalizations, and 8 congenital malformations): 44 in the control group, 48 in the monthly SP group, and 33 in the AZI-SP group ($P = 0.18$). Other types of neonate SAEs were evenly distributed between the groups, but significantly fewer (0.7%) neonates were hospitalized in the AZI-SP group than in the control group (2.7%) or monthly SP (2.9%) group ($P = 0.02$). For mothers, we observed 14 SAEs (1 death, 4 hospitalizations, and 9 cases of severe anemia): 3 in the control group, 5 in the monthly SP group, and 6 in the AZI-SP group ($P = 0.71$). Most SAEs were not considered related to trial interventions and no infant or mother had more than one SAE.

DISCUSSION

In the enrolled sample, the incidence of preterm delivery and LBW were approximately 35% lower among participants who were treated with monthly SP and two azithromycin doses than among those who received standard antenatal care with two doses of SP. There was also a significant difference in the mean duration of pregnancy and in the prevalence of malaria parasitemia at 32 gestation weeks. The difference in gestational duration was concentrated in the lower half of the distribution. Outcome differences between the monthly SP and the control group were to the same direction but smaller, and often not statistically significant.

The probabilities of selection and implementation bias or random error were low because of a population-based sampling, random group allocation, comprehensive follow-up, ultrasound-based assessment of the duration of pregnancy, partial

TABLE 4

Stratified analysis of preterm delivery (< 37 gw) by study group based on number of previous pregnancies, maternal HIV status, and maternal bed net use at enrollment, Malawi*

Characteristic	No. preterm/all births with known gestational age at delivery (%)				Comparison between monthly SP and control group		Comparison between AZI-SP and control group	
	Control	Monthly SP	AZI-SP	*P*	Risk ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*
No. previous pregnancies								
0	33/110 (30.0)	20/107 (18.7)	13/89 (14.6)	0.02	0.62 (0.38–1.01)	0.06	0.49 (0.27–0.87)	0.01
1	15/86 (17.4)	19/78 (24.4)	15/80 (18.8)	0.50	1.40 (0.76–2.55)	0.34	1.08 (0.56–2.05)	0.84
≥ 2	30/239 (12.6)	29/256 (11.3)	24/271 (8.9)	0.37	0.90 (0.56–1.46)	0.68	0.71 (0.42–1.17)	0.20
Maternal HIV status								
Positive	14/48 (29.2)	9/64 (14.1)	6/48 (12.5)	0.07	0.48 (0.23–1.02)	0.06	0.43 (0.18–1.02)	0.08
Negative	58/347 (16.7)	55/336 (16.4)	45/348 (12.9)	0.31	0.98 (0.70–1.37)	0.92	0.77 (0.54–1.11)	0.17
Unknown	6/40 (15.0)	4/41 (9.8)	1/44 (2.3)	0.11	0.65 (0.20–2.13)	0.52	0.15 (0.02–1.20)	0.0499
Maternal bed net use at enrollment								
No	33/167 (19.8)	22/179 (12.3)	21/174 (12.1)	0.09	0.62 (0.38–1.02)	0.08	0.61 (0.37–1.01)	0.06
Yes	45/268 (16.8)	46/262 (17.6)	31/266 (11.7)	0.11	1.05 (0.72–1.52)	0.82	0.69 (0.45–1.06)	0.11

* gw = gestation weeks; HIV = human immunodeficiency virus; SP = sulfadoxine-pyrimethamine; AZI = azithromycin; CI = confidence interval.

use of placebo-control, blinding of the outcome assessors, and a relatively large sample size. There was a small inter-group difference at baseline in the number of previous pregnancies and malaria parasitemia, but adjusted and stratified analyses indicated that this did not bias the results. Thus, the observed results are likely to be reliable and representative of the target population and suggest that in the study area pregnancy outcomes can be markedly improved by treatment of pregnant women with monthly SP and two doses of azithromycin. Monthly SP alone is likely to decrease the prevalence of malaria parasitemia during pregnancy. Other positive effects are also possible, but the higher likelihood of random error makes population inference less conclusive for this treatment arm.

