A randomized open-label evaluation of the antimalarial prophylactic efficacy of azithromycin-piperaquine versus sulfadoxine-pyrimethamine in pregnant Papua New Guinean women

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ABSTRACT

Background: Emerging sulfadoxine-pyrimethamine (SP) malaria parasite resistance has prompted assessment of alternatives for intermittent preventive treatment in pregnancy (IPTp).

Objective: To evaluate the tolerability and prophylactic efficacy of azithromycin (AZ) plus piperaquine (PQ) in pregnant Papua New Guinean women.

Study design: Open-label, randomized, parallel-group trial.

Methods: 122 women (median gestation 26 [range 14-32] weeks) were randomized 1:1 to three daily doses of 1g AZ plus 960 mg PQ tetraphosphate or single-dose SP (4,500 mg sulfadoxine, 225 mg pyrimethamine) based on computer-generated block randomization. Tolerability was assessed to Day 7, and efficacy to Day 42 (when participants were returned to usual care) and at delivery.

Results: Data from 119 participants (AZ-PQ n=61, SP n=58) were analyzed. Both regimens were well tolerated, but AZ-PQ was associated with more gastrointestinal side-effects (31%) and dizziness (21%). Eight women (6.7%) were parasitemic at recruitment but all were aparasitemic by 72 hours. There was no difference in blood smear positivity between AZ-PQ and SP up to Day 42 (0% versus 5.2%; relative risk (RR) (95% CI) 0.14 (0.01,2.58), *P*=0.18; absolute risk reduction (ARR) (95% CI) 5.2 (-1.3,11.6)%) and by the time of delivery (0% versus 8.7%; RR 0.11 (0.01,2.01), *P*=0.14; ARR 8.7 (-0.2,17.6)%). Of 92 women followed to parturition, 89 (97%) delivered healthy babies and there were three stillbirths (SP n=1, AZ-PQ n=2 (twins)). There was a higher mean±SD live birthweight in the AZ-PQ group (3.13±0.42 versus 2.88±0.55 kg; *P*=0.016 (mean difference (95% CI) 0.25 (0.02,0.48) kg).

Conclusion: AZ-PQ is a promising candidate for IPTp.

INTRODUCTION

Malaria in pregnancy remains a major cause of maternal anemia, low infant birth weight and increased perinatal mortality (1). Intermittent preventive treatment in pregnancy (IPTp), which is the periodic presumptive administration of curative courses of antimalarial drugs to clear existing peripheral and placental parasitemia and prevent subsequent new infections, is recommended by the World Health Organization (WHO) to minimize these and other adverse obstetric outcomes (2). The WHO currently recommends administering sulfadoxine-pyrimethamine (SP) as IPTp at each scheduled antenatal visit after the first trimester in moderate and high-malaria transmission areas (3, 4). However, the widespread development of SP-resistant *Plasmodium falciparum* has prompted the search for alternative IPTp therapies (5-7) including those containing the macrolide antibiotic azithromycin (AZ) (8-20).

Although the antimalarial activity of AZ is of slow onset and relatively weak (21), it has properties that are favorable for its use in IPTp including prolonged tissue concentrations (22, 23), activity against other clinically significant pathogens such as those causing sexually transmissible diseases, and proven safety in all trimesters of pregnancy (24). Its modest antimalarial efficacy as monotherapy (21, 25-27) is increased when it is co-administered with a pharmacologically compatible partner drug (25). To date, AZ has been combined successfully in IPTp with SP and chloroquine (CQ) in a number of African countries (16, 18, 20, 25) and Papua New Guinea (PNG) (9, 10). However, the effectiveness of combinations with these conventional agents can be compromised by using failing drugs as partners (28), suggesting that novel antimalarials should also be assessed for this role.

Piperaquine (PQ) has proven to be a safe, well tolerated and efficacious antimalarial drug when used in combination with dihydroartemisinin (DHA) for treatment of uncomplicated

malaria and as an alternative to SP for IPTp (29-32). However, given the worrying emergence of *P. falciparum* resistance to artemisinin derivatives and PQ in South-east Asia, there are concerns as to whether DHA-PQ should be recommended as prophylaxis since it would not be easy to minimize indiscriminate use in this context (33). The combination of AZ-PQ could provide significant advantages over SP and other candidate replacement therapies, while allowing appropriate restriction of artemisinin combination therapies such as DHA-PQ to the treatment of acute infections.

