



RESEARCH ARTICLE

Impact of Adherence to a Full Course of Intermittent Preventive Treatment of Malaria in Pregnancy on Pregnancy Outcome in Muyuka Health District: A Cross-Sectional Study

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Abstract

Background: Intermittent preventive treatment of malaria in pregnancy with sulphadoxine-pyrimethamine (IPTp-SP) is a key strategy for the control of malaria in pregnancy in Sub-Saharan Africa.

Objectives: In Cameroon, the revised IPTp-SP policy requiring that pregnant women take at least three doses of SP was adopted in 2013 but the adherence and its association with pregnancy outcomes remains largely unknown in most rural parts of Cameroon.

Methods: To address these issues, the present study was designed as a cross-sectional community-based survey in which a structured questionnaire and chart review (medical record reviews) were used to collect relevant information from 430 mothers of children below one year of age residing in 14 clusters selected randomly from the Muyuka Health District. Data were entered and analysed using Epi Info 7.

Results: The adherence to a full course of IPTp-SP was 32.09%. Women who adhered to a full course of IPTp-SP had higher mean birth weight infants and mean gestation age at delivery compared to their counterparts who took a partial course (mean birth weight difference = 263 g, $p < 0.001$; mean gestation age at delivery difference = 0.69 weeks, $p = 0.003$). Adherence to a full course of IPTp-SP significantly reduced the odds of malaria in pregnancy (AOR = 0.30, $p < 0.001$) but not that of low birth weight and pre-term birth. The effectiveness of a full course of IPTp-SP in preventing clinical malaria in pregnancy was 70%.

Conclusion: Generally, the adherence to full course of IPTp-SP was low. Adherence to full course of IPTp improved birth outcomes. Data generated from the study should be used by health planners to improve on the quality of maternal and infant health care services.

Keywords

Adherence, Full course IPTp-SP, Pregnancy outcomes

Abbreviations

ANC: Antenatal Care; AOR: Adjusted Odds Ratio; DHS-MICS: Demographic and Health Survey and Multiple Indicator Cluster Survey; IPTp-SP: Intermittent Preventive Treatment in Pregnancy using Sulphadoxine-Pyrimethamine; FHSIRB: Faculty of Health Sciences Institutional Review Board; ITN: Insecticide-Treated Nets; LBW: Low Birth Weight; MIP: Malaria in Pregnancy; NMCP: National Malaria Control Programme; PPS: Probability Proportionate to Size; PTD: Pre-term delivery; SP: Sulphadoxine-Pyrimethamine; WHO: World Health Organization

Background

Malaria is an acute febrile disease caused by infection of the red blood cells with intracellular protozoan parasites of the genus *Plasmodium*. The parasites are inoculated into the human host by feeding female Anopheles mosquitoes [1]. Malaria infection during pregnancy presents significant risks for the pregnant woman, the developing foetus and the newborn infant. The negative consequences associated with malaria in pregnancy include severe malaria, severe anaemia, pre-term delivery, maternal death, and placental malaria [2]. Placental malaria is linked to intrauterine growth restriction, stillbirth, and delivery of low birth weight (LBW) infants. Pre-term delivery and LBW are the risk factors for neo-



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natal and infant deaths [3,4]. In 2013, an estimated 30 million pregnant women were at risk of getting malaria worldwide. There were an estimated 584,000 malaria deaths worldwide. Ninety percent of global malaria deaths occurred in sub-Saharan Africa [2]. In Cameroon, the morbidity due to severe malaria in pregnant women was 52% while mortality stood at 14% [5].

In high-malaria transmission zones like sub-Saharan Africa, women are semi-immune, and most malaria infections in pregnancy are asymptomatic. Thus, a preventive approach is appropriate to handle malaria in pregnancy in the said areas. The World Health Organisation (WHO) recommends a three-pronged intervention for the prevention and control of Malaria in Pregnancy (MIP) in areas of stable transmission of malaria namely Intermittent Preventive Treatment in pregnancy using sulphadoxine-pyrimethamine (IPTp-SP), use of insecticide treated nets (ITN) and ensuring effective case management of malaria illnesses and anaemia [6]. In Cameroon, the National Malaria Control Program also insists on this three-pronged intervention for the prevention and control of MIP. In 2012, a Cameroon survey suggested that 59.7% of households possessed at least one net while only 42.6% of households slept under these nets [7]. Indoor Residual Spray is not a policy option in Cameroon.

