


# Effectiveness of intermittent preventive treatment in pregnancy with sulphadoxine-pyrimethamine (IPTp-SP) in Ghana

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## ABSTRACT

**Introduction** Ghana adopted the revised WHO recommendation on intermittent preventive treatment in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP) in 2012. This study has assessed the effectiveness and safety of this policy in Ghana.

**Methods** A total of 1926 pregnant women enrolled at antenatal care (ANC) clinics were assessed for birth outcomes at delivery, and placental histology results for malaria infection were obtained from 1642 participants. Association of reduced placental or peripheral malaria, anaemia and low birth weight (LBW) in women who received  $\geq 4$  IPTp-SP doses compared with 3 or  $\leq 2$  doses was determined by logistic regression analysis.

**Results** Among the 1926 participants, 5.3% (103), 19.2% (369), 33.2% (640) and 42.3% (817) of women had received  $\leq 1$ , 2, 3 or  $\geq 4$  doses, respectively. There was no difference in risk of active placental malaria (PM) infection in women who received 3 doses compared with  $\geq 4$  doses (adjusted OR (aOR) 1.00, 95% CI 0.47 to 2.14). The risk of overall PM infection was 1.63 (95% CI 1.07 to 2.48) in 2 dose group and 1.06 (95% CI 0.72 to 1.57) in 3 dose group compared with  $\geq 4$  dose group. The risk of LBW was 1.55 (95% CI 0.97 to 2.47) and 1.06 (95% CI 0.68 to 1.65) for 2 and 3 dose groups, respectively, compared with the  $\geq 4$  dose group. Jaundice in babies was present in 0.16%, and 0% for women who received  $\geq 4$  doses of SP.

**Conclusion** There was no difference in the risk of PM, LBW or maternal anaemia among women receiving 3 doses compared with  $\geq 4$  doses. Receiving  $\geq 3$  IPTp-SP doses during pregnancy was associated with a lower risk of overall PM infection compared with 2 doses. As there are no safety concerns, monthly administration of IPTp-SP offers a more practical opportunity for pregnant women to receive  $\geq 3$  doses during pregnancy.

## INTRODUCTION

Malaria during pregnancy is a major public health problem that can lead to unfavourable pregnancy and birth outcomes such as abortion, preterm delivery, stillbirth, maternal

## Key questions

### What is already known?

- Malaria in pregnancy can lead to unfavourable pregnancy and birth outcomes such as abortion, preterm delivery, stillbirth, maternal anaemia and low birth weight (LBW).
- Intermittent preventive treatment during pregnancy using 3 or more doses of sulfadoxine-pyrimethamine (SP) has previously been shown to be more effective than 2 or fewer doses in controlling malaria in pregnancy.
- The National Malaria Control Programme of Ghana has transitioned from a 3-dose intermittent preventive treatment in pregnancy using SP (IPTp-SP) policy to the revised WHO policy, which recommends monthly administration of SP to pregnant women, starting early in the second trimester.

### What are the new findings?

- Placental malaria was detected in 16.1%, 16.8%, 10.4% and 9.7% of women who received  $\leq 1$ , 2, 3 or  $\geq 4$  IPTp-SP doses, respectively.
- Risk of placental malaria, LBW and anaemia were not different in women who received 3 doses compared with  $\geq 4$  doses.
- Incidence of jaundice in babies was present in 0%, 0.28%, 0.32% and 0% for women who received  $\leq 1$ , 2, 3 or  $\geq 4$  doses of SP, respectively.

### What do the new findings imply?

- There is no added benefit to receiving more than 3 doses of IPTp-SP. However, a monthly dosing schedule would facilitate women receiving at least 3 doses of IPTp-SP recommended by the WHO.

anaemia and low birth weight (LBW).<sup>1-3</sup> In 2018, an estimated 11 million of 38 million (29%) pregnancies were exposed to malaria in sub-Saharan Africa with 35% of pregnancies in West Africa exposed to malaria during the same period.<sup>4</sup>

To prevent malaria during pregnancy, and the unfavourable maternal and foetal outcomes associated with *Plasmodium falciparum* infections in areas of moderate to high malaria transmission, the WHO previously recommended the use of long-lasting insecticide-treated bednet (ITN), case management through prompt diagnosis and treatment as well as intermittent preventive treatment in pregnancy (IPTp) with at least 2 full treatment doses of sulfadoxine-pyrimethamine (SP) given after quickening in the second and third trimesters and before 36 weeks of gestation at intervals not less than 1 month.<sup>5</sup> Effective IPTp, given at predetermined intervals during pregnancy, clears maternal parasitaemia and prevent subsequent reinfections.<sup>6,7</sup> Ghana adopted this IPTp-SP policy in 2003, recommending that three tablets of SP should be given orally three times during pregnancy.<sup>8</sup>

The duration of the malaria prophylactic effect of SP has been reduced by the emergence of resistance to SP, for which reason it has been proposed that more frequent dosing may be needed.<sup>7,9</sup> This supposition was supported by a meta-analysis of seven studies, which compared the efficacy of 2 doses to  $\geq 3$  doses of IPTp-SP<sup>9</sup>) and showed the latter to be more efficacious. WHO policy on IPTp-SP was consequently revised and now recommends starting IPTp as early as possible in the second trimester, with administration at each scheduled ANC visit until the time of delivery, provided that the doses are given at least 1 month apart. Ghana adopted this revised policy in 2012.<sup>10</sup> As a consequence of this change in policy, it has become possible for women to receive as many as six doses of SP during pregnancy, but the efficacy and safety of  $>3$  doses of IPTp-SP have not been rigorously investigated. This study has, therefore, been undertaken to evaluate the impact of additional SP doses on PM, other malaria indicators, birth outcomes and safety, among pregnant Ghanaian women and their new borns.