A single safety and pharmacokinetic study of AZ-PQ given as 1 g AZ plus 960 mg PQ daily for 3 days to pregnant PNG women showed that it was safe and generally well tolerated (14), apart from the gastrointestinal side effects which have also been reported when AZ (10, 18, 21) and PQ (32, 34) are given separately. As an extension of this study, we have conducted a randomized efficacy study using the same AZ-PQ regimen and conventional SP treatment in pregnant women from PNG. It was hypothesized that the three-day divided-dose regimen of AZ and PQ would be well tolerated and more efficacious than single-dose SP.

METHODS

Study design, site, approvals and participants

The present randomized, open-label, parallel group trial was conducted at the Alexishafen Health Center, Madang Province, PNG, where there is endemic transmission of *P. falciparum* and *P. vivax* malaria (35). Pregnant women between 14 and 32 weeks of gestation who were attending their first antenatal clinic visit were eligible for recruitment if i) they had not taken any study drugs in the previous 28 days, ii) they had no history of allergy to study drugs, iii) there was no significant comorbidity or features of severe malaria, iv) they had no history/family history of congenital prolongation of the electrocardiographic QT_c interval or

any clinical condition associated with QT_c prolongation, vi) they had no history of complicated pregnancies or deliveries including a history of previous Cesarean section, stillbirth or late gestational miscarriage, or high blood pressure during pregnancy, and vii) they could attend all follow-up visits. Informed consent was obtained from each participant, and verbal consent was obtained from each husband/father as is culturally appropriate in PNG. Ethical approval was obtained from the PNG Institute of Medical Research Institutional Review Board, the Medical Research Advisory Committee of the PNG Health Department, and the Human Research Ethics Committee of the University of Western Australia.

Baseline assessment and treatment allocation

A detailed medical history (including a standardized symptom questionnaire) was completed and a physical examination (including estimation of gestational age, axillary temperature, pulse rate, blood pressure, and respiratory rate) was performed. Thick and thin blood smears were prepared for microscopy, and blood was drawn for measurement of hemoglobin and blood glucose (HemoCue, Radiometer Pacific Pty Ltd, Victoria, Australia). A mixed capillary blood sample (250 µL) was collected into EDTA anticoagulant for *P. falciparum* and *P. vivax* quantitative PCR.

Each participant was allocated 1:1 to i) three daily doses (at 0, 24 and 48 h) of 1 g AZ as film coated 500 mg tablets (Sandoz, Pyrmont, NSW, Australia) given with 960 mg PQ tetraphosphate (three 320 mg tablets; Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Italy) or ii) single dose SP (three tablets of 1,500 mg of sulfadoxine and 75 mg of pyrimethamine; Fansidar, Roche, Basel, Switzerland). Treatment allocation was by computer-generated randomized design in blocks of 20. Allocated treatments were concealed

120 in sealed numbered envelopes that were opened in sequence by the study medical or nursing
121 staff, and the specified treatment administered. Treatments were open label given that
122 endpoints were based on objective clinical and parasitologic data. All drug doses were, as per
123 the manufacturer's recommendation for PQ, administered with water on an empty stomach
124 (no food consumption in previous two hours and for an hour post dose) under direct
125 supervision by study staff. Women vomiting within 30 minutes of dosing were to be
126 retreated. All participants were supplied with daily iron and folate supplements for
127 unsupervised self-administration for the duration of their pregnancy as part of PNG standard
128 antenatal care (36), the latter at a dose (300 μg) that does not influence SP efficacy (37).
129
130 *Monitoring, sampling and follow-up*
131 Detailed assessment, including lying/standing blood pressure and pulse rate, respiratory rate,
132 axillary temperature, thick/thin blood smears, hemoglobin and malarial PCR, was carried out
133 at follow-up visits on Days 1, 2, 3, 7, 14, 21, 28 and 42. Additional monitoring comprised i)
134 administration of a standardized side-effect questionnaire on Days 1, 2, 3, 4 and 7, ii) blood
135 glucose measurement on Days 1, 2 and 3, iii) assessment of fetal viability (maternally
136 detected movements and fetal heart beat on auscultation) daily on Days 1-4 and then at each
137 subsequent follow-up visit, iv) ultrasonography if required to confirm gestational age, fetal lie
138 and presentation, and v) a single blood sample on Day 4 for AZI/PQ or SP assay (data to be
139 presented subsequently). Clinical review on Days 14, 28 and 42 included assessment of
140 symptoms even though the standardized questionnaire was not administered at these visits.
141 As AZ-PQ is not yet a WHO-recommended treatment for malaria in pregnancy, all
142 monitoring data were reviewed for each participant and at each study visit by the on-site
143 study clinician (JMB, MO-K or ML). In cases where there were clinical concerns, the women

were transferred promptly to Modilon Hospital in Madang Town (the provincial referral hospital) for further management.

