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# Effectiveness of antenatal intermittent preventive treatment for malaria with sulphadoxine-pyrimethamine on peripartum outcomes

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***Abstract***

**Background:** Following the World Health Organization (WHO) recommendations for 4-weekly antenatal intermittent preventive treatment of malaria in pregnancy using sulphadoxine-pyrimethamine (IPTp-SP), there is a need to evaluate the drug performance in order to determine their effectiveness as tools in malaria control policy.

**Objectives:** To determine prevalence of cord blood malaria, compliance gap and adverse pregnancy outcomes (anaemia, preterm delivery, spontaneous abortion, intra-uterine foetal death and low birth weight) among antenatal IPTp-SP users compared with non-users.

**Methods:** A cross-sectional analytical study was conducted among consenting 390 participants who were administered a questionnaire, and paired blood samples were collected from the venous blood of participants and neonatal cord immediately after delivery. The participants were categorised as IPTp-SP users and non-users. Adverse pregnancy outcomes were assessed. Neonatal birth weights were also measured within 1 h after delivery. Malaria parasitaemia and anaemia were analysed using standard parasitological and haematological methods of examination. Data were analysed using SPSS version 25 for Windows and $p$-value of $< 0.05$ considered significant.

**Results:** Of 390 women, 336 (86.2%) were IPTp-SP users, while 54 (13.8%) were non-users. The compliance gap was 13.8%. Malaria parasitemia in pregnant women (21.7% *versus* 53.7%; $p < 0.001$) and their babies (12.2% *versus* 25.4%; $p = 0.002$) were observed for IPTp-SP users and non-users, respectively. The prevalence of maternal anaemia was 27(8.0%) in IPTp-SP users and 5 (9.3%) in non-users ($p = 0.789$). Mean parasite density was reduced in IPTp-SP users than in non-users ($p < 0.001$). Correlation of birth weight according to their sex showed a weak correlation [correlation coefficient ($r$) = 0.027; $p = 0.736$]. Pregnant women with preterm delivery, spontaneous abortion, intra-uterine foetal death, and low birth weight were significantly lower ($p < 0.001$, for all) in IPTp-SP users compared with non-users.

**Conclusion:** Although the compliance gap was low, IPTp-SP users had significantly better pregnancy and foetal outcomes compared with non-users. Efforts should be intensified towards achieving total compliance in IPTp-SP usage by pregnant women.

***Keywords:*** intermittent preventive treatment, malaria parasitaemia, maternal morbidity, pregnancy

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## Introduction

Malaria is a disease of public health significance with an estimated 219 million cases and 435,000 deaths.[1] Furthermore, due to the temporary suppression of immunity during foetal development, pregnant women are at a higher risk of plasmodial infection than non-pregnant women.[2] Malaria remains a threat to the lives of the majority of pregnant women living in infection-prone areas.[3] In south-west Nigeria, the prevalence of malaria parasitaemia in pregnant women was 22.8%.[4] In Ghana, the overall prevalence of 8.9% in pregnant women was reported,[5] while 9.8%,[6] 10.9%,[7] 18.1%[8] were recently reported in Papua New Guinea, Angola and Burkina Faso, respectively. In Yaoundé Cameroon, malaria parasite was seen in 69.2% of pregnant women with symptoms of suspected malaria in pregnancy.[9] Also, malaria-associated maternal morbidity and poor birth weight outcomes, including preterm delivery and low birth weight, are primarily due to *Plasmodium falciparum* infection and occur mostly in Africa.[10] Malaria in pregnancy is a major public health problem in sub-Saharan Africa.[10]

Intermittent preventive treatment of malaria in pregnancy (IPTp) is a strategy to prevent the consequences of infections among pregnant women living in areas of moderate to high transmission of the malaria parasite.[10] Intermittent preventive treatment of malaria in pregnancy involves the administration of an effective antimalarial drug at predefined intervals during pregnancy, beginning after quickening (a fluttery sensation experienced by the pregnant woman when she first feels the movement of her unborn baby).[11] Sulphadoxine-pyrimethamine (500 mg sulphadoxine and 25 mg pyrimethamine per tablet) is currently the only recommended antimalarial drug for IPT.[11] The benefits of IPTp include a reduced incidence of malaria in pregnancy, reduced malaria-related anaemia in pregnancy and reduced low birth weight. Sulphadoxine-pyrimethamine (SP) is effective in preventing the adverse consequences of malaria on maternal and foetal outcomes even in areas where a high proportion of *Plasmodium falciparum* carries quintuple mutations associated with *in vivo* resistance.[11]

In 2001, the Federal Ministry of Health in Nigeria recommended that pregnant women receive IPT for malaria during pregnancy using two doses of SP. Regarding IPT, pregnant women are expected to receive a minimum of 3 doses of SP at an interval of at least 4 weeks, under directly observed therapy (DOT) in the antenatal clinic.[11] The drug may be given on an empty stomach and with SP as IPT is safe up to 40 weeks of pregnancy and even one dose is beneficial for women presenting late in pregnancy.[12] According to the recommendation, women known to be HIV infected on daily co-trimoxazole chemoprophylaxis should be exempted from IPT.[11] The burden of malaria in pregnancy in Nigeria is still appreciable.[13]