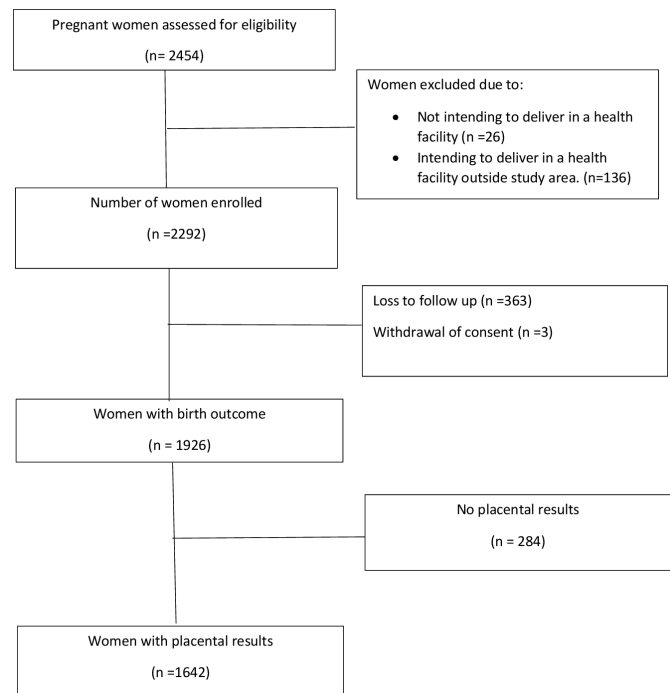
## METHODS

### Study areas

This study was conducted in three different ecological zones of Ghana. The Dodowa area in the Greater Accra Region is in the forest-coastal savannah zone; Kintampo area in the Bono East Region is in the transition forest-savannah zone; Navrongo, in the Upper East Region, is in the Guinea savannah zone. Malaria transmission is low and perennial in the forest-coastal savannah zone,<sup>11</sup> high and perennial in the transitional forest savannah zone<sup>12</sup> and high but seasonal in the guinea savannah zone.<sup>13</sup> The study was carried out between March 2017 and September 2019.

### Study design

This was a prospective, observational, cohort study of pregnant women who attended ANC in the three study



**Figure 1** Flowchart of study.

sites. The study evaluated the effectiveness and safety of four or more doses of IPTp-SP on malaria in pregnancy and its consequences. The primary endpoint was active PM infection and secondary endpoints were overall PM infection, maternal anaemia, LBW, maternal peripheral blood malaria parasitaemia, placental blood and cord blood parasitaemia and maternal and fetal outcomes at delivery. Women of any gravidity attending an ANC who were aged 18 years and above with an intention to deliver in a health facility were eligible to join the study. Women with serious illness requiring hospitalisation, known HIV infection or known full deficiency of glucose-6-phosphate dehydrogenase, were excluded.

### Sample size

The prevalence of active PM infection within the middle belt of Ghana in 2013 was 7.4%.<sup>14</sup> Although this prevalence could have changed, it represents the best estimate for active PM in this part of the country where the majority of the women was enrolled. To detect a reduction in active *P. falciparum* PM infection from 7.4% to 3.4%, with a 0.05 level of significance and 80% power, a sample of at least 502 women who receive  $\geq 4$  doses of IPTp-SP compared with an equal number of those who received 3 doses of IPTp-SP was required. Assuming a 10% loss to follow-up during the course of pregnancy, an additional 50 women were needed for each group making a total of 1104 women required for the study (Open Epi Software). Annual data from the study areas in 2015 and 2016 showed approximately 50% of pregnant women received 3 doses of IPTp-SP. There was, therefore, the need to increase the sample size by a minimum of 50% (ie, 552) to be able to achieve at least 502 participants at delivery for each group.

**Table 1** Characteristic of study participants at enrolment by doses of SP used by the time of delivery

Characteristic	Overall (N=1926)		≤1 dose (N=103)		2 doses (N=369)		3 doses (N=640)		≥4 doses (N=814)	
	N	%	N	%	N	%	N	%	N	%
<b>Study site</b>										
Kintampo	1128	58.6	40	38.8	202	54.7	365	57.0	521	64.0
Dodowa	404	21.0	34	33.0	105	28.5	159	24.8	106	13.0
Navrongo	394	20.4	29	28.2	62	16.8	116	18.1	187	23.0
<b>Age</b>										
Mean (SD)	27.69 (6.01)		27.26 (6.62)		27.25 (6.28)		27.90 (6.02)		27.78 (5.78)	
<b>Age group</b>										
18–24 years	647	33.6	40	38.8	141	38.2	202	31.6	264	32.4
25–34 years	995	51.7	45	43.7	177	48.0	345	53.9	428	52.6
≥35 years	284	14.7	18	17.5	51	13.8	93	14.5	122	15.0
<b>Level of education</b>										
No education	425	22.1	25	24.3	103	27.9	141	22.0	156	19.2
Primary	306	15.9	16	15.5	63	17.1	100	15.6	127	15.6
Junior high	695	36.1	38	37.0	133	36.0	242	37.8	281	34.5
Secondary or higher	500	25.9	24	23.3	70	19.0	157	24.5	250	30.7
<b>Marital status</b>										
Married/married before	1450	75.3	75	72.8	242	65.6	490	76.6	643	79.0
Living together with man, unmarried	263	13.7	17	16.5	72	19.5	91	14.2	83	10.2
Single, unmarried	213	11.0	11	10.7	55	14.9	59	9.2	88	10.8
<b>Religious background</b>										
Christian	1475	76.6	83	80.6	267	72.4	485	75.8	640	78.6
Muslim	389	20.2	17	16.5	85	23.0	132	20.6	155	19.0
Traditionalist	11	0.6	0	0.0	5	1.4	4	0.6	2	0.3
Other	51	2.6	3	2.9	12	3.3	19	3.0	17	2.1
<b>Household SES</b>										
Poorest	386	20.0	27	26.2	96	26.0	129	20.2	134	16.5
More poor	385	20.0	23	22.3	62	16.8	124	19.4	176	21.6
Poor	385	20.0	20	19.4	78	21.1	113	17.7	174	21.4
Less poor	385	20.0	19	18.5	73	19.8	138	21.6	155	19.0
Least poor	385	20.0	14	13.6	60	16.3	136	21.3	175	21.5
<b>Gravidity</b>										
Primigravidae	436	22.6	29	28.2	89	24.1	133	20.8	184	22.6
Secundigravidae	474	24.6	22	21.4	92	24.9	163	25.5	197	24.2
Multigravidae	1016	52.8	52	50.5	188	51.0	344	53.8	433	53.2
<b>ITN use</b>										
Yes	1242	64.5	70	68.0	232	62.9	393	61.4	547	67.2
No	684	35.5	33	32.0	137	37.1	247	38.6	267	32.8

ITN, insecticide-treated bednet; SES, socioeconomic status; SP, sulfadoxine-pyrimethamine.