All blood smears were examined by light microscopy and any parasitemia was quantified by two WHO-certified independent microscopists in a central laboratory. Discrepancies were adjudicated by a senior expert level microscopist (WHO External Competency Assessment Level 1). Parasite densities were calculated from the number of parasite/200 white cells (or /500 white cells if there were <25 parasites/200 white cells) and an assumed total white cell count of 8000 μL^{-1}, with the final density calculated as the geometric mean of the two or three values from expert microscopy (38). Those participants who developed or redeveloped parasitemia during the 42-day follow-up period were to be treated with artemether-lumefantrine as per the PNG National Treatment Guidelines (39). Subsequent PCR analysis of baseline and follow-up blood samples in these cases were used to determine if the parasitemia was a recrudescence or reinfection.

Participants were returned to usual antenatal care after the Day 42 assessment but they were given insecticide-treated bed-nets to use up to delivery as an alternative to monthly SP at scheduled antenatal visits. Education on bed-net use was provided and local clinic staff were alerted to study recruitment and the requirement for no subsequent SP doses through a sticker placed on the front of each participant's antenatal clinic book. All participants were requested to attend the Alexishafen Health Center when they went into labor, or to notify study staff if they delivered at an alternative local healthcare facility or at home. If delivery occurred at the Alexishafen Health Center, maternal thick/thin blood films were prepared and the maternal hemoglobin concentration was measured. Three thick/thin cord blood smears and a placental

smear were prepared, and a section of placenta was collected into 10% neutral buffered formalin for evaluation if cord/placental smears were positive for malaria parasites.

Sample size

Based on data relating to the frequency of malaria in pregnancy in PNG of up to 40% at delivery when the study was designed in 2009 (40), on previous studies of the efficacy of CQ-SP in this patient group (41), and on AZ and PQ efficacy data from all relevant studies of combination treatments in the same geographic area (10, 32, 42), we assumed that 35% of those allocated SP would develop or redevelop parasitemia over 42 days of follow-up versus <10% of those treated with AZ-PQ. Under these assumptions and using an α of 0.05, at 80% power and allowing for 20% attrition, a total sample size of 120 patients (60 in each arm) was required. Pre-specified secondary endpoints were the development of any parasitemia during follow-up to delivery and infant birthweight.

Statistical analysis

Per-protocol pre-specified analyses included women with complete follow-up (to Day 42) or confirmed malaria infection during the study period, and excluded those who withdrew consent after receiving allocated therapy or who defaulted from follow-up despite repeated attempts at contact. A separate analysis for delivery outcomes included all women who presented to the study clinic/health centre at time of delivery or who contacted study staff within 24 hours of a birth in their village, and excluded women who delivered outside the catchment area or who failed to notify study staff within 24 hours of delivery.

Statistical analysis was performed using SigmaPlot 13.0 (Systat Software Inc., Germany). Data are summarized as means ± standard deviations (SD) or medians and interquartile

ranges [IQRs] as appropriate. Two-sample comparisons for normally distributed variables were performed using Student's *t*-test, for non-normally distributed variables the Mann-Whitney U test was used, and the Fisher's exact test was used for proportions. For multiple samples, analysis of variance (ANOVA) or the Kruskal-Wallis test was used. Fisher's exact test was used to determine differences in frequencies of side-effects and parasitemia by treatment group. Relative risk (RR) and absolute risk reduction (ARR) were calculated for between-group comparisons of prophylactic efficacy. A two-tailed level of significance of 0.05 was used throughout.