There are cases of maternal morbidity and neonatal morbidity in Nigerian communities despite the introduction of IPT and long lasting insecticidal nets (LLINs) programmes in antenatal clinics.[4,13] Following the WHO recommendations for four-weekly antenatal IPT administration, there is a need to evaluate the drug performance and use of LLINs in order to determine their effectiveness as tools in malaria control policy.[14] In a randomised study in Zambia on antenatal pregnant women who received either daily co-trimoxazole (non-IPTp-SP users) or routine sulphadoxine-pyrimethamine (IPTp-SP users), it was revealed that preterm deliveries (non-IPTp-SP users 3.6%; IPTp-SP 3.0%); still births (non-IPTp-SP 3.0%; IPTp-SP users 2.1%), neonatal deaths (non-IPTp-SP 0%; SP 1.4%), and spontaneous abortions (non-IPTp-SP users 0.6%; IPTp-SP users 0%) were similar between study arms.[15] Also, the low birth weight rates were 9% for non-IPTp-SP users and 13% for IPTp-SP users.[15] However, evaluation of the efficacy of IPT has not been updated in the study environment despite efforts being made on malaria prophylaxis. In addition, no previous study in Nigeria has evaluated the effects of IPT on rates of preterm delivery, spontaneous abortion, intra-uterine foetal death and low birth weight among IPTp-SP users when compared with non-users of SP. Therefore, the purpose of this study was to assess IPT performance and its effect on maternal morbidity and pregnancy outcomes in women attending antenatal clinics in Nigeria.

## Methods

### *Study design*

The study was a cross-sectional analytical study.

### *Study setting/area*

The study was conducted in Nnewi, Anambra State, Nigeria. Nnewi is the second largest city in

Anambra state. Nnewi is a metropolitan city that encompasses two local government areas: Nnewi South and Nnewi North. Nnewi North is commonly referred to as Nnewi central and comprises of four quarters which includes Otolo, Umudim, Uruagu and Nnewichi. The main occupation of Nnewi people is trading and farming. Therefore, they depend mainly on agriculture and commerce for their daily livelihood. The rainy season in the area begins from April to October every year, while the dominant vector species that transmit malaria parasites are *Anopheles gambiae* and *Anopheles funestus* species.[12] Apart from the Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria, there is a concentration of private maternity hospitals and primary healthcare centres (PHCCs) in the area. In a study in Anambra State, Nigeria, the prevalence of malaria parasitaemia in pregnant women attending an antenatal clinic was 73.1%.[16]

### *Study population*

The study recruited pregnant women who were on antenatal visits to maternity hospitals, primary healthcare centres (PHCCs) and Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Nigeria. The study was conducted from 1 February 2019 to 30 November 2020.

### *Study procedure*

Venous blood samples from pregnant women were used to diagnose malaria and examine maternal outcomes, while cord blood samples were used to diagnose malaria in neonates. The data were collected by means of structured questionnaires. The study variables included sociodemographic factors, history of use of SP for malaria treatment or other antimalarial drugs taken during pregnancy, use of insecticidal nets, knowledge of the reason for IPT and obstetrical and gynaecological records. Relevant data on maternal morbidity (adverse pregnancy outcomes) and neonatal birth weights were obtained from maternity hospitals, antenatal clinics and primary health centres, respectively. Microscopy using the Giemsa staining method was used for the assessment of malaria parasites while maternal haemoglobin was determined using Haemiglobinocyanide (HiCN) technique. Sickle cell disease and HIV diagnosis were established from records in the hospitals and health centres. Neonates were weighed within one hour after birth using the Bassinet scale, and the sex of each new born was recorded.

### *Outcome measures*

The primary outcome measure was the prevalence of participants with the presence of malaria parasitaemia and the IPTp-SP compliance gap, while the secondary outcome measures included: proportion of participants with maternal anaemia, preterm delivery, spontaneous abortion, intra-uterine foetal death and low birth weight in IPTp-SP users when compared with non-users of IPTp-SP.

### *Operational definition*

IPTp-SP users and non-users was based on participants who had received SP and had not received SP during pregnancy, respectively, irrespective of other antimalarial drugs used in pregnancy. The compliance gap is the percentage of participants who were adherent to IPTp-SP during pregnancy and those not on IPTp-SP.

### *Sample size estimation*

The sample size was estimated using the formula $N = Z^2 \times P\,(1 - P)\,/d^2$; where $N$ = Minimum sample size; $P$ = Prevalence rate; $d$ = Desired level of significance; $Z$ = Standard deviation for 95% confidence interval (1.96). The prevalence of malaria among pregnant women attending antenatal clinics in hospitals in Anambra State is 73.1 %.[16]

$N = 1.96^2 \times 0.731\ (1–0.731) / 0.05^2$

$N = 3.8416 \times 0.731\ \ (0.269)\ \ /\ \ 0.0025 = 302.16$, which was approximately 302.2

However, to adjust for non-response: $n_s = n\ /\ n–f$ [where $n_s$ = adjusted sample size; $n$ = unadjusted sample size (302.2); $f$ = non-response rate (10%) = 0.1]; $n_s = 302.2\ /\ 1\ –\ 0.1$; $n_s = 302.2/0.9 = 335.78$; $n_s = 336$. Therefore, the minimum sample size was 336.