### Enrolment procedures

Fieldworkers, laboratory personnel and midwives were trained on study procedures prior to commencement of the study. Informed consent was obtained from all eligible pregnant women and a structured questionnaire was completed as previously described.<sup>15</sup> Gestational age was determined by midwives at the first ANC visit using the symphysis-fundal height measurement method<sup>16</sup> and subsequently using the

ultrasound technique. IPTp-SP was administered by nurses at ANC clinics, following the WHO-revised policy guidelines and SP administration was recorded in the participant's antenatal book at each visit.

### Delivery

At delivery, cord blood (5 mL) was collected, after clamping the umbilical cord, into a K<sub>2</sub>-EDTA tube

**Table 2** Placental malaria infection by number of SP doses received during pregnancy

Infection	≤1 dose (N=87)		2 doses (N=316)		3 doses (N=549)		≥4 doses (N=690)		Combined (1642)		P value*
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	
Past	8	9.2 (4.6 to 17.4)	40	12.7 (9.4 to 16.8)	45	8.2 (6.2 to 10.8)	52	7.5 (5.8 to 9.8)	145	8.8 (7.6 to 10.3)	0.06
Acute	2	2.3 (0.6 to 8.8)	8	2.5 (1.3 to 5.0)	8	1.5 (0.7 to 2.9)	12	1.7 (1.0 to 3.0)	30	1.8 (1.3 to 2.6)	0.63
Chronic	4	4.6 (1.7 to 11.7)	5	1.6 (0.7 to 3.8)	4	0.7 (0.3 to 1.9)	3	0.4 (0.1 to 1.3)	16	1.0 (0.6 to 1.6)	0.01
Overall	14	16.1 (9.7 to 25.4)	53	16.8 (13.0 to 21.3)	57	10.4 (8.1 to 13.2)	67	9.7 (7.7 to 12.2)	191	11.6 (10.2 to 13.3)	0.004
Active	6	6.9 (3.1 to 14.6)	13	4.1 (2.4 to 7.0)	12	2.2 (1.2 to 3.8)	15	2.2 (1.3 to 3.58)	46	2.8 (2.1 to 3.7)	0.03

\*P value describes 2x4 X<sup>2</sup>.

(Becton Dickinson, England) for determination of haemoglobin (Hb) concentration and malaria parasitaemia by microscopy. A placental biopsy (approximately 2.5 cm<sup>3</sup>) was taken from the maternal side of the placenta within 1 hour of placental expulsion and placed in a prelabelled bottle containing 50 mL of 10% neutral buffered formalin. Incisions were also made on the maternal side of the placenta and 0.5 mL of placental blood collected, using a Pasteur pipette, into an EDTA Microtainer tube (Becton Dickinson, England). A capillary blood sample (0.2 mL) was collected from the mother prior to delivery for malaria microscopy. All biological samples were transported in a cold box to the nearest clinical laboratory (Kintampo Health Research Centre, Navrongo Health Research Centre or Shai-Osudoku District Hospital) for processing. New-borns were weighed on a calibrated digital scale (Jactermac, Germany) to the nearest 0.1 kg within 24 hours of birth. Screening for congenital abnormalities was performed by 2 midwives using clinical examination.

**Laboratory procedures**

**Hb estimation**

Hb concentration was estimated using a validated ABX Pentra 60C+Haematology analyser (Horiba-ABX, Montpellier, France) or a HemoCue 200+haemoglobinometer (HemoCue, Angelholm, Sweden) according to manufacturers’ operating instructions. Quality controls were performed to ensure quality of the results generated.

**Malaria parasitaemia determination**

Thick and thin malaria blood smears were prepared from peripheral, placental and cord blood and stained using standard procedures, as described previously.<sup>17 18</sup> Briefly, thick and thin blood smears were prepared on the same slide, air-dried and the thin smear fixed with absolute methanol. Both smears were stained with 10% Giemsa for 10 min and air-dried. Parasites were detected and counted in the thick smear when <100 parasites were seen in a high power field, otherwise, counting was done using the thin smear. Parasite density was calculated using absolute or, if white blood cell or red cell count was not available, using an assumed leucocyte (8 000/cm<sup>3</sup>) or erythrocyte (5 000 000/cm<sup>3</sup>) count. A slide was declared as negative when no parasites were seen after examining at least 200 high power fields. Slides were examined by two certified independent microscopists and by a third in cases of discordance between the two initial readers. Differences were resolved by taking the result of the third reader and that of the earlier reader who agreed with him/her and in case of positive slides the average parasite density was used.

**PM infection determination**

Placental biopsies, placed in 10% neutral buffered formalin, were stored in an air-conditioned room and transported to the Pathology Department of the School of Biomedical and Allied Health Sciences of the University

**Table 3** Crude and adjusted ORs of 2 doses of IPTp-SP versus 3 or more doses

Outcome variable	Unadjusted analysis			Adjusted analysis*		
	cOR	95% CI	P value	aOR	95% CI	P value
<b>Maternal parasitemia</b>						
2 doses	2.08	1.14 to 3.81	0.02	1.56	0.84 to 2.93	0.16
≥3 doses	1			1		
<b>Active placental infection</b>						
2 doses	1.96	1.01 to 3.81	0.05	1.45	0.73 to 2.89	0.29
≥3 doses	1			1		
<b>Overall placental infection</b>						
2 doses	1.82	1.29 to 2.57	0.001	1.58	1.08 to 2.29	0.02
≥3 doses	1			1		
<b>Maternal anaemia</b>						
2 doses	1.32	1.03 to 1.70	0.03	1.19	0.92 to 1.54	0.18
≥3 doses	1			1		
<b>Low birth weight</b>						
2 doses	1.72	1.14 to 2.58	0.01	1.52	0.99 to 2.32	0.05
≥3 doses	1			1		

\*Adjusted for age, education, household SES, marital status, gravidity, ITN use, malaria treatment in past 2 weeks and malaria treatment during pregnancy.

aOR, adjusted OR; IPTp-SP, intermittent preventive treatment in pregnancy using sulfadoxine-pyrimethamine; ITN, insecticide-treated bednet; SES, socioeconomic status.

of Ghana and processed as described previously.<sup>19</sup> Briefly, biopsies processed and embedded in paraffin wax blocks were sectioned and two slides were stained with H&E and Giemsa stains and examined microscopically by a pathologist for the presence of malaria parasites and/or pigment. Results were reported as no infection, acute infection, chronic infection or past infection, based on the Ishmail modification of Bulmer's classification. Active PM infection was defined as the presence of either acute or chronic placental infection.<sup>20</sup> As part of quality control, 10% of slides were examined by an independent pathologist and results compared with those of the first reader (online supplemental table 1).