RESULTS

Participant characteristics

A total of 122 pregnant women were recruited between November 2014 and March 2016, of whom three withdrew their consent soon after antimalarial therapy was administered (see Figure 1). The baseline characteristics of the remaining 119 are summarized by allocated treatment in Table 1. The two groups were well matched across a range of demographic, obstetric, clinical and laboratory variables. No recruited participant had been treated with any antimalarial drug in the previous month. Five participants were symptomatic at time of recruitment of whom two (both randomized to AZ-PQ) were positive for *P. falciparum* on blood film microscopy. Of the remaining 117 asymptomatic participants, blood film examination at recruitment showed a further six women (5.0%) with asexual parasitemia (*P. falciparum*, n=5 (4.2%); *P. vivax*, n=1 (0.8%)). The median [IQR] asexual *P. falciparum* parasite density was 12,118 [10,212-14,024] /μL and 322 [54-730] /μL for symptomatic and asymptomatic participants, respectively. Of those who were parasitemic at recruitment, three were randomized to the SP treatment group and the remaining six to AZ-PQ. One participant had *P. falciparum* gametocytes on the baseline blood film. No participant had clinical

evidence of HIV and none were positive for HIV through antenatal screening.

Antimalarial efficacy

All baseline asexual parasitemias cleared by Day 3, although one woman in the AZ-PQ group had a gametocytemia that persisted to Day 7. Five women in the SP treatment group, all of whom were slide-negative at baseline, developed peripheral parasitemia subsequently during follow-up, one on Day 28 (*P. vivax*, asymptomatic), two on Day 42 (*P. falciparum* with fever; *P. vivax*, asymptomatic) and two at delivery (*P. falciparum* and *P. vivax*; both asymptomatic). All cases were successfully treated with a three-day course of artemether-lumefantrine, as per PNG treatment guidelines (39, 43). No participant in the AZ-PQ treatment group developed malarial parasitemia during the study period (0% (95% CI 0-5.9%)).

There was no statistically significant difference in blood smear positivity between AZ-PQ and SP up to Day 42 (0% versus 5.2%; RR (95% CI) 0.14 (0.01,2.58), *P*=0.18; ARR (95% CI) 5.2 (-1.3,11.6)%) and by the time of delivery (0% versus 8.7%; RR 0.11 (0.01-2.01), *P*=0.14; ARR 8.7 (-0.2,17.6)%).

Safety and tolerability

Both treatments were well tolerated. Self-reported side-effects during the first seven days are summarized in Table 2. AZ-PQ was associated with an increased frequency of adverse effects including nausea (25%), dizziness (21%), vomiting (18%), and abdominal pain (11%). Compared to women treated with single-dose SP, those who received AZ-PQ were more likely to report vomiting (*P*=0.016) and dizziness (*P*=0.035). However, all reported events were assessed as mild (they did not interfere with daily activities) and limited to within the 24

hours after last dose (see Figure 2). Two women in the AZ-PQ group presented with transient skin rashes on Days 0 and 4, respectively, which were of unknown etiology and not thought to be related to drug administration. There were no cases of hypoglycemia (blood glucose <2.5 mmol/L) only one of severe anemia (hemoglobin <50 g/L) during the 42-day follow-up period. There were no significant between-group differences in blood glucose or hemoglobin at any time-point (data not shown).

Obstetric outcomes

Ninety-two participants (77.3% overall; 46 in each group) were followed to parturition. The obstetric outcomes of the participants by treatment allocation are summarized in Table 3. There were no significant differences between the two treatment arms for timing of delivery in relation to enrolment or gestational age, where the delivery occurred, and where the data were available, in maternal observations or infant characteristics apart from a mean 0.25 kg higher birthweight in the AZ-PQ group (mean±SD birth weight 2.88±0.55 and 3.13±0.43 kg for SP and AZI-PQ, respectively; P=0.016; mean difference 0.25 (95% CI 0.02-0.48) kg).

In the AZ-PQ group, one mother delivered by Cesarean section at Modilon Hospital due to pre-eclampsia and a second mother was referred to Modilon Hospital for transfusion (hemoglobin 37 g/L at 24 hours post-delivery). Two participants had stillbirths. One woman reported a history of fever but was afebrile when recruited. She complained of distended painful breasts when assessed at the Day 14 follow-up, and had a stillbirth in her village seven days later at 29 weeks' gestation (21 days after AZ-PQ). The placenta and fetus were not available for examination. The second woman presented at Alexishafen Health Center with cervical effacement and a footling breech presentation at 32 weeks of gestation (73 days after AZ-PQ). Examination of the birth products showed heavy meconium staining, a dark

brown odorous placenta, and two 0.5 kg macerated male foetuses each with significant skin sloughing.