In 2013, the WHO revised its IPTp guideline which continues to recommend the use of Sulphadoxine-Pyrimethamine (SP), but at more frequent dosing due to a reduction in SP half-life associated with parasite resistance [8]. Following the implementation of this revised IPTp-SP protocol, only 17% of the pregnant women received a full course (three or more doses of SP) of IPTp worldwide. In 2014, a Cameroon household survey indicated that 26% of pregnant women received a full course of IPTp-SP [9]. All these studies revealed low uptake of IPTp-SP by pregnant women. This increase in the frequency of SP dosing is challenging in sub-Saharan Africa characterised by low IPTp-SP uptake.

Many studies in the area of IPTp-SP uptake have focused on the barriers and pregnancy outcomes associated with the uptake of optimal (two) doses of SP [10]. Following the revision of the IPTp-SP protocol in 2013, little is known on the level of uptake, predictors and pregnancy outcomes associated with the revised recommendation (\geq three doses of SP) in most of the malaria endemic areas of Sub-Saharan Africa. Thus, the aim of this study was to assess the adherence and pregnancy outcomes associated with the uptake of a full course of IPTp-SP.

Materials and Methods

Study design

The study was a cross-sectional community-based survey that took place in the months of April to June 2015.

Study area and setting

The study took place in the Muyuka Health District located on the leeward side of Mount Cameroon. Muyuka Health District is one of the eighteen health districts of the South West Region of Cameroon. It is situated in Fako Division. The Muyuka Health District as of 2014 had an estimated population of 100,759 inhabitants (3829 women with children less than one year i.e. 3.8% of the total population) distributed into 5 health areas; Bafia, Meanja, Ekona, Malende and Muyuka. Each health area is divided into administrative units called "quarters". Twenty health units; public, confessional, and private are found in the Muyuka Health District. Of this number, fifteen have been identified for effectively carrying out ANC services and deliveries. This health district is in a malaria-endemic zone where the transmission of malaria is stable. The morbidity of malaria is 28% for the general population, with 45% in children less than five years and 17% in pregnant women [5]. Severe malaria represents 56% and 52% of hospitalizations respectively for children below five years and pregnant women respectively. The mortality due to malaria in the entire population is 8%, with 21% and 14% in children below five years and pregnant women respectively [5].

Study sites

We collected data from the Muyuka Health District. The number of participants involved in the study per health area was determined by sampling proportionate to the size of the population.

Target population

The target population was made up of mothers of children less than one-year-old.

Inclusion criteria

Any mother of a child less than one-year-old residing in any of the selected health areas in Muyuka Health District for more than nine months or who attended ANC in any of the health facilities.

Exclusion criteria

Any mother of any woman who gave birth to twins, triplets or quadruplets was excluded birth weight analysis.

Sample size

The following formula was used to compute the sample size [11]:

$$n = \frac{Z^2 * P * (1-P)}{d^2}$$

n = Number of participants needed for the study

Z = 1.96 for 95% confidence interval

P = Proportion of IPT1 in community survey in Cameroon (47%) [5]

d = Precision (5%)

$$n = \frac{1.96^2 * 0.47 * (1 - 0.47)}{0.05} = 382 \text{ (minimum number of}$$

participants in the study).

The sample size was then increased to 430 participants (approximately 10%) to account for anticipated non-respondents and poorly filled questionnaires.

Sampling Method

Multistage cluster sampling method was used to select participants from the study area. Three of the five health areas that make up the MHD namely Bafia, Malende and Muyuka were randomly selected. Based on the sample size, 14 clusters ('quarters') were randomly selected from the 47 clusters in our study area. Approximately 30 nursing mothers were selected per clusters (*quarter*: Has a population of approximately 1000 people and 35 nursing mothers with babies less than one-year-old). Probability proportionate to size (PPS) sampling procedure was applied to determine proportionate sample size and number of clusters for each health area [12].

$$n_o = f * N_o$$

Where n_o = health area sample size; f = The sampling fraction (n_i/N_i); N_o = The health area population; desired sample size (n_i) and the target population (N_i). The sampling fraction f is 0.1609. The number of clusters and sample size of each health area was established (Table 1). In the cluster, all participants were sampled until the sample size was reached.