### *Sampling method*

A convenience sampling was employed in the study.

### *Sampling approach*

Participants were enrolled from each of the four quarters in the Nnewi North Local Government

Area, namely Otolo, Umudim, Uruagu and Nnewichi. The participants were recruited consecutively until the sample size was reached.

### *Inclusion/exclusion criteria*

Pregnant women aged 18–45 years were included in the study. Pregnant women with sickle cell disease and pregnant women with HIV/AIDS were excluded from the study.

### *Data collection procedure*

The participants were consecutively recruited into the study. Three millilitres of maternal venous blood and 3 ml of neonatal cord blood samples were aseptically collected from each participant and placed into ethylene diamine tetraacetic acid (EDTA) containers. The blood samples were properly labelled with coded numbers and transported to the laboratory for immediate analysis. The data were collected by means of structured questionnaires. The study variables included socio-demographic factors, history of use of SP for malaria treatment or other antimalarial drugs taken during pregnancy, use of insecticidal nets, knowledge of the reason for IPT and obstetrical and gynaecological records. Relevant data on maternal morbidity (adverse pregnancy outcomes) and neonatal birth weights were obtained from maternity hospitals, antenatal clinics and primary health centres, respectively. Neonates were weighed within 1 h after birth using Bassinet scale and the sex of each new born was recorded.

### *Quality control*

We made sure that the same senior laboratory scientist analysed all the samples using the same reagents. To avoid errors during the study performance, several precautions were taken: only one person performed the samples per evaluation method; samples were analysed blindly during the study; and all members of the research team were trained in a responsible evaluation method.

### *Data processing and statistical analysis*

Data were analysed using SPSS version 25 (SPSS Inc., Chicago, IL, USA). The strength of association was analysed using Pearson's correlation coefficient. Analysis of Variance (ANOVA) was used for the test of association. The Pearson's chi-square ($\chi^2$) test or Fisher's exact test [for small numbers: cell(s) $\leqslant 5$] were used to analyse categorical data (the proportion of participants with malaria, anaemia, intrauterine foetal death, etc according to SP status (cases and controls group). A $p$-value of $< 0.05$ was considered significant.

## Results

A total of 390 pregnant women were enrolled in the study. Of the 390 women, 336 were IPTp-SP users while 54 were non-users (Figure 1). Fifty-four non-users of SP, although a small sample size, represented the compliance gap observed in the study and this category of non-users were also studied. The socio-demographic status of the participants is shown in Table 1. The majority, 197 (50.5%) of participants were between the ages of 30 and 39 years. The women were composed of primigravidae 73 (18.7%), secundigravidae 104 (26.7%), and multigravidae 213 (54.6%). For the majority, 234 (60.0%) of the participants had their first antenatal visits during their second trimester (Table 1).

The findings revealed that 336 (86.2%) of the pregnant women were using IPTp-SP, however, the compliance gap of 13.8% was recorded. The prevalence of maternal malaria was 73 (21.7%) and 29 (53.7%) among IPTp-SP users and non-users of SP, respectively (Table 2). The difference was statistically significantly ($p < 0.001$). Forty-one of neonates among SP-users were infected with malaria parasite while the number of neonates infected with malaria among non-users of SP was 14 (12.9% *versus* 25.9%; $p < 0.001$).

The distribution and comparative analysis of mean haemoglobin levels of pregnant women according to gestational age distribution of haemoglobin levels by gestational age of the pregnant women is shown in Table 3. Eight percent of IPTp-SP users had anaemia while 9.3% of non-SP users had anaemia. The difference in anaemia prevalence in SP users and non-users of SP in the present study was not statistically significant ($p = 0.789$). The mean haemoglobin levels of the pregnant women with gestational age $\leqslant 35$ weeks, 36–38 weeks and 39–41 weeks were 10.8842, 11.9100 and 11.8746(g/dl), respectively. There were significant differences in the mean haemoglobin levels of the participants according to their