### Outcome definitions

Active PM infection was defined as the presence of malaria parasites in the placenta with or without the presence of pigment, while overall placental infection was defined as the presence of parasite and/or pigment.<sup>20 21</sup> Maternal anaemia was defined as a Hb concentration <110 g/L.<sup>22</sup> LBW was defined as a singleton baby weighing <2.5 kg measured within 24 hours after birth; stillbirth as a delivery of a non-living fetus ≥28 weeks gestation; preterm delivery as a newborn with a gestational age <37 weeks at delivery. Neonatal anaemia was defined as a cord blood Hb concentration <125 g/L.<sup>23</sup>

### Data management and statistical analysis

All data were recorded on structured questionnaires, checked for completeness, double-entered and verified using a database designed with C-Sharp application as

front end and SQL-Server as back end. Statistical analysis was carried out using Stata V.15 (StataCorp, College Station, USA).

Uptake of IPTp-SP was grouped into ≤1, 2, 3 and ≥4 doses.  $\chi^2$  tests were used to explore the association between the characteristics of study participants at enrolment and the number of doses of IPTp-SP received. The association between the number of doses of IPTp-SP received and PM infection (past, acute, chronic, overall and active) and birth outcomes (preterm delivery, LBW, mode of delivery, delivery complication, congenital abnormalities, neonatal jaundice, neonatal anaemia) were assessed using  $\chi^2$  or Fisher's exact tests, where applicable.

Logistic regression was used to assess the association between the number of doses of IPTp-SP received and active PM infection, overall PM infection, maternal peripheral malaria parasitaemia, maternal anaemia at delivery and LBW. In each regression model, together with number of doses of IPTp-SP received, univariate analyses with age, education, household wealth, marital status, gravidity, ITN use, malaria treatment in the past 2 weeks and malaria treatment during pregnancy were performed first. Variables found in the univariate analyses to be significant at 0.15 level of significance were included in the multivariate analyses. In the multivariate analyses, variables with a p value <0.05 were considered to be statistically significant. Active PM was found in only 2.8% (46/1642) of the participants with histologically examined placental biopsies, while 2.9% (54/1886) of the participants had peripheral blood asexual *P. falciparum*

**Table 4** Factors associated with overall placental malaria parasitaemia at delivery

Factors	Overall placental infection			Univariate analysis			Multivariate analysis		
	Total (N=1642) n	Present (N=191) n (%)	Absent (N=1451) n (%)	cOR	95% CI	P value	aOR	95% CI	P value
Age, years									
<25	556	116 (60.7)	440 (30.3)	3.55	2.60 to 4.85	<0.001	1.77	1.18 to 2.65	0.01
≥25	1086	75 (39.3)	1011 (69.7)	1			1		
Education									
No education	354	33 (17.3)	321 (22.1)	0.92	0.57 to 1.48	0.13	1.09	0.61 to 1.91	0.23
Primary	271	33 (17.3)	238 (16.4)	1.24	0.76 to 2.01		1.31	0.77 to 2.25	
Junior high	600	83 (43.4)	517 (35.6)	1.43	0.97 to 2.13		1.50	0.97 to 2.31	
High school or above	417	42 (22.0)	375 (25.9)	1			1		
Household SES									
Most poor	310	59 (30.9)	251 (17.3)	3.00	1.80 to 4.92	<0.001	2.47	1.40 to 4.35	<0.001
More poor	327	45 (23.6)	282 (19.4)	2.02	1.20 to 3.40		1.60	0.91 to 2.81	
Poor	336	34 (17.8)	302 (20.8)	1.43	0.83 to 2.46		1.22	0.69 to 2.18	
Less poor	341	29 (15.2)	312 (21.5)	1.18	0.67 to 2.07		1.05	0.59 to 1.88	
Least poor	328	24 (12.5)	304 (21.9)	1			1		
Marital status									
Married/married before	1211	114 (59.7)	1097 (75.6)	1		<0.001	1		0.33
Living together with man, unmarried	245	33 (17.3)	212 (14.6)	1.50	0.99 to 2.27		1.17	0.75 to 1.84	
Single, unmarried	186	44 (23.0)	142 (9.8)	2.98	2.02 to 4.40		1.40	0.86 to 2.17	
Gravidity									
Primigravidae	357	87 (45.5)	270 (18.6)	4.47	3.12 to 6.39	<0.001	2.95	1.83 to 4.75	<0.001
Secundigravidae	408	45 (23.6)	363 (25.0)	1.72	1.14 to 2.58		1.40	0.89 to 2.18	
Multigravidae	877	59 (30.9)	818 (56.4)	1			1		
ITN use									
No	605	66 (34.6)	539 (37.2)	0.89	0.65 to 1.23	0.48			
Yes	1037	125 (65.4)	912 (62.8)	1					
SP doses received									
≤1	87	14 (7.3)	73 (5.0)	1.78	0.95 to 3.33	0.01	1.38	0.70 to 2.69	0.13
2	316	53 (27.8)	263 (18.1)	1.87	1.27 to 2.76		1.63	1.07 to 2.48	
3	549	57 (29.8)	492 (33.9)	1.08	0.74 to 1.56		1.06	0.72 to 1.57	