Data Collection Tools

An interviewer-administered structured questionnaire and a chart review (medical record review) form were used to collect relevant information from the participants.

The structured questionnaire was used to collect socio-demographic data and factors related to the knowledge of participants on IPTp-SP.

The chart review (medical record review) was used to collect information on the practice of IPTp-SP by participants. This information was reviewed from the ANC card of the participant.

Study Procedures

Ethical approval and administrative authorisations

After developing the research protocol, the investigator obtained ethical approval from the Faculty of

Health Sciences Institutional Review Board (FHSIRB), University of Buea. Administrative authorisations were then obtained from the Dean of the Faculty of Science, the Regional Delegate of Public Health for South West and the District Medical Officer (DMO) of Muyuka Health District.

Pre-testing of data collection tools

The investigator pre-tested the questionnaire and the chart review form on 20 participants in a community not involved in the study. This exercise helped to readjust some of the questions in order to increase validity of the data collection tools.

Field data collection

Participants for the study were selected from the 14 clusters in the study area. In all the clusters, the researcher went from house to house to enrol consenting participants who were present at the time of the visit until the sample size was reached. In the communities, the investigator together with community representatives identified the households with children age less than one year. The consent of participants was sought and those who gave their written consent were interviewed in a convenient location in the participant home. This process continued until the sample size was reached. A structured questionnaire (interviewer-administered), was used to collect socio-demographic data and knowledge of the participants on IPTp-SP. Chart review forms were used to collect information (secondary data) from the antenatal care (ANC) cards and delivery note of the participants. Self-reported uptake of SP was verified using the ANC card and was recorded.

Data management

Data collected were entered into an electronic questionnaire (template) created in Epi Info version 7 by the investigator. During the data entry process, 10% of data entered at the beginning was checked to ensure correct entry. The data were then cleaned or edited. The computer in which the data were stored was password protected and the information was accessible only to the researcher. The hard copies of the questionnaire were locked in a cupboard with the key accessible only to the researcher.

Operational Definition of Terms

Intermittent Preventive Treatment of malaria in pregnancy (IPTp)

Intermittent Preventive Treatment is the use of an-

Table 1: Proportionate samples for each health area.

Health area	Population of mothers with a child less than one-year-old (a)	Sample of mothers with a child less than one-year-old (a*f)	Number of clusters selected (a*f)/30
Bafia	712	114	4
Malende	801	129	4
Muyuka	1158	187	6
Total	2671	430	14

ti-malarial drugs given in treatment doses at predefined intervals after 16 weeks or after “quickenings” to clear a presumed burden of placental malaria parasites. This is based on the assumption that malaria in pregnancy is asymptomatic in areas of stable malaria transmission.

A full course of IPTp

The administration of at least three doses of IPT during the pregnancy.

A partial course of IPTp

The administration of less than three doses of IPT during the pregnancy.

Outcomes of pregnancy

This was measured in terms of selected outcomes; birth weight, malaria in pregnancy and gestational age at delivery.

Low birth weight

Any birth weight lower than 2500 grams.

Pre-term delivery

Birth at gestation age earlier than 37 weeks.

Clinical malaria in pregnancy

Self-report of having been treated against clinical malaria during pregnancy. This was confirmed by verification from antenatal care (ANC) cards.

Data Analysis

Data collected were analysed using Epi info version 7. Participants’ background characteristics data were analysed using means, standard deviation, frequency and proportion.

To determine the adherence to a full course of IPTp-SP

A univariate analysis was done using frequency and proportions.

To determine the impact of adherence to full course of IPTp-SP on pregnancy outcome

One-way analysis of variance (ANOVA) and multivariate binary logistic were used. Significant difference was established at p-value less than 0.05.

Ethical Considerations

All participants included in the study had to give their written consent after receiving the information contained in the consent form. They signed the consent form in two copies and retained one. Those who were not able to read or write had to put their thumbprint on the form as signature after being sufficiently informed on the study. In this case, in addition, a legally acceptable representative of the participant who could read and write participated in the information session and

Table 2: Summary of socio-demographic characteristics of the participants.