Of those participants randomized to SP, one participant had a spontaneous stillbirth at home at 28 weeks' gestation (67 days after SP). The placenta and fetus were not available for examination. One maternal death, due to cardiac arrest secondary to postpartum hemorrhage, occurred due to a third degree high vaginal tear during an unsupervised aid-post delivery. Once made aware of the clinical situation, arrangements were made for urgent transportation of the mother and her infant to Modilon Hospital for specialist care. However, she suffered a cardiac arrest during suturing and could not be resuscitated. The infant was discharged well. Two other babies required admission to the special care nursery for supportive care, and were discharged in good health within 48 hours of admission.

All serious adverse obstetric events were reviewed by a panel of three independent physicians. It was concluded that the three stillbirths (3.3% of delivery cohort) and one maternal death (1.1%) were not related to study medication, and that they reflected the background risks of such events in pregnant PNG women even when treated in hospital (44-46).

DISCUSSION

The present study investigated the tolerability and prophylactic efficacy of AZ-PQ compared to SP for the prevention of malaria in pregnant PNG women. In the relatively few women (<7%) who were parasitemic at baseline, parasite clearance was achieved within 72 hours regardless of allocated treatment. There was no significant difference in the prophylactic efficacy of SP versus AZ-PQ after 6 weeks of follow-up and at delivery a mean of 12.4

weeks after enrolment, but there were no cases of malaria detected in the AZ-PQ group whereas 8% of women treated with single dose SP had developed parasitemia by parturition. The infants of the mothers allocated to AZ-PQ had a higher birthweight than those in the SP group. There was a greater incidence of expected largely gastrointestinal side-effects with AZ-PQ, but these were generally mild and self-limiting.

There were fewer cases of malaria in the SP group than expected when the study was designed in 2009, a feature of other contemporaneous studies of malaria in pregnant PNG women (9). This suggests that there was insufficient statistical power to show superiority of AZ-PQ over single-dose SP as IPTp for prevention of parasitemia in our participants. The most likely explanation for the lower rate of malaria in pregnancy during the present study is that the PNG National Malaria Control Plan was implemented between 2008 and 2014. This involved widespread distribution of long-lasting insecticide-treated bed-nets and rapid diagnostic tests, and a change of treatment policy to artemether-lumefantrine from older drugs such as CQ and SP with implications for reduced transmission (47). There was a subsequent decline in national malaria prevalence from 11.1% in 2009 to 0.9% in 2014 (47). Although all the present participants were provided an insecticide-treated bed-net on Day 42 as an alternative to monthly SP prophylaxis, it is likely that many had already been using a bed-net before this. Although a secondary endpoint, the greater efficacy of AZ-PQ in preventing parasitemia from enrolment to delivery suggests that the combined use of bed-nets and the longer half-life partner drug PQ provided a clinically important extended period of post-treatment prophylaxis (32).

Gastrointestinal side-effects including nausea, vomiting and abdominal pain occurred in 31% of participants allocated AZ-PQ. In the case of nausea, 25% of the participants treated with

AZ-PQ reported this symptom, a percentage that was higher than the 7% to 24% observed in previous studies of pregnant PNG women treated with AZ or PQ combined with other antimalarial drugs (10, 14, 32). In addition, 18% of the AZ-PQ participants in the present study reported episodes of vomiting after treatment, also a higher rate than in previous studies. All episodes of vomiting in the present study occurred after the one hour of direct observation post dose and should not have contributed to attenuated drug absorption, but the data from Day 4 plasma concentrations (to be reported subsequently) should allow an assessment of this possibility. The high incidence of nausea and vomiting after AZ-PQ relative to other regimens in which they are components reflects the fact that both drugs have a well recognized propensity to cause gastrointestinal adverse effects (21, 34). However, given that DHA-PQ has an excellent tolerability profile in pregnancy (32, 48) it is likely that the 3 g dose of AZ is responsible for the modest intolerance observed in the present study. Reassuringly, all reported events were mild in that they did not interfere with daily activities, they resolved within 24 hours of the final dose of AZ-PQ, and they were not associated with withdrawal from the study. Dizziness was reported by approximately one in five participants receiving AZ-PQ. This symptom was not associated with clinically significant changes in blood pressure or blood glucose, and was limited to the duration of treatment. By comparison, only 2% of participants in the SP group reported dizziness.