Continued

Table 4 Continued

Factors	Overall placental infection		Univariate analysis			Multivariate analysis			
	Total (N=1642) n	Present (N=191) n (%)	Absent (N=1451) n (%)	cOR	95%CI	P value	aOR	95%CI	P value
≥4	690	67 (35.1)	623 (42.9)	1			1		
Malaria treatment in past 2 weeks									
No	1444	156 (81.7)	1288 (88.8)	1		0.01	1		0.15
Yes	198	35 (18.3)	163 (11.2)	1.77	1.19 to 2.65		1.42	0.89 to 2.27	
Malaria treatment during pregnancy									
No	1129	117 (61.3)	1012 (69.7)	1		0.02	1		0.15
Yes	513	74 (38.7)	439 (30.3)	1.46	1.07 to 1.99		1.30	0.90 to 1.87	

aOR, adjusted OR; cOR, crude OR; ITN, insecticide-treated bednet; SES, socioeconomic status; SP, sulphadoxine-pyrimethamine.

infection at delivery. Consequently, in accounting for the bias associated with using logistic regression for rare events, the penalised likelihood approach, which reduces the small-sample bias in maximum likelihood estimation was used.<sup>24</sup>

### Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

## RESULTS

### Characteristics of study participants

A total of 2454 pregnant women were screened for eligibility and 93.5% (2292/2454) were enrolled. Delivery outcomes were obtained for 84.0% (1926/2292) and placental results were available for 85.3% (1642/1926) (figure 1). There was no difference in characteristics between participants with or without placental results (online supplemental table 2). At enrolment, 52.2% (1006/1926) and 47.8% (920/1926) of participants had gestational age determined using ultrasound and fundal height, respectively.

Among the participants with birth outcomes, those who had taken 0, 1, 2, 3 or ≥4 doses by the time of delivery were 0.7% (14), 4.6% (89), 19.2% (369), 33.2% (640) and 42.3% (814), respectively. Majority of the study population, 58.6% (1128/1926) came from Kintampo area and 51.2% (978/1926) were aged between 25 and 34 years. Primigravidae and secundigravidae formed 22.6% (435/1926) and 24.7% (475/1926) of the study population, respectively, and 64.5% (1242/1926) had used an ITN the previous night (table 1). Only 29% (562/1926) of the women reported treatment for malaria during pregnancy while 11.6% (223/1926) reported receiving antimalarial treatment within 14 days prior to delivery. Characteristics of study participants by study area are presented in online supplemental table 3.

### Impact of IPTp-SP on PM infection

The prevalence of overall PM among the 1642 placental biopsies examined histologically was 11.6% (95% CI 10.2% to 13.3%). This comprised 2.8% active infections (1.8% acute and 1.0% chronic) and 8.8% past infections.

The prevalence of active placental infection was highest in women who received ≤1 dose (6.9%), followed by those who received 2 doses (4.1%) but the same, 2.2% in each case, among those who received 3 or ≥4 doses of IPTp-SP (table 2). In the univariate analysis, age, household socioeconomic status (SES), marital status, gravidity and the number of SP doses received during pregnancy were associated with active placental infection. In the multivariate analysis, there was no difference in the risk of active PM infection among women who received 3 or ≥4 doses of IPTp-SP (adjusted OR (aOR) 1.00, 95% CI 0.47 to 2.15) nor between those who received 2 versus ≥4 doses (aOR 1.48, 95% CI 0.69 to 3.18) (online supplemental table 4). There was also no difference in risk of active PM

infection in women who received 2 doses compared with those who received  $\geq 3$  doses IPTp-SP (aOR 1.45, 95% CI 0.73 to 2.89) (table 3).

Lower age, lower household SES, being single, primigravid or secundigravid and receiving malaria treatment during pregnancy were associated with overall PM infection in the univariate analysis. In the multivariate analysis, risk of overall PM infection was high in women aged  $< 25$  years compared with those aged  $\geq 25$  years (aOR 1.77, 95% CI 1.18 to 2.65); the most poor household SES compared with the least poor (aOR 2.47, 95% CI 1.40 to 4.35); primigravidae compared with multigravidae (aOR 2.95, 95% CI 1.83 to 4.75) and those who received  $\leq 2$  doses IPTp-SP compared with those who received  $\geq 4$  doses (aOR 1.63, 95% CI 1.07 to 2.48) (table 4). The risk of overall PM infection was also higher in women who received 2 doses compared with those who received  $\geq 3$  doses IPTp-SP (aOR 1.58, 95% CI 1.08 to 2.29) (table 3).

The overall prevalence of malaria parasitaemia in placental blood was 1.8% (25/1387). The prevalence of placental blood malaria was highest in women who received  $\leq 1$  dose (2.9%; 2/69) and lowest in those who received  $\geq 4$  doses (1.4%; 8/587). The number of IPTp-SP doses received during pregnancy had no impact on the prevalence of placental blood malaria.

### The impact of IPTp-SP on maternal peripheral and cord blood malaria parasitaemia at delivery

Overall, the prevalence of peripheral blood asexual *P. falciparum* infection at delivery among study women was 2.9% (54/1886). Among women who received  $\leq 1$ , 2, 3 and  $\geq 4$  doses of IPTp-SP, the prevalence was 6.2% (6/97), 4.5% (16/357), 2.6% (16/627) and 2.0% (16/805), respectively, but differences between groups were not statistically significant. In the univariate analysis, age, household SES, number of SP doses received and malaria treatment during pregnancy were associated with a higher risk of maternal peripheral malaria parasitaemia at delivery. In the multivariate analysis, there was no difference in risk of peripheral malaria parasitaemia in women who received 3 or  $\geq 4$  doses of SP (aOR 1.29, 95% CI 0.64 to 2.60) nor 2 doses versus  $\geq 4$  doses of SP (aOR 1.74, 95% CI 0.85 to 3.56). Being in a household of lower SES remained strongly associated with a risk of peripheral malaria parasitaemia (table 5). The overall prevalence of cord blood *P. falciparum* parasitaemia was 0.4%, and 0% (0/74), 0% (0/294), 0.8% (4/503) and 0.3% (2/643) among women who received  $\leq 1$ , 2, 3 and  $\geq 4$  doses of SP, respectively. There was no difference by number of IPTp-SP doses received.