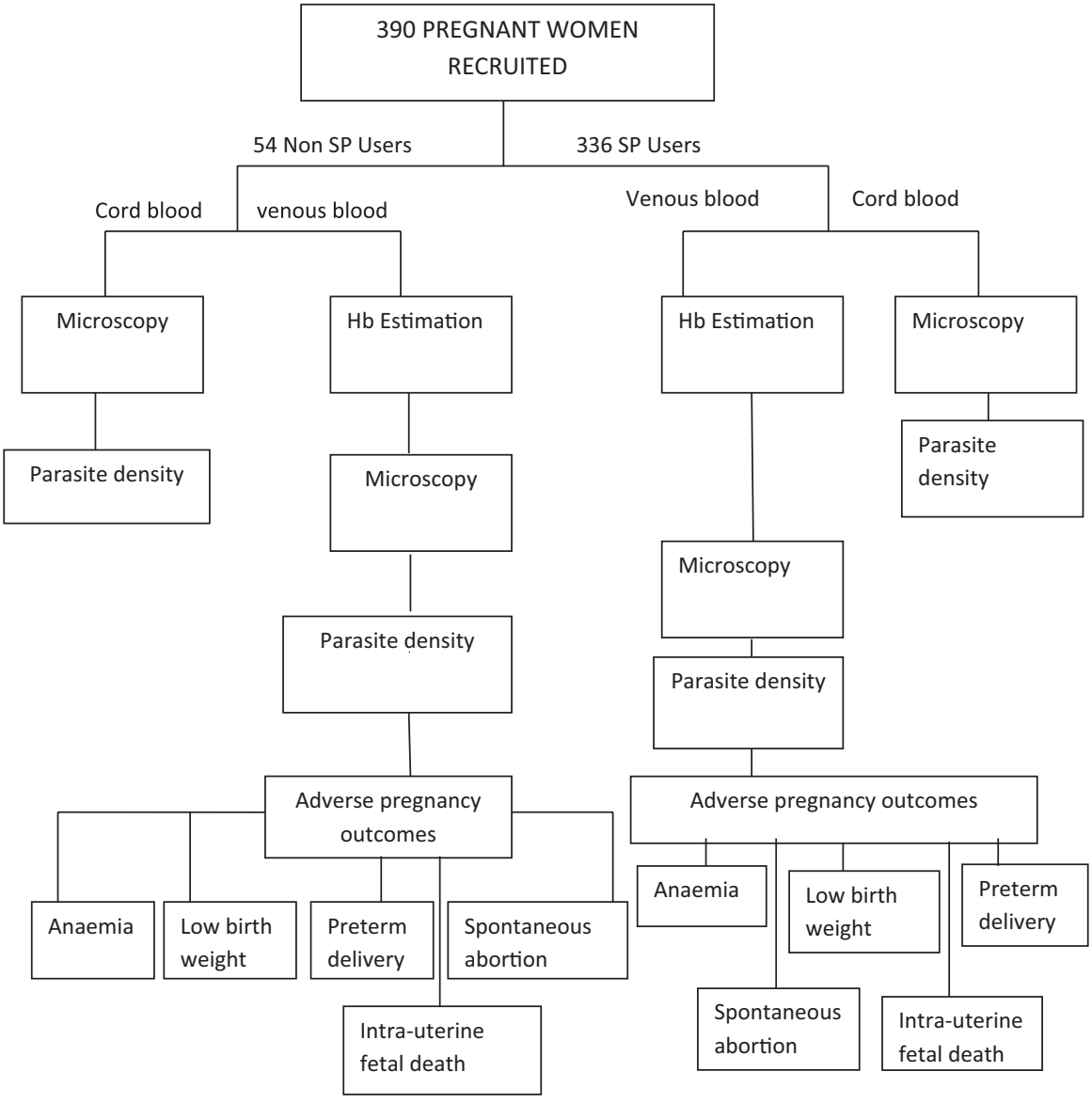


**Figure 1.** Profile of work flow for pregnant women recruited in the study.

gestational age of the participants ($p = 0.004$). Pregnant women of gestational age ⩽ 35 weeks when compared with those of gestational age 36–38 weeks and those of gestational age 39–41 weeks showed a significant difference in their mean haemoglobin levels ($p = 0.004$). Pregnant women of gestational age 36–38 weeks when compared with pregnant women of gestational age 39–41 weeks, showed no significant difference in their mean haemoglobin levels ($p > 0.999$). However, when pregnant women of gestational age 36–38 weeks were compared with pregnant women of gestational age ⩽ 35 weeks, there was a significant difference in their mean haemoglobin levels ($p = 0.004$).

A comparative analysis of mean haemoglobin levels of pregnant women according to doses of IPTp-SP is shown in Table 4. Those that took SP once, twice, thrice and four times and above were represented by IPT 1, IPT 2, IPT 3 and IPT 4, respectively. Those that took IPT1 were 26 (7.7%), those that took IPT 2 were 181 (53.9%), and those that took IPT 3 were 97 (28.9%), while those that took IPT 4 or more were 32 (9.5%). However, SP doses did not have any significant

**Table 1.** Background characteristics of respondents.

| Total no. recruited | *n* (390) (%) |
|---|---|
| Age | |
| ⩽ 19 | 5 (1.3%) |
| 20–29 | 168 (43.1%) |
| 30–39 | 197 (50.5%) |
| ⩾ 40 | 20 (5.1%) |
| Parity | |
| Primigravidae | 73 (18.7%) |
| Secundigravidae | 104 (26.7) |
| Multigravidae | 213 (54.6%) |
| Marital status | |
| Married | 387 (99.2%) |
| Single | 3 (0.8%) |
| Educational level | |
| None | 3 (0.8%) |
| Primary | 140 (35.9%) |
| Secondary | 165 (42.3%) |
| Tertiary | 82 (21.0%) |
| Antenatal care first visit | |
| First trimester | 117 (30.0%) |
| Second trimester | 234 (60.0%) |
| Third trimester | 39 (10.0%) |
| Religion | |
| Christian | 388 (99.5%) |
| Moslem | 2 (0.5%) |

adverse effect on mean haemoglobin levels of the participants ($p = 0.167$). Knowledge of SP and its benefits as a drug for malaria prevention can help in the uptake of the drug. The majority (86.2%) of the pregnant women used SP and also had good knowledge of the drug.