Given the importance of maternal RTIs in the etiology of preterm delivery and the difficulty of screening for high-risk women in low-resource settings,[31] preventive antibiotic treatment of all pregnant women appears a logical intervention. However, only a few earlier trials have studied this approach in Africa. A multi-site trial, enrolling mainly HIV-infected persons reported no benefits among participants treated with metronidazole, erythromycin, and ampicillin.[32] In contrast, two other trials that used either a broad-spectrum combination of metronidazole, kefixime, and azithromycin (Uganda), or cefetamet-pivoxil (Kenya) showed positive results.[13,33] In the trial in Uganda, the rate ratio of a proxy for LBW was 0.68 (95% CI = 0.53–0.86) and that of a preterm delivery was 0.77 (0.56–1.05) among women treated with antibiotics,[13] which is similar to the results of our trial in which we also used azithromycin.

In contrast to our findings, a trial from Malawi (APPLe) recently reported no impact on the incidence of preterm delivery or mean duration of pregnancy among pregnant women treated with two doses of azithromycin.[21] The dose and timing of azithromycin was the same as in our trial, but the APPLe intervention combined azithromycin to preventive malaria treatment with two doses of SP, whereas in our trial SP was administered monthly, either with or without azithromycin. Furthermore, the participants in the APPLe trial were more often primigravida, and the prevalenceof syphilis at enrollment and peripheral malaria parasitemia were higher at enrollment and at the time of the second azithromycin trial. These differences in the burden and preventive treatment of malaria could modify the effect of azithromycin and explain the seemingly conflicting results from the two studies.

Three earlier trials have assessed the health effects of monthly SP treatment on pregnant women. A small trial in Kenya suggested that the monthly regimen might offer benefits over two-dose SP treatment among primigravid and secundigravid women.[34] Another trial in Malawi confirmed a reduced risk of peripheral blood malaria parasitemia among women in their first or second pregnancy.[35] A trial in Zambia in a malaria mesoendemic area found no benefit from more than two SP doses among HIV-infected, primigravid, secundigravid, and multigravid women.[36] In our trial, the modest efficacy of the monthly SP regimen without azithromycin may partly be caused by increasing SP resistance in the study area or by a lower than expected prevalence of malaria among the participants. A previous study in Malawi found that more than 90% of malaria isolates from three study sites expressed quintuple DNA mutations, which are molecular markers for SP resistance and associated with SP treatment failure.[37] We attribute the unexpectedly low prevalence of malaria to the recent

TABLE 5

Secondary maternal outcomes, Malawi*

Outcome	No. (%) outcomes/participants				Comparison between monthly SP and control group		Comparison between AZI-SP and control group	
	Control	Monthly SP	AZI-SP	*P*	Risk ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*
Peripheral blood malaria parasitemia at 32 weeks of pregnancy	20/394 (5.1)	9/396 (2.3)	7/400 (1.8)	0.02	0.45 (0.21–0.97)	0.04	0.34 (0.15–0.81)	0.01
Peripheral blood malaria parasitemia at delivery	8/160 (5.0)	3/150 (2.0)	3/171 (1.8)	0.19	0.40 (0.11–1.48)	0.22	0.35 (0.09–1.30)	0.13
Placental blood malaria parasitemia at delivery	4/161 (2.5)	3/143 (2.1)	3/167 (1.8)	0.92	0.84 (0.19–3.71)	1.0	0.72 (0.16–3.18)	0.72
Chlamydia at 4 weeks after delivery	1/391 (0.3)	1/384 (0.3)	1/391 (0.3)	1.00	1.02 (0.06–16.22)	1.00	1.00 (0.06–15.93)	1.00
Gonorrhea at 4 weeks after delivery	3/391 (0.8)	8/384 (2.1)	2/391 (0.5)	0.13	2.72 (0.73–10.16)	0.14	0.67 (0.11–3.97)	1.00
Trichomonas at 4 weeks after delivery	69/411 (16.8)	62/411 (15.1)	46/419 (11.0)	0.05	0.90 (0.66–1.23)	0.57	0.65 (0.46–0.93)	0.02

* SP = sulfadoxine-pyrimethamine; AZI = azithromycin; CI = confidence interval.

influx and frequent use of insecticide-impregnated bed nets at the trial site.