### Impact of IPTp-SP on maternal anaemia at delivery

The overall mean Hb concentration (SD) for study women at delivery was 11.5 (2.0) g/dL. Overall, the prevalence of maternal anaemia (Hb  $< 11.0$  g/dL) was 34.2%. The prevalence of anaemia by number of IPTp-SP doses received was 40.4% (40/90), 38.8% (130/335) 35.5% (206/581)

and 30.0% (222/741) in women who received  $\leq 1$ , 2, 3 and  $\geq 4$  doses of IPTp-SP respectively.

In a univariate analysis, low household SES, being unmarried, receiving fewer IPTp-SP doses during pregnancy and having been treated for malaria (apart from SP) were associated with a higher risk of maternal anaemia at delivery (online supplemental table 5). In the multivariate analysis, the risk of anaemia was higher in women from most poor household compared with those from least poor households (aOR 1.51, 95% CI 1.09 to 2.06) and women who received 2 IPTp-SP doses during pregnancy compared with those who received  $\geq 4$  doses (aOR 1.34, 95% CI 1.02 to 1.77). There was no statistically significant difference in risk of anaemia among women who received 3 doses compared with those who received  $\geq 4$  doses (aOR 1.24, 95% CI 0.99 to 1.56) (online supplemental table 5) and also in women who received 2 doses compared with those who received  $\geq 3$  doses (aOR 1.19, 0.92–1.54) (table 3).

### Impact of IPTp-SP on LBW and other birth outcomes

Overall, 0.5% (10/1926) and 0.9% (17/1926) of pregnancies resulted in a miscarriage or stillbirth, respectively. The mean gestational age at delivery overall was 38.4 (SD 2.5) weeks and increased significantly with an increase in the number of IPTp-SP doses received (table 6).

Mean birth weight for all live singleton deliveries was 3.07 (SD 0.48) kg, and 2.84 kg, 2.99 kg, 3.09 kg and 3.11 kg in babies of women who received  $\leq 1$ , 2, 3, or  $\geq 4$  SP doses, respectively. The overall prevalence of LBW was 7.5% (140/1856) and 17.9% (17/95), 10.2% (36/354), 6.5% (40/615) and 5.9% (47/792) in babies of women who received  $\leq 1$ , 2, 3 or  $\geq 4$  SP doses, respectively. Factors strongly associated with LBW in the univariate analysis were household SES, gravidity and the number of IPTp-SP doses received. In the multivariate analysis, the risk of LBW was higher in babies born to women of most poor households compared with those from least poor households (aOR 4.26, 95% CI 2.23 to 8.04). There was no difference in risk of LBW between babies of women who received 3 doses of SP and those who received  $\geq 4$  doses (aOR 1.06, 95% CI 0.68 to 1.65) nor between those who received 2 doses and those who received  $\geq 4$  doses (table 7). The risk of LBW in babies born to mothers who received 2 doses of IPTp-SP did not differ significantly compared with those who received  $\geq 3$  doses (aOR 1.52, 0.99 to 2.32) (table 3).

### Impact of IPTp-SP doses on the safety of the baby

A low prevalence of jaundice, defined as yellowish coloration of the baby's eyes (0.16%, 9/1899), was observed in the babies overall, with none in those born to women who received  $\geq 4$  doses of SP during pregnancy (table 6). The mean haemoglobin concentration in study babies overall was 14.53 g/dL and highest (14.62 g/dL) in the babies born to women who received  $\geq 4$  doses of SP during pregnancy, but with no significant differences between the groups. The overall prevalence of neonatal

**Table 5** Factors associated with maternal peripheral blood malaria parasitaemia at delivery

Factors	Maternal parasitemia		Univariate analysis				Multivariate analysis			
	Total (N=1886) n	Present (N=54) n (%)	Absent (N=1832) n (%)	cOR	95% CI	P value	aOR	95% CI	P value	
Age, years										
<25	636	29 (53.7)	607 (33.1)	2.33	1.36 to 4.00	0.002	1.61	0.80 to 3.23	0.18	
≥25	1250	25 (46.3)	1225 (66.9)	1			1			
Education										
No education	418	10 (18.5)	408 (22.3)	0.98	0.42 to 2.25	0.55				
Primary	297	12 (22.2)	285 (15.6)	1.67	0.75 to 3.71					
Junior high	682	20 (37.1)	662 (36.1)	1.18	0.58 to 2.41					
High school or above	489	12 (22.2)	477 (26.0)	1						
Household SES										
Most poor	382	16 (29.6)	366 (20.0)	6.76	1.77 to 25.77	0.003	5.76	1.47 to 22.55	0.001	
More poor	379	6 (11.1)	373 (20.4)	2.61	0.60 to 11.32		2.35	0.53 to 10.34		
Poor	379	20 (37.1)	359 (19.6)	8.56	2.29 to 32.09		7.85	2.06 to 29.85		
Less poor	369	10 (18.5)	359 (19.6)	4.39	1.10 to 17.56		3.98	0.99 to 16.03		
Least poor	377	2 (3.7)	375 (20.4)	1			1			
Marital status										
Married/married before	1422	31 (57.4)	1391 (76.0)	1		0.004	1		0.20	
Living together with man, unmarried	257	9 (16.67)	248 (13.5)	1.63	0.77 to 3.46		1.11	0.51 to 2.40		
Single, unmarried	207	14 (25.93)	193 (10.5)	3.25	1.70 to 6.23		1.97	0.95 to 4.08		
Gravidity										
Primigravidae	425	19 (35.2)	406 (22.2)	1.99	1.08 to 3.67	0.08	1.12	0.50 to 2.51	0.83	
Secundigravidae	463	12 (22.2)	451 (24.6)	1.15	0.57 to 2.30		0.89	0.41 to 1.92		
Multigravidae	998	23 (42.6)	975 (53.2)	1			1			
ITN use										
No	663	25 (46.3)	638 (34.8)	1.62	0.94 to 2.77	0.08	1.53	0.87 to 2.67	0.14	
Yes	1223	29 (53.7)	1194 (65.2)	1			1			
SP doses received										
≤1	97 (5.1)	6 (11.1)	91 (5.0)	3.40	1.34 to 8.64	0.02	2.84	1.08 to 7.43	0.17	
2	357 (18.9)	16 (29.6)	341 (18.6)	2.31	1.15 to 4.63		1.74	0.85 to 3.56		
3	627 (33.2)	16 (29.6)	611 (33.4)	1.29	0.65 to 2.58		1.26	0.63 to 2.55		