Characteristic	Frequency	Percentage (%)
Maternal age (years)	25.9 ± 5.2 (Mean ± SD)	14-40 (Range)
14-20	71	16.5
21-30	273	63.5
31-40	86	20
Marital status		
Single/widow/divorced	94	21.9
Married	336	78.1
Health Area		
Muyuka	187	43.5
Bafia	114	26.5
Malende	129	30
Level of Education		
No formal Education/Primary	187	43.5
Secondary/University	243	56.5
Occupation		
Farmer/Student/No job	283	65.8
Employed/Trader	147	34.2
Religion		
Christians	425	98.8
Muslims	5	1.2
Gravidity*		
Paucigravidae (G1/G2)	268	62.3
Multigravidae (G3+)	162	37.7

*G1 = primigravidae; G2 = secundigravidae; G3+ = gravida 3 and above SD = Standard deviation.

also signed the consent form. They were given enough time to think, ask questions before taking their decision. For the cases of participants below 21-years-old, in addition to the consent that was obtained from the legal representative (parent or guardian), an assent was also obtained from the participant. Participation in the study was voluntary and there was no compensation. The participants were assured that they would be briefed on the research results. The risks related to the study were minimal. The time for the interview was between 10 to 15 minutes. The participants did not receive any penalty if they decided not to participate or to withdraw from the study at any time they wished to. The data from those who withdrew was not included in the analysis. Participants were assured of confidentiality and anonymity; their names did not figure on any of the data collection tools but contact numbers were collected for follow up if the need be.

Results

Socio-demographic characteristics of participants

The socio-demographic characteristics of the 430 participants included in this analysis are presented in [Table 2](#). The mean age of the participants was 25.9 years and the range were 14-40 years. Majority (63.5%) of the participants were aged between 21-30 years-old. The sample population was just over three quarters (78%) married/cohabiting women. The makeup of participants was 43.5% from Muyuka health area, 30% from

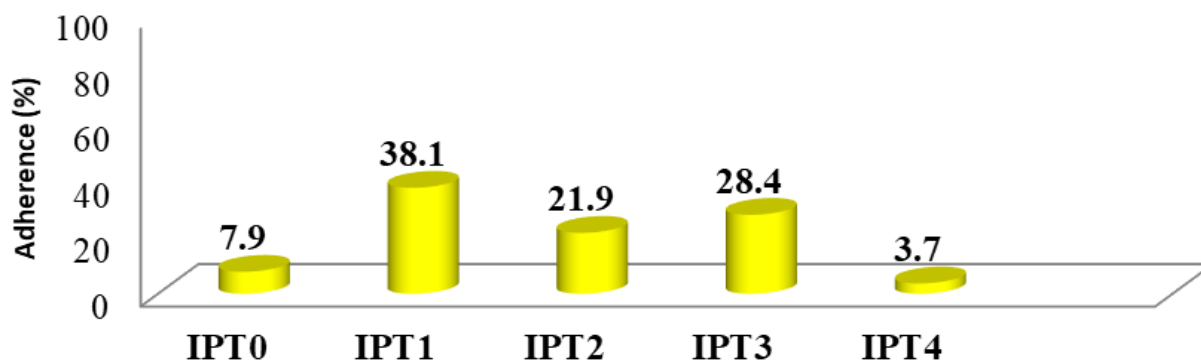


Figure 1: Adherence to IPT₀, IPT₁, IPT₂, IPT₃ and IPT₄.