Table 5 shows correlation results of the birth weight of neonates according to their sex. There was no significant relationship between birth weight and male sex ($p > 0.999$) but there was a significant relationship with that of female sex ($p = 0.027$).

Tables 6–10 show the adverse pregnancy outcomes (maternal anaemia, preterm delivery, spontaneous abortion, intra-uterine foetal death and low birth weight) and their relationships with uptake of SP, respectively. The prevalence of maternal anaemia among SP users and non-users was 8.0% and 9.3%, respectively, as shown in Table 6 below.

The percentage of pregnant women who were on IPTp-SP who had preterm delivery was 4.8% while 95.2% had normal delivery.

However, among non-users of SP, 7.9% had preterm delivery. There was a significant difference in preterm delivery between SP users and non-SP users (Pearson's $\chi^2$ test, $p$ value was $< 0.001$).

The effect of uptake of SP on spontaneous abortion or miscarriage showed that none of the users of SP had spontaneous abortion.

However, 3.7% of the pregnant women who did not receive SP had spontaneous abortions. There was a significant difference in spontaneous abortion between SP users and non-SP users (Pearson's $\chi^2$ test, $p < 0.001$).

**Table 2.** Prevalence of maternal and neonatal plasmodial infection in the respondents.

| Respondents | IPTp-SP users (*n* = 336) | | Non-users (*n* = 54) | |
|---|---|---|---|---|
| | Positive | Negative | Positive | Negative |
| Pregnant women | 73 (21.7%) | 263 (78.3%) | 29 (53.7%) | 25 (46.3%) |
| Babies<br>$\chi^2$ (*p* value): 65.086 (⩽ 0.001) | 41 (12.2%) | 295 (87.8%) | 14 (25.9%) | 40 (74.1%) |
| Statistical significant $p < 0.05$. | | | | |

**Table 3.** Comparative analysis of mean haemoglobin levels of pregnant women according to their gestational age.

| GA (weeks) | *n* | Mean | Std. deviation | Std. error | 95% confidence interval for mean | |
|---|---|---|---|---|---|---|
| | | | | | Lower bound | Upper bound |
| ⩽ 35 | 19 | 10.8842 | 1.69419 | .38867 | 10.0676 | 11.7008 |
| 36–38 | 261 | 11.9100 | 1.41282 | .08745 | 11.7378 | 12.0822 |
| 39–41 | 110 | 11.9618 | 1.03932 | .09910 | 11.7654 | 12.1582 |
| Total | 390 | 11.8746 | 1.34926 | .06832 | 11.7403 | 12.0089 |
| | **ANOVA** | | | | | |
| | **Sum of Squares** | | ***df*** | **Mean square** | ***F*** | **Sig.** |
| Between Groups | 19.800 | | 2 | 9.900 | 5.566 | 0.004 |
| Within Groups | 688.379 | | 387 | 1.779 | | |
| Total | 708.179 | | 390 | | | |

ANOVA, analysis of variance.
*p* value = 0.004.

**Table 4.** Comparative analysis of mean haemoglobin levels of pregnant women according to doses of $IPT_P$-SP.

| Dose | *n* | Mean | Std. deviation | Std. error | 95% confidence interval for mean | |
|---|---|---|---|---|---|---|
| | | | | | Lower bound | Upper bound |
| IPT1 | 26 | 12.0077 | 1.03959 | .20388 | 11.5878 | 12.4276 |
| IPT2 | 181 | 11.8326 | 1.49599 | .11120 | 11.6132 | 12.0520 |
| IPT3 | 97 | 12.1979 | 1.18857 | .12068 | 11.9584 | 12.4375 |
| IPT4 | 32 | 11.8063 | 1.04107 | .18404 | 11.4309 | 12.1816 |
| Total | 336 | 11.9491 | 1.34750 | .07351 | 11.8045 | 12.0937 |
| | **Sum of squares** | | **ANOVA** | | | |
| | | | ***df*** | **Mean square** | ***F*** | **Sig.** |
| Between groups | 9.205 | | 3 | 3.068 | 1.700 | 0.167 |
| Within groups | 599.074 | | 332 | 1.804 | | |
| Total | 608.280 | | 335 | | | |

ANOVA, analysis of variance; IPT, intermittent preventive treatment.

The effect of uptake of SP on intra-uterine foetal death or stillbirth showed that the percentage of users of SP that had intra-uterine foetal death was 1.5%, while 9.3% of non-users of SP had intra-uterine foetal death or stillbirth.

There was a significant difference in intra-uterine foetal death or stillbirth between SP users and non-SP users (Pearson's $\chi^2$ test, $p < 0.001$).