Continued

Table 5 Continued

Factors	Maternal parasitemia		Univariate analysis			Multivariate analysis			
	Total (N=1886) n	Present (N=54) n (%)	Absent (N=1832) n (%)	cOR	95% CI	P value	aOR	95% CI	P value
≥4	805 (42.7)	16 (29.6)	789 (43.1)	1			1		
Malaria treatment in past 2 weeks									
No	1669	48 (88.9)	1621 (88.5)	1		0.95			
Yes	217	6 (11.1)	211 (11.5)	1.03	0.45 to 2.36				
Malaria treatment during pregnancy									
No	1335	29 (53.7)	1306 (71.3)	1		0.01	1		0.01
Yes	551	25 (46.3)	526 (28.7)	2.15	1.25 to 3.68		2.05	1.17 to 3.59	

aOR, adjusted OR; cOR, crude OR; ITN, insecticide-treated bednet; SES, socioeconomic status; SP, sulphadoxine-pyrimethamine.

anaemia was 15.4% (266/1731); 21.1% (19/90), 16.5% (55/333), 16.6% (96/580) and 13.2% (96/728) in babies of mothers who received ≤1, 2, 3 and ≥4SP doses, respectively (table 6). The overall prevalence of congenital abnormalities was 0.5% (9/1899) and there was no statistical difference in the incidence of congenital abnormalities by the number of IPTp-SP doses that the mother had received (table 6).

DISCUSSION

This observational, prospective cohort study demonstrated a low prevalence of both active and overall histologically confirmed PM infection in three ecological zones in the northern guinea-savannah, middle forest-savannah and southern forest-coastal-savannah zones of Ghana. Our finding of no statistically significant benefit of receiving ≥4 doses IPTp-SP over the standard 3-dose in Ghana against PM (active or overall), peripheral maternal malaria, LBW or maternal anaemia is consistent with findings in Zambia.<sup>25 26</sup>

The nearly two-fold risk of overall PM infection in women who received 2 doses compared with those who received 3 or more doses in the present study is consistent with previous ones that reported 3 or more doses of IPTp-SP to be more effective in reducing PM than 2 doses.<sup>27</sup> The prevalence of active PM found in this study was lower than in the northern and middle zones of Ghana in 2013 and 2015, respectively, prior to implementation of the WHO monthly IPTp-SP policy.<sup>14 28</sup> The prevalence of overall PM infection of 11.6% was lower than in the southern coastal (35.9%) and middle forest-savannah (37.5%) zones of Ghana, respectively, before introduction of the new policy. This marked reduction in the prevalence of PM infection could be attributed in part to high ITN use, use of other malaria prevention interventions as well as to a high uptake of IPTp-SP in the study cohort. A baseline study on the prevalence of malaria parasitaemia among pregnant women at first ANC visit in our study area in the middle belt of Ghana showed one-fifth of the women carried malaria parasites.<sup>15</sup> The low malaria parasite prevalence reported in this study can further be reduced if IPTp-SP uptake continues to increase over time.

Contrary to findings in previous studies in Ghana<sup>29 30</sup> and elsewhere,<sup>2 9</sup> this study showed no difference in risk of LBW in babies born to women who received 3 or more doses of IPTp-SP.

A major strength of this study is that unlike other studies that compared only ≥3 doses of IPTp-SP to 2 doses, this study assessed the additional benefits or otherwise of receiving ≥4 doses of IPTp-SP. This is one of very few studies<sup>30 31</sup> to evaluate the impact of the new WHO IPTp-SP policy and it was conducted in different ecological zones of Ghana with varied malaria transmission intensities, thereby producing generalisable results. A limitation of this study is that the study team was not directly involved in the administration of SP at the ANC

**Table 6** Birth outcomes by number of SP doses received during pregnancy

Character	Overall (N=1926)		≤1 dose (N=103)		2 doses (N=369)		3 doses (N=640)		≥4 doses (N=814)		P value
	N	%	N	%	N	%	N	%	N	%	
<b>Pregnancy outcome</b>											
Delivered	1899	98.6	97	94.2	362	98.1	634	99.1	806	99.0	<0.001
Aborted	10	0.5	6	5.8	2	0.5	2	0.3	0	0.0	
Stillbirth	17	0.9	0	0.0	5	1.4	4	0.6	8	1.0	
<b>The following data are based on live births</b>											
<b>Overall (N=1899)</b>											
Mean gestational age at delivery (±SD), weeks	38.4 (2.4)		37.2 (4.7)		38.2 (1.9)		38.4 (1.8)		38.6 (2.5)		<0.001
	N=1888		N=95		N=359		N=630		N=804		
Preterm delivery <37 weeks gestation	226	12.0	21	22.1	58	16.2	70	11.1	77	9.6	<0.001
Mean birth weight (±SD) kg	3.07 (0.48)		2.84 (0.58)		2.99 (0.49)		3.09 (0.47)		3.11 (0.45)		<0.001
	N=1856		N=95		N=354		N=615		N=792		
Low birth weight <2.5 kg	140	7.5	17	17.9	36	10.2	40	6.5	47	5.9	<0.001
<b>Mode of delivery</b>											
Spontaneous vaginal delivery	1593	83.9	81	83.5	310	85.6	519	82.1	683	84.5	0.52
Vacuum extraction	18	1.0	1	1.0	1	0.3	6	1.0	10	1.2	
Caesarean section	288	15.2	15	15.5	51	14.1	107	16.9	115	14.2	
<b>Delivery complication</b>											
Post-partum haemorrhage	26	1.37	5	5.15	8	2.21	7	1.1	6	0.7	0.001
Eclampsia	4	0.21	2	2.06	1	0.28	0	0.00	1	0.12	0.01
Puerperal sepsis	3	0.16	0	0.00	1	0.28	1	0.16	1	0.12	0.82
Obstructed labour	6	0.32	0	0.00	2	0.55	2	0.32	2	0.25	0.83
Other	21	1.11	1	1.03	5	1.38	7	1.11	8	0.99	0.91
Congenital abnormalities	9	0.47	0	0.00	1	0.28	6	0.95	2	0.25	0.28
Jaundice	3	0.16	0	0.00	1	0.28	2	0.32	0	0.0	0.34
Hgb, cord blood, mean (±SD), g/L	145 (2.38)		143 (2.15)		145 (2.47)		145 (2.38)		146 (2.35)		0.37
	N=1731		N=90		N=333		N=580		N=728		
Neonatal anaemia (cord Hgb <125 g/L)	266	15.37	19	21.11	55	16.52	96	16.55	96	13.19	0.12

P values based on  $\chi^2$  test (categorical variables) and Kruskal-Wallis test (continuous variables). Hgb, haemoglobin; ; SP, sulphadoxine-pyrimethamine.