We found that AZ-PQ was associated with a significantly higher birthweight than SP. This outcome was consistent with the results of another randomized trial conducted in the same area of PNG as the present study in which pregnant women allocated to AZ-SP delivered babies that were an average 42 g heavier than those treated with CQ-SP (9). The authors postulated that AZ may prevent low birthweight by clearing genitourinary infections which are common in PNG, but also suggested that AZ may also exert immunomodulatory effects

343 favouring fetal growth (49). Although SP also has broad-spectrum antibiotic activity that
344 could protect against non-malarial causes of LBW and preterm birth (50, 51), the present data
345 suggest that this effect is not as great as that from AZ. Nevertheless, dose finding studies of
346 SP IPTp have demonstrated that monthly courses are more effective than single or two-
347 course regimens in preventing LBW babies (2). Thus the birthweight difference favoring AZ-
348 PQ in the present study may not have been as great if participants had received monthly
349 antenatal regimens of SP and/or AZ-PQ. A positive correlation between birthweight and
350 gestational weight gain has been reported (8), but this could not be assessed in the present
351 study since serial maternal bodyweights were not recorded.
352
353 The present study had limitations. Although all 119 women who did not withdraw straight
354 after completing treatment were successfully followed to Day 28, nine (7.6%) did not attend
355 the Day 42 assessment and 27 (22.7%) were not assessed at delivery. Most of the latter group
356 delivered outside the study catchment area because of temporary disruptions of local services
357 or holidays during which they returned to their home provinces when they were close to term.
358 Nevertheless the number and baseline characteristics of those lost to follow-up did not differ
359 significantly between the two groups (data not shown), and our attrition rate was less than
360 that (28%) in the study of AZ-SP versus CQ-SP conducted in pregnant women recruited from
361 the same geographical area (9). We did not monitor the electrocardiographic QT interval as
362 our previous pharmacokinetic and safety evaluation of AZ-PQ in pregnancy did not show any
363 evidence of cardiotoxicity over and above that with the individual agents (14), while we
364 respected manufacturer's recommendations regarding timing of dosing in relation to meals to
365 minimize the effect of increased PQ bioavailability and thus potential adverse QT effects
366 associated with fat intake.
367

The present data show that AZ-PQ is a promising candidate for IPTp in pregnant Melanesian women that could also be of use in other regions with moderate or high malaria transmission. There is good evidence from African studies that monthly DHA-PQ is more efficacious than monthly SP for malaria-specific endpoints, although it is not superior to SP in preventing adverse neonatal outcomes (pre-term birth and LBW) (48, 52, 53). AZ-PQ administered each month from the second trimester should also be evaluated against monthly SP given the likely additional antibacterial effects of AZ that could further improve key maternal and infant outcomes such as birthweight. Where resources and access are limited, the present study suggests that a single three-day AZ-PQ treatment regimen given in the second trimester combined with use of an insecticide-impregnated bed-net provides better outcomes than single-dose SP. Further assessment of AZ-PQ, including alternative total dosing of AZ and a focus on tolerability, should be undertaken in a variety of endemic settings to ensure this alternative therapy would be accepted as an alternative to SP.

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582 **Table 1**. Baseline characteristics of the women included in each treatment group. Data are
583 percentages, mean ± SD or median [IQR].
584

	Sulfadoxine-pyrimethamine	Azithromycin-piperaquine
Number	58	61
Age (years)	23 [21-25]	23 [20-26]
Gestational age (weeks)	25 [22-28]	26 [22-28]
Gravidity	1 [1-3]	2 [1-3]
Parity	0 [0-2]	1 [0-2]
Weight (kg)	55 [50-60]	54 [51-59]
Height (cm)	156 [153-159]	156 [153-160]
Axillary temperature (ºC)	36.4 [36.0-36.7]	36.6 [36.1-36.9]
Respiratory rate (/min)	20 [20-20]	20 [20-20]
Pulse rate (/min)	82 [78-90]	80 [80-88]
Systolic blood pressure (mmHg)	100 [98-100]	100 [92-100]
Diastolic blood pressure (mmHg)	60 [60-70]	60 [60-70]
Systolic fall on standing (mmHg)	-9 [-10 to -4]	-8 [-10 to -2]
Diastolic fall standing (mmHg)	-8 [-10 to -1]	-7 [-10 to 1]
Parasitemic (%)	5.2	9.8
Hemoglobin (g/L)	91 ± 14	90 ± 14
Blood glucose (mmol/L)	6.0 ± 1.5	5.9 ± 1.0

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Table 2. Side effects reported by participants during the first week after treatment. Data are numbers of participants and (percentages) within each group.