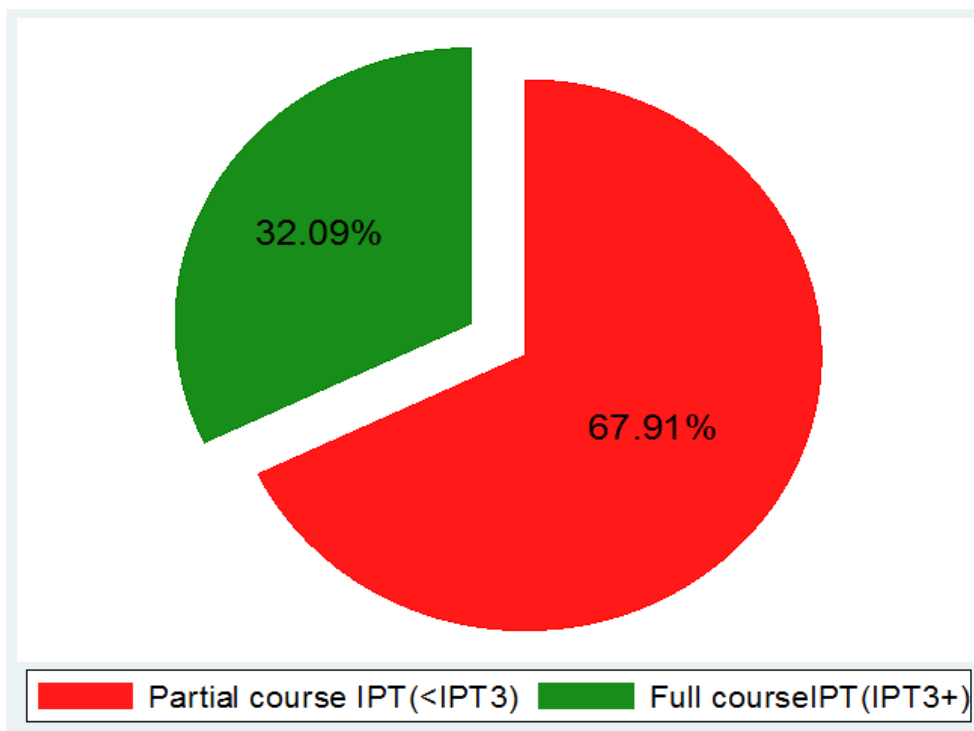


Figure 2: The prevalence of the uptake \geq three doses SP among participants.

Table 3: Outcome of pregnancy among women who adhered and those who did not adhere to a full course of IPTp-SP.

	Adhered to IPT ³⁺	Did not adhere to IPT ³⁺	p-value
Birth weight (kg) (Mean \pm SD)	3.40 \pm 0.55	3.14 \pm 0.58	< 0.001
Gestation age at delivery (weeks) (Mean \pm SD)	38.02 \pm 2.2	37.33 \pm 2.3	0.003

Malende Health area and 26.5% from Bafia health area. Just over half (56.5%) of the participants had attended secondary school and beyond. The proportion of Pauci Gravidae women stood at 62.3%. Very few (1.2%) of the participants were Muslims by faith.

Adherence to a full course of IPTp-SP

Of the 430 participants, 34 (7.9%), 164 (38.1%), 94 (21.9%), 122 (28.4%) and 16 (3.7%) reported taking none, one, two, three and four doses of SP during pregnancy respectively (Figure 1).

The proportion of participants who adhered to a full course (\geq three doses) of IPTp-SP was 32.09% (95% CI:

27.7-36.8) as depicted in Figure 2.

Impact of adherence to full course of IPTp-SP on birth weight and gestation age at delivery

Birth weight was significantly ($p < 0.001$) higher in pregnant women who took a full course (3.40 \pm 0.55) compared to those who took a partial course (3.14 \pm 0.58). The difference in mean birth weight was 263 g. Gestation age at delivery was significantly ($p = 0.003$) higher in pregnant women who took a full course (38.02 \pm 2.2) compared to those who took a partial course (37.33 \pm 2.3) of IPTp (Table 3). The difference in mean gestation age at delivery was 0.69 weeks.

Table 4: Secondary analysis of factors associated with Low birth weight (LBW) among participants.

Variable	LBW (< 2500 g)			
	COR (95% CI)	P-value	AOR (95% CI)	P-value
Maternal age				
14-20 years	1		1	
21-30 years	0.48 (0.22-1.04)	0.057	0.41 (0.16-1.05)	0.064
31-40 years	0.60 (0.30-1.45)	0.07	0.59 (0.25-1.50)	0.075
Gravidity				
Paucigravidae	1		1	
Multigravidae	1.2 (0.6-2.4)	0.606	1.72 (0.74-3.97)	0.206
ANC visits				
< 4 visits	1		1	
≥ 4 visits	0.15 (0.06-0.37)	< 0.001	0.22 (0.07-0.71)	0.012
SP doses taken				
< 3 doses	1		1	
≥ 3 doses	0.24 (0.08-0.7)	0.005	0.82 (0.2-3.3)	0.775
Gestational age				
Term delivery	1		11	
Pre-term delivery	5.98 (2.95-12.15)	< 0.001	5.0 (2.38-10.58)	< 0.001

ANC = Antenatal care; SP = Sulphadoxine-pyrimethamine; LBW = Low birth weight; COR = Crude odds ratio; AOR = Adjusted odds ratio; 95% CI = 95% confidence interval; Significant p-values are presented in bold.

Table 5: Secondary analysis of factors associated with pre-term delivery among participants.

Variable	Pre-term delivery			
	COR (95% CI)	P-value	AOR (95% CI)	P-value
Maternal age				
14-20 years	1		1	
21-30 years	0.84 (0.45-1.58)	0.589	1.06 (0.54-2.08)	0.866
31-40 years	0.90 (0.52-1.70)	0.324	1.20 (0.65-2.20)	0.412
Gravidity				
Paucigravidae	1		1	
Multigravidae	0.74 (0.44-1.24)	0.25	0.67 (0.39-1.16)	0.151
ANC visits				
< 4 visits	1		1	
≥ 4 visits	0.40 (0.24-0.67)	< 0.001	0.29 (0.14-1.16)	< 0.001
SP doses taken				
< 3 doses	1		1	
≤ 3 doses	0.69 (0.40-1.20)	0.187	1.63 (0.75-3.50)	0.215

ANC = Antenatal care; SP = Sulphadoxine-pyrimethamine; PTD = Pre-term delivery; 95% CI = 95% confidence interval; Significant p-values are presented in bold.

Impact of adherence to full course of IPTp-SP on Low Birth Weight

The adherence to a full course IPTp-SP was not significantly associated with a reduction in the odds of low birth weight. The number of ANC visits and gestation age at delivery were significantly associated with a reduction in the odds of low birth weight. Attending more than 4 ANC visits conferred a 0.22 (95% CI: 0.07-0.71) reduction in the odd of having an LBW compared to those who attended less than 4 ANC visits. Also, the odds of having an LBW in those who had a pre-term delivery was 5.0 times (95% CI: 2.38-10.58) that of those who had a term delivery (Table 4).

Impact of adherence to full course of IPTp-SP on pre-term delivery

The adherence to a full course IPTp-SP was not significantly associated with a reduction in the odds of pre-term birth. The odds of having a pre-term birth in those

who attended more than 4 ANC visits was 0.29 times (95% CI: 0.14-1.16) that of those who attended less than 4 ANC visits (Table 5).

Impact of adherence to full course of IPTp-SP on malaria in pregnancy

The uptake of ≥ three doses of SP (adherence) was associated with reduced odds of coming down with malaria in pregnancy (AOR = 0.30, p < 0.001) compared to the uptake of < three doses. Age and number of doses of SP significantly predicted the occurrence of malaria in pregnancy (Table 6). The effectiveness of IPTp-SP in preventing clinical malaria in pregnancy was 70% [Effectiveness = (1 - odds ratio) × 100].

Discussion

Adherence to a full course of IPTp-SP

The proportion of participants who adhered to a full

Table 6: Secondary analysis of factors associated with clinical malaria in pregnancy.

Variable	Treated for MIP		AOR (95% CI)	P-value
	COR (95% CI)	P-value		
Maternal age				
14-20 years	1		1	
21-30 years	0.51 (0.30-0.85)	0.009	0.57 (0.33-0.99)	0.047
31-40 years	0.40 (0.20-0.64)	0.005	0.45 (0.25-0.70)	0.03
Gravidity				
Paucigravidae (G1/G2)	1		1	
Multigravidae (\geq G3)	0.80 (0.53-1.22)	0.3	0.82 (0.56-1.30)	0.35
ANC visits				
< 4 visits	1		1	
\geq 4 visits	0.64 (0.43-0.96)	0.031	1.23 (0.76-2.03)	0.398
SP doses taken				
< 3 doses	1		1	
\geq 3 doses	0.33 (0.19-0.53)	< 0.001	0.30 (0.17-0.54)	< 0.001

ANC = Antenatal care; SP = Sulphadoxine-pyrimethamine; MIP = Malaria in pregnancy; 95% CI = 95% confidence interval; Significant p-values are presented in bold.

course of IPTp-SP was 32.1%. This value is higher compared to household surveys carried out in other parts of Africa and Cameroon which revealed that the uptakes of full course of IPTp were 17% and 26% respectively [2,9]. This may reflect geographical variations in the coverage of IPTp-SP. The high prevalence of IPTp3+ observed in this study could be explained by the fact that most participants resided in areas accessible to health facilities providing ANC. Distance from health facility negatively correlates with the uptake of a full course of IPTp [13]. The last two years have seen the scaling up interventions towards the fight against maternal and child mortalities in Cameroon through the increase use of IPTp-SP interventions at the district levels.