**Table 7** Factors associated with low birth weight

Factors	Low birth weight		Univariable analysis			Multivariable analysis			
	Total (N=1856) n	Yes (N=140) n (%)	No (N=1716) n (%)	cOR	95% CI	Overall p value	aOR	95% CI	Overall p value
	Age, years								
<25	628	57 (40.7)	571 (33.3)	1.38	0.97 to 1.96	0.08	0.83	0.52 to 1.30	0.41
≥25	1228	83 (59.3)	1145 (66.7)	1			1		
Education									
No education	399	36 (25.7)	363 (21.2)	1.69	1.01 to 2.84	0.21			
Primary	295	23 (16.4)	272 (15.8)	1.44	0.81 to 2.57				
Junior high	674	54 (38.6)	620 (36.1)	1.49	0.92 to 2.40				
High school or above	488	27 (19.3)	461 (26.9)	1					
Household SES									
Most poor	364	49 (35.0)	315 (18.4)	4.37	2.33 to 8.20	<0.001	4.26	2.23 to 8.04	<0.001
More poor	369	31 (22.1)	338 (19.7)	2.58	1.33 to 5.00		2.51	1.28 to 4.93	
Poor	376	21 (15.0)	355 (20.7)	1.66	0.82 to 3.37		1.61	0.79 to 3.30	
Less poor	369	26 (18.6)	343 (20.0)	2.13	1.08 to 4.21		2.09	1.05 to 4.05	
Least poor	378	13 (9.3)	365 (21.2)	1			1		
Marital status									
Married/married before	1392	94 (67.2)	1298 (75.64)	1		0.08	1		0.27
Living together with man, unmarried	259	24 (17.1)	235 (13.69)	1.41	0.88 to 2.25		1.46	0.90 to 2.38	
Single, unmarried	205	22 (15.7)	183 (10.66)	1.66	1.02 to 2.71		1.28	0.74 to 2.19	
Gravidity									
Primigravidae	423	45 (32.1)	378 (22.0)	1.72	1.15 to 2.57	0.03	1.79	1.07 to 2.99	0.09
Secundigravidae	460	32 (22.9)	428 (25.0)	1.08	0.70 to 1.68		1.20	0.74 to 1.95	
Multigravidae	973	63 (45.0)	910 (53.0)	1			1		
ITN use									
No	654	43 (30.7)	611 (35.6)	0.80	0.55 to 1.16	0.24			
Yes	1202	97 (69.3)	1105 (64.4)	1					
SP doses received									
≤1	95	17 (12.1)	78 (4.6)	3.45	1.89 to 6.31	<0.001	2.96	1.60 to 5.47	0.01
2	354	36 (25.7)	318 (18.5)	1.79	1.14 to 2.82		1.55	0.97 to 2.47	
3	615	40 (28.6)	575 (33.5)	1.10	0.71 to 1.70		1.06	0.68 to 1.65	

Continued

Table 7 Continued

Factors	Low birth weight		Univariable analysis			Multivariable analysis		
	Total (N=1856) n (%)	Yes (N=140) n (%)	No (N=1716) n (%)	cOR	95% CI	Overall p value	aOR	95% CI
≥4	792	47 (33.6)	745 (43.4)	1			1	
Malaria treatment in past 2 weeks								
No	1638	124 (88.6)	1514 (88.2)	1				
Yes	218	16 (11.4)	202 (11.8)	0.97	0.56 to 1.66			0.90
Malaria treatment during pregnancy								
No	1311	100 (71.4)	1211 (70.6)	1				
Yes	545	40 (28.6)	505 (29.4)	0.96	0.66 to 1.40			0.83

aOR, adjusted OR; cOR, crude OR; ITN, insecticide-treated bednet; SES, socioeconomic status; SP, sulphadoxine-pyrimethamine.

clinics, and consequently the number of doses of SP received was based on the number recorded in the ANC booklets of the pregnant women at the time of delivery. However, ANC nurses, who had previously been trained by the Ghana Health Service on administration of SP at the clinics, were given refresher training by the study team to ensure SP administration was directly observed at the clinic and accurately recorded in the women's booklets. A second limitation is that the possible impact of higher numbers of ANC visits on pregnancy outcomes could not be considered during the analysis. Previous studies have, however, shown that women with higher numbers of ANC visits have better pregnancy outcomes.<sup>32 33</sup> Third, there is also the possibility that there were some important confounders associated with the number of doses given that could not be detected and corrected for in the multiple regression analysis. Fourth, another important limitation in this study is the lack of randomisation. With the commencement of the revised WHO policy on IPTp-SP, it would have been unethical to assign participants to number of doses below the recommended number. This poses a risk for selection bias for which controlling was not possible. Another limitation was that multiple comparisons were done, so some statistically significant differences could have been found by chance. However, in general, the results were very consistent. Finally, even though no serious safety concerns were associated with monthly IPTp-SP dosing, this study was not powered to detect differences in safety indicators such as jaundice and congenital malformations, and measurement of serum bilirubin could have provided a more accurate estimates than clinical jaundice. Bilirubin could, however, not be measured due to logistical constraints.

This study did not show significant additional benefits of receiving ≥4 doses compared with 3 doses IPTp-SP during pregnancy. Receiving 3 or more doses, however, showed a reduction in the risk of overall PM infection compared with 2 doses. The WHO policy of monthly administration of IPTp-SP to pregnant women in the second and third trimesters remains a more practical way of ensuring adequate doses are received during delivery, instead of restricting the number of doses to a maximum of three.

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