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Uptake of Four or More Doses of Sulfadoxine Pyrimethamine for Intermittent Preventive Treatment of Malaria during Pregnancy in Zambia: Findings from the 2018 Malaria in Pregnancy Survey

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Uptake of Four or More Doses of Sulfadoxine Pyrimethamine for Intermittent Preventive Treatment of Malaria during Pregnancy in Zambia: Findings from the 2018 Malaria in Pregnancy Survey

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Abstract

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Introduction: The Zambian government is implementing the malaria in pregnancy (MiP) policy which includes intermittent preventive treatment of malaria during pregnancy with sulfadoxine pyrimethamine (IPTp-SP). However, the latest (2018) malaria indicator surveys (MIS) showed very low uptake of four doses of IPTp-SP at 5%. This study aimed to determine the prevalence and predictors of the uptake of four or more doses of IPTp-SP in Zambia.

Methods: We conducted a secondary analysis of the 2018 MIS dataset. Descriptive statistical analysis was carried out to summarise participant characteristics and IPTp-SP uptake. Univariate logistic regression was carried out to determine association between the explanatory and outcome variables. Explanatory variables with a p-value less than 0.20 on univariate analysis were included in the multivariable logistic regression model and crude and adjusted odds ratios along with their 95% CIs, p-value <0.05 were computed.

Results: Of the total sample of 1,163, only 7.5% of participants received IPTp-SP 4+. The province of residence and wealth quintile were significantly associated with uptake of IPTp-SP doses; participants from Luapula (aOR=8.72, 95%CI [1.72—44.26, p=0.009]) and Muchinga (aOR=6.67, 95%CI [1.19—37.47, p=0.031]) provinces were significantly more likely to receive IPTp-SP 4+ compared to those from the Copperbelt province. Conversely, women in the highest wealth quintile were significantly less likely to receive IPTp-SP 4+ doses compared to those in the lowest quintile (aOR=0.32; 95%CI [0.13—0.79, p=0.014])

Conclusion: These findings confirm a low uptake of four or more doses of IPTp-SP in the country. Women in urban provinces with low malaria burden and high wealth quintile are less likely to receive adequate doses compared to rural counterparts in low wealth quintile. Strategies are needed to target women in urban provinces to ensure adherence to the IPTp-SP guidelines.

Word count: 285

Key words: Malaria in Pregnancy, Intermittent Preventive Treatment, Uptake, Policy, Zambia.

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Strengths and weakness

- Use of the large dataset 2018 malaria in pregnancy data which covered all the 10 provinces of Zambia reduces makes the findings representative of the whole country.
- Use of multi-stage random sampling technique reduced selection bias and increased validity of the findings
- Inclusion into analysis only women of reproductive age who gave birth after the new IPTp-SP policy was introduced reduced information bias and increased internal validity of the study
- Use of secondary data limited the choice of variables to be included in the analysis
- Exclusion of participants with incomplete data could have reduced the power of the study

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Introduction

Malaria is a parasitic disease caused by a protozoan of genus Plasmodium. The five main species of the parasite are *Plasmodium falciparum*, *P. malariae, P.ovale*, *P.vivax and P. knowlesi.* It is widespread in tropical and sub-tropical regions (1). Among the Plasmodium species, *Plasmodium falciparum* is the leading cause of maternal and neonatal illness and death due to malaria, especially in Africa (2). Malaria infection during pregnancy (MiP) can lead to miscarriage, premature delivery, low birth weight, congenital infection, and/or perinatal death (3