The effect of uptake of SP on neonatal low birth weight showed that the birth weights of babies

**Table 5.** Correlation results of birth weight of neonates according to their sex.

| | | Weight of male babies | Weight of female babies |
|---|---|---|---|
| Weight of male babies | Pearson correlation | 1 | 0.027 |
| | Sig. (two-tailed) | | 0.736 |
| | *n* | 165 | 163 |
| Weight of female babies | Pearson correlation | 0.027 | 1 |
| | Sig. (two-tailed) | 0.736 | |
| | *n* | 163 | 221 |

**Table 6.** Maternal anaemia.

| | | | Response to adverse pregnancy outcomes (anaemia Hb < 10.0 g/dl) | | Total |
|---|---|---|---|---|---|
| | | | Yes | No | |
| SP users and non-users | | | | | |
| SP usage | SP | Count | 27 | 309 | 336 |
| | | % within SP usage | 8.0% | 92.0% | 100.0% |
| | Non-SP | Count | 5 | 49 | 54 |
| | | % within SP usage | 9.3% | 90.7% | 100.0% |
| Total | | Count | 32 | 358 | 390 |
| | | % within SP usage | 8.2% | 91.8% | 100.0% |

SP, suphadoxine pyrimethamine.
$\chi^2$ test, *p* value: 0.789, Fisher's exact test *p* value: 0.789.

from pregnant women who received SP were better than the birth weights of babies whose mothers did not receive SP.

Uptake of SP in this study improved birth weights of neonates among users of SP. Non-users of SP had a greater percentage (29.6%) of low birth weight babies. However, among users of SP, 8.3% of babies had low birth weight. The percentage of neonatal normal birth weight in SP users and non-users of SP were 91.7% and 70.4%, respectively. There was a significant difference in neonatal birth weight between SP users and non-SP users (Pearson's $\chi^2$ test, *p* value was $< 0.001$).

## Discussion

Adverse pregnancy outcomes assessed in this study included: anaemia, preterm delivery, spontaneous abortion, intra-uterine foetal death and low birth weight. The effect of SP uptake on preterm delivery in pregnant women showed a better pregnancy outcome when compared with those who did not receive SP during pregnancy.

Malaria cases were high in non-users of SP (53.7%) and their neonates (25.9%) as compared with SP users (21.7%) and their neonates (12.9%). This result supports a study in Rivers State, Nigeria in which 25.3% of SP users had maternal Plasmodial infection while 43.6% of non-users of

**Table 7.** Preterm deliveries.

| | | | Response to adverse pregnancy outcomes (Preterm delivery) | | Total |
|---|---|---|---|---|---|
| | | | Yes | No | |
| SP users and non-users | | | | | |
| SP usage | SP | Count | 16 | 320 | 336 |
| | | % within SP usage | 4.8% | 95.2% | 100.0% |
| | Non-SP | Count | 15 | 39 | 54 |
| | | % within SP usage | 27.8% | 72.2% | 100.0% |
| Total | | Count | 31 | 359 | 390 |
| | | % within SP usage | 7.9% | 92.1% | 100.0% |

SP, suphadoxine pyrimethamine.
$p$ value $< 0.001$.

**Table 8.** Spontaneous abortion (miscarriage).

| | | | Response to adverse pregnancy outcomes (Spontaneous abortion) | | Total |
|---|---|---|---|---|---|
| | | | Yes | No | |
| SP users and non-users | | | | | |
| SP Usage | SP | Count | 0 | 336 | 336 |
| | | % within SP usage | 0.0% | 100.0% | 100.0% |
| | Non-SP | Count | 2 | 52 | 54 |
| | | % within SP usage | 3.7% | 96.3% | 100.0% |
| Total | | Count | 2 | 388 | 390 |
| | | % within SP usage | 0.5% | 99.5% | 100.0% |

SP, suphadoxine pyrimethamine.
$p$ value $< 0.001$.

SP had maternal plasmodial infection.[17] Also, in a study,[17] the overall maternal malaria prevalence was 27.7%, while the overall placental and cord blood malaria infection was 35.3%. However, our findings were lower than 22.8% reported by Adesina-Adewole *et al.*[4] in south-west Nigeria, but higher than 8.9% in Ghana,[5] 9.8% in Papua New Guinea,[6] 10.9% in Angola[7] and 18.1% in Burkina Faso.[8] The low malaria prevalence observed among IPTp-SP participants could be attributed to adherence to SP treatment and use of ITNs as observed in a recent study in Mali.[18] This is because, in the present study, the majority of participants were not only adherent to the use of insecticidal nets but also to the IPTp-SP directives. Therefore, monitoring compliance and acceptability of intermittent preventive treatment of malaria among pregnant women using sulphadoxine-pyrimethamine should be intensified as documented in previous studies.[19–21]

**Table 9.** Intra-uterine foetal death (stillbirth).

| | | | Response to adverse pregnancy outcomes(intrauterine foetal death) | | Total |
|---|---|---|---|---|---|
| | | | Yes | No | |
| SP users and non-users | | | | | |
| SP usage | SP | Count | 5 | 331 | 336 |
| | | % within SP usage | 1.5% | 98.5% | 100.0% |
| | Non-SP | Count | 5 | 49 | 54 |
| | | % within SP usage | 9.3% | 90.7% | 100.0% |
| Total | | Count | 10 | 380 | 390 |
| | | % within SP usage | 2.6% | 97.4% | 100.0% |

SP, suphadoxine pyrimethamine.
*p* value: $< 0.001$.