	SP (n=58)	AZI-PQ (n=61)	*P*-value
Fever	7 (12)	5 (8)	0.55
Headache	12 (21)	7 (11)	0.21
Nausea	6 (10)	15 (25)	0.054
Vomiting	2 (3)	11 (18)	0.016
Abdominal pain	5 (9)	8 (13)	0.56
Diarrhea	1 (2)	0 (0)	0.49
Dizziness	1 (2)	13 (21)	0.035
Rash	1 (2)	2 (3)	0.50
Anorexia	2 (3)	2 (3)	1.00
Insomnia	0 (0)	2 (3)	0.50
Total number of side effects	37	65	
Number (%) with ≥1 side effect	21 (36)	30 (49)	0.20

Table 3. Details of pregnancy and delivery in the women in each treatment group who were followed to parturition. Data are percentages, mean ± SD or median [IQR].

	SP (n=46)	AZI-PQ (n=46)	*P*-value
Gestation at time of enrolment (weeks)	25 [22-28]	26 [22-28]	0.25
Gestation at time of delivery (weeks)	38 [35-40]	38 [35-41]	0.91
Time from first dose (days)	87 [67-122]	86 [59-112]	0.44
Delivery site:			
Home	13	12	
Alexishafen Health Center	30	31	0.94
Modilon Hospital	3	3	
Maternal characteristics:			
Axillary temperature (ºC)	36.4±0.42	36.4±0.43	0.94
Hemoglobin (g/L)	97± 17	95±14	0.55
Blood glucose (mmol/L)	6.9 ± 1.8	6.6±2.3	0.65
Malaria slide positivity (n [%])	2 [4.3]	0 [0.0]	0.50
Infant characteristics:			
Gender (% male)	50	55	0.84
Weight (kg)*	2.88±0.55	3.13 ± 0.43	0.016
Apgar at 1 min (/10)	9 [7-9]	9 [8-9]	0.29
Apgar at 5 min (/10)	10 [10-10]	10 [10-10]	0.27

*average neonatal weight based on live singleton deliveries

FIGURE CAPTIONS

Figure 1. Trial profile showing numbers of participants from screening to time of delivery.

Figure 2. Frequency of most commonly reported side effects during treatment by participants randomized to the AZI-PQ group.