A major limitation of our trial was its semi-complete factorial design, i.e., lack of an intervention group that would have received two doses of SP with two doses of azithromycin. Adding a fourth group was discussed before the onset of the trial, but it was not considered ethically justified to expose one-fourth of the trial participants to a drug regimen combining a drug that was experimental for the defined indication (azithromycin) with a possibly failing regimen that was being considered to be abandoned by national and international authorities (two-dose SP). Second, such a design would have required a larger sample size, which in turn would have had considerable implications in terms of additional time and resource needs. The study was also not powered to test formal hypotheses between the two intervention groups or to adjust for multiple comparisons.

Because of the above limitations, the exact pathway leading to reduced incidence of preterm delivery in our trial remains unknown. Both the monthly SP and the AZI-SP regimens were associated with reduced malaria parasitemia at 32 gestation weeks and possibly at delivery. Otherwise, there were more positive outcomes in the AZI-SP group, and participants in this group, unlike in the monthly SP group, seemed to avoid very preterm (< 35 gestation weeks) deliveries. Thus, some of the positive effect was probably mediated through the antimalarial activity of SP and possibly azithromycin, but the added efficacy of the AZI-SP regimen was likely due to the effect of azithromycin on infections in the reproductive tract of the participants.[25,26] The lower incidence of hospitalizations among babies born to women in the AZI-SP group further supports such a hypothesis and suggests that azithromycin treatment may also reduce the incidence of bacterial infections acquired by the fetus during its passage through the birth canal.

We noted a 35% lower prevalence of *T. vaginalis* infection among participants who received azithromycin. However, because we had no information on its prevalence at enrollment and because azithromycin is not indicated for the treatment of *T. vaginalis* infection,[26] we cannot explain this finding and call for future trials to monitor this outcome. The low prevalence of *C. trachomatis* and *N. gonorrhoeae* infections after delivery was contrary to our expectations and earlier results from the same district.[29] It is possible that even our control regimen had an impact on the prevalence of these RTIs because SP and other sulfonamides have *in vitro* antimicrobial activity against them.[38,39] Also, some of the samples were stored longer than recommended, and we can not rule out problems with the testing procedures.

Similar to several dietary supplementation trials in infants and young children,[40] our data suggest a modest increment between the control and intervention groups in the mean or median duration of pregnancy and a larger difference below the 50th percentile of the distribution. This concentration of the treatment effect at the lower end of the curve has important clinical implications because it targets the benefits of the intervention to those who are at greatest risk for LBW, death, and other adverse outcomes,[6–11] but does not increase the risk of obstructed labor among babies born at term.

Previous studies have suggested that SP and azithromycin are safe to use during pregnancy.[13,25,27,34,35,41] Our results and those of an earlier smaller trial in Malawi also suggest that a combination of these drugs causes no immediate major health problems.[42] However, a long-term follow-up is needed to rule out problems that become evident only after the neonatal period. A recent analysis from the United Kingdom documented an increased prevalence of functional impairment and cerebral palsy among seven-year-old children whose mothers had received erythromycin during spontaneous preterm labor.[43]

Our results on the safety and efficacy of a gestational intervention with monthly SP and two doses of azithromycin suggest that such an intervention could yield major public health benefits in sub-Saharan Africa. However, the study data were collected 3–7 years ago and widespread SP resistance in Malawi has since been reported.[37] Because the impact of this intervention would heavily depend on the local epidemiology and antimicrobial resistance of malaria, RTIs, and other etiologic factors for preterm delivery, further trials in Malawi and other settings are warranted. The cost-benefit of different interventions and their impact on parasite or bacterial drug resistance and pathogen specific immunity should also be clarified. Our team is working on several of these topics and will report them in subsequent publications.

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