**Table 10.** Neonatal low birth weight.

| | | | Response to adverse pregnancy outcomes (Low birth weight) | | Total |
|---|---|---|---|---|---|
| | | | Yes | No | |
| SP users and non-users | | | | | |
| SP usage | SP | Count | 19 | 317 | 336 |
| | | % within SP usage | 5.7% | 94.3% | 100.0% |
| | Non-SP | Count | 14 | 40 | 54 |
| | | % within SP usage | 25.9% | 74.1% | 100.0% |
| Total | | Count | 33 | 357 | 390 |
| | | % within SP usage | 8.5% | 91.5% | 100.0% |

SP, suphadoxine pyrimethamine.
*p* value $\leqslant 0.001$.

In this study, pregnant women exhibited varying degrees of differences in their mean haemoglobin levels according to the gestational age of the participants. For instance, pregnant women of gestational age between 36 and 38 weeks, when compared with pregnant women of gestational age between 39 and 41 weeks, showed no significant difference in their mean haemoglobin levels ($p > 0.999$). However, when pregnant women of gestational age 36–38 weeks were compared with pregnant women of gestational age $\leqslant 35$ weeks, there was a significant difference in their mean haemoglobin levels ($p = 0.004$). Although there is an expected fall in haemoglobin concentration, haematocrit and red blood cell count during pregnancy because the expansion of the plasma volume is greater than that of the red blood cell mass. However, a plausible explanation for our peculiar finding was that there was a rise in total circulating haemoglobin directly related to the increase in red blood cell mass. This in turn depends partly on the iron status of the pregnant woman.[22]

This study also revealed the comparative analysis of mean haemoglobin levels of pregnant women according to doses of IPTp-SP. Although the knowledge of SP doses is important, however, SP doses did not have any significant adverse effect on mean haemoglobin levels of the participants ($p = 0.167$). The majority (86.2%) of the pregnant women used SP and also had good knowledge of the drug. Knowledge of SP and its benefits as a drug for malaria prevention during pregnancy can also help in the uptake of the drug. In this study, 86.2% of the study participants had knowledge about SP and utilised it. This corroborates with the report of Chukwurah *et al.*,[23] in which 77.0% of participants had good knowledge of SP. In another study, it was estimated that 38% of pregnant women had anaemia and 0.9% had severe anaemia globally.[24] Pregnant women in central and west Africa appear particularly affected (56.0% had anaemia and 1.8% was severely so).[24] However, global prevalence trends have improved since 1995.[24]

Admittedly, in the present study, the use of SP among the participants did not appear to improve their haemoglobin levels. This is because only 8% of the pregnant women had anaemia among SP users, but among non-users of SP, 9.3% had anaemia. The result of this study was in contradiction with the report of other researchers,[2] in which the number of participants that had anaemia was significantly lower among pregnant women who received IPTp-SP during pregnancy when compared with pregnant women who did not receive it.

In this study, 7.9% of non-users of SP had preterm delivery. There was a significant difference in preterm delivery between SP users and non-SP users (Pearson's $\chi^2$ test, $p < 0.001$). This result corroborates the findings by the World Health Organization (WHO) that uptake of SP during pregnancy improves pregnancy outcomes.[1] This result is also in agreement with the previous studies that discovered that uptake of SP during pregnancy improves pregnancy outcomes.[25,26]

However, 3.7% of the pregnant women who did not receive SP had spontaneous abortions. There was a significant difference in spontaneous abortion between SP users and non-SP users (Pearson's $\chi^2$ test, $p < 0.001$). This result corroborates the findings by the WHO that uptake of SP during pregnancy improves pregnancy outcomes.[10] This result is also in agreement with the previous reports that discovered that uptake of SP during pregnancy improves pregnancy outcomes.[1,17,26–28]

There was also a significant difference in intrauterine foetal death or stillbirth between SP users and non-SP users (Pearson's $\chi^2$ test, $p < 0.001$). The result of the present study is in agreement with the report of the WHO that uptake of SP produces better pregnancy outcomes.[1]

In addition, there was a significant difference in neonatal birth weight between SP users and non-SP users (Pearson's $\chi^2$ test, $p$ value was $< 0.001$). Low birth weight (LBW) and prematurity are associated with neonatal mortality.[1,17] The present result is in agreement with the previous studies that IPTp-SP is known to be effective in reducing maternal malaria episodes, low birth weight and preterm delivery.[1,17,26,27] Previous studies[17,28] have shown that low birth weight in SP-users was 3 (1.2%), while in non-SP users low birth weight was 6 (16.2%).

In a previous study,[29] 27% of pregnant women in a case management approach had placental malaria compared with 12% ($p < 0.001$) of women who received two doses of SP and 9 % ($p < 0.001$) of women who received monthly SP. In other previous study,[28] IPTp-SP was found to significantly reduce placental malaria ($p < 0.001$) and anaemia ($p < 0.001$) and low birth weight ($p < 0.008$).