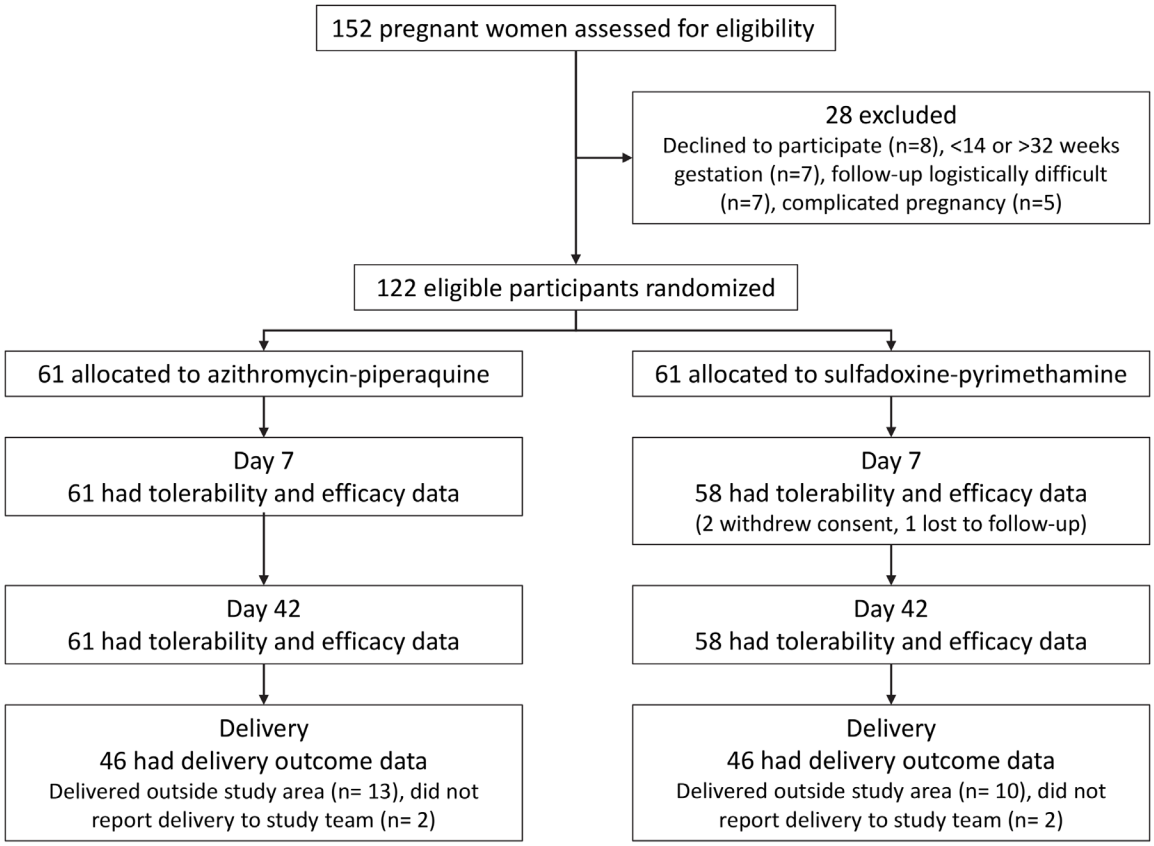

Figure 1. Trial profile showing numbers of participants from screening to time of delivery.

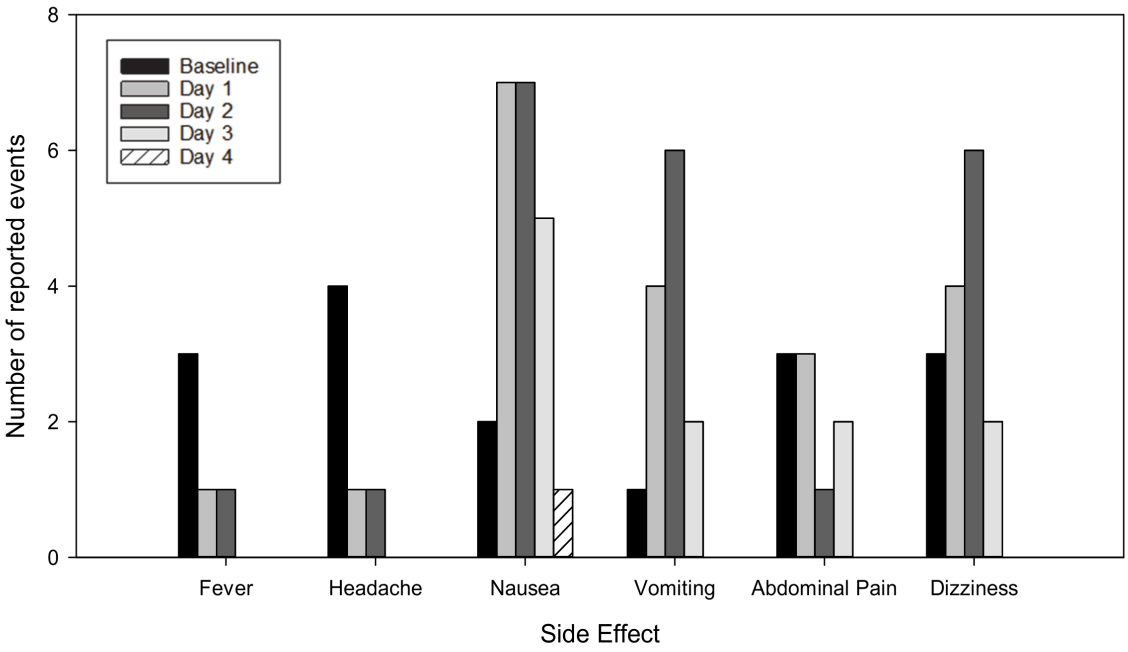

Figure 2. Frequency of most commonly reported side effects during treatment by participants randomized to the AZI-PQ group.