However, the prevalence observed in our study is low compared to the 80% set as objective by the Cameroon Ministry of Public Health in its 2014-2018 strategic plans for the fight against Malaria [5]. This low uptake of a full of IPTp could be attributed to the low rate of ANC visits by participants. One hundred and ninety-eight participants (46%) attended less than 4 ANC visits during pregnancy thus reducing the chances of taking a full course of IPTp. Our results were similar to those obtained in a study carried out in Ghana in a group of pregnant women where the prevalence of the adherence to a full course of IPTp-SP was 33% [14].

Impact of adherence to full course of IPTp-SP on outcomes of pregnancy

Women who received a full course of IPTp-SP had better outcomes of their pregnancy. Low birth weight and prematurity are the greatest risk factors for neonatal mortality and a major contribution to infant mortality. In this study, babies born to mothers who received a full course of SP on the average weighed more than babies born to women who received a partial course of IPTp. They also had longer gestation age at delivery which reduced the risk of pre-term birth. This is similar to reports from a previous study in Ado-Ekiti, Nigeria

where birth weight was significantly higher in PW who took SP compared to those who did not [15]. The high birth weight of babies in this study may not only be attributed to the low prevalence of malaria in pregnancy in them since other factors such as socio-economic level may also play a role.

The uptake of \geq 3 SP doses (adherence) was significantly associated with a 70% reduction in the prevalence of malaria in pregnancy. This demonstrates the efficacy of a full course of SP in improving the outcomes of pregnancy. This is comparable to reports from previous studies which indicated a reduction in the prevalence of malaria among women of all parities [10,15,16]. This supports the WHO recommendation to continue the use of SP as IPTp even in areas with high levels of SP resistance [2].

The adherence to three or more doses of SP was not associated with a significant reduction in the prevalence of LBW. The small sample size of the current study may not have provided the power needed to detect the effect on LBW. Infants born to women who attended ANC clinics four or more times were on average 156.7 g heavier than infants of women who had attended ANC clinics less than three times. This is similar to reports from a previous study carried out in Geita, Northwest of Tanzania which indicated a significant reduction in the prevalence of LBW in women who attended four or more ANC visits [9]. More ANC visits are associated with the receipt of more SP when readily available, women supplemented with haematinics, counseling on nutrition during pregnancy, all of which are associated with improved birth weight.

The adherence to full course of IPTp-SP was not significantly associated with reduced risk of pre-term delivery. However, women who attended more than 4 ANC visits (probably receiving the last dose of IPTp-SP within four weeks of delivery) had a 70% odds reduction of delivering pre-term infants.

Conclusions

The adherence to of a full course of IPTp-SP was low compared to the national target of 80%. The adherence to IPTp-SP showed significant geographical variations between health areas with Bafia health area having a significant lower adherence level.

The outcomes of pregnancy (birth weight, gestation age at pregnancy and malaria in pregnancy) were significantly better in women who took a full course of IPTp. Adherence to full course of IPTp-SP was significantly associated with reduced odds of coming down with malaria in pregnancy but not LBW and pre-term delivery.

Recommendations

Accelerate and scale up the implementation of the revised WHO policy on intermittent preventive treatment with sulphadoxine-pyrimethamine so as to improve on the adherence to a full course of IPTp-SP.

The continuous use of SP in preventing malaria in pregnancy bearing in mind that adherence improves pregnancy outcomes.

Competing Interests

The authors declare that they have no competing interests.

Authors Contributions

ATY conceptualized the problem, designed the study, performed data analysis and drafted the manuscript. TN and FJ supervised the work, were involved in designing the study, sorted clinical issues around the problem, and reviewed the manuscript critically. NEN, CTD, FSW and KEN collected and analysed the data. All authors read and approved the final draft of the manuscript.

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