It was observed in this study that some of the pregnant women were not using SP for IPT. The reasons adduced for non-usage included: non-availability of SP drugs sometimes, presence of many private sectors that may use other drugs available to them to treat their patients and drug reactions. However, the use of SP remains effective in reducing malaria related anaemia in pregnancy and reducing the rate of low birth weight. Sulphadoxine-pyrimethamine remains effective in preventing adverse consequences of malaria on maternal and foetal outcomes even in areas where a high proportion of *P. falciparum* parasites carry quintuple mutations associated with *in vivo* resistance.[10,11]

In this study, participants on other anti-malarial drugs such as Amodiaquine, Artemisinin-based combination therapy (ACT), Artesunate monotherapy (AM) and Proguanil or Paludrine were classified as non-SP users. However, their

relationship with adverse pregnancy outcomes is of note. In a recent network meta-analysis by Sridharan *et al.*[30] on the safety of anti-malarial drugs used to treat malaria in pregnant women, it was concluded that the WHO recommended anti-malarials in pregnancy have similar risk profiles with regard to abortion, stillbirth and neonatal deaths. Nevertheless, in a recent study, the use of less than 2 doses of IPTp-SP increased the risk of maternal anaemia.[31] However, sub-optimal doses ($\leqslant$ 2 doses) were not associated with increased risk of malaria parasitaemia, foetal anaemia and preterm delivery among pregnant women in low malaria transmission setting.[31]

The significantly percentage of compliance recorded in this study may be due to the increased awareness, distribution of SP, mass campaign and health education by the government in the study area.[32] The 13.8% compliance gap recorded in this study was in concordance with a previous report[17] and could be as a result of awareness, proximity to health facilities and availability of drugs as accessibility and coverage of malaria interventions are affected by poverty, limited health infrastructure, ineffective drug policy regulations and other healthcare marker imperfections.[19] Pregnant women who took SP had lower malaria parasitaemia than those who did not take SP. This finding also agrees with the result of a study carried out by other researchers[20] which showed that pregnant women that took SP once had higher malaria parasitaemia than those that took SP twice and thrice, respectively. However, low compliance to SP directives increases the risk of maternal, placental and neonatal malaria in endemic regions,[20] although maternal anaemia is multifactorial.[21]

Maternal venous blood malaria parasitaemia in pregnant women and cord blood malaria parasitaemia of babies in IPTp-SP users and non-users of SP were assessed in the present study. Results from IPTp-SP users were compared with non-users of SP, which served as the control group. Evaluation of IPT performance and its efficacy was updated in the study environment. In addition, no previous study in the study environment has evaluated the effects of IPT on rates of preterm delivery, spontaneous abortion, intra-uterine foetal death and low birth weight in the study environment.

Despite these strengths, the main limitations of our cross-sectional study stem from the potential presence of cofounders. Although this study showed a number of clear associations between IPT and beneficial pregnancy outcomes, these factors could be confounded by various factors.[32] For instance, participants who comply with a given public health intervention are usually more likely to comply with others, such as use of ITNs or effective anti-malaria treatment. Participants who eventually comply are often better educated, more wealthy, have better housing and live closer to health facilities. Therefore, the inferences on causality can only be tentative in the present study. The findings of the prevalence of maternal anaemia show only a very small, not significant difference between SP users and non-SP users. The explanation for these non-significant differences may be that others using other anti-malarial drugs were described as non-SP users. A recent meta-analysis concluded that the WHO recommended anti-malarials in pregnancy have similar risk profiles.[30] There was also a huge disparity in numbers between SP users and non-users, which potentially have imposed appreciable bias.

## Conclusion

The result showed that malaria is still a public health problem in the study area and IPTp-SP provided some measure of protection against malaria parasites with a significantly reduced prevalence found in IPTp-SP users. The IPTp-SP users had significantly better pregnancy and foetal outcomes compared with non-users of SP. The percentage of non-users of SP and their consequent higher level of parasitaemia showed the gap in compliance and there is an urgent need to address this problem in the light of the high infection levels observed in the neonates' cord blood of this group. Efforts should be intensified towards total compliance with SP usage by pregnant women.

## Declarations

### *Ethics approval and consent to participate*

Ethical approval was obtained from the NAUTH Ethical Committee (NAUTH/CS/66/VOL.11/158/2018/092, 22/01/2019) and authorization from primary health care centres and maternity hospital administrations. Written informed consent was obtained from participants before administering the questionnaires and anonymity of participants involved in the study, as well as confidentiality of information collected was respected.

### *Consent for publication*

Written informed consent was obtained from each woman recruited for inclusion into the study and publication of the work.

### *Author contributions*

**Isaac Okezie Godwin:** Conceptualization; Data curation; Investigation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing.

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**George Uchenna Eleje:** Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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### *Competing interests*

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### *Availability of data and materials*

All relevant data are within the manuscript and its Supporting Information files.

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## Supplemental material

Supplemental material for this article is available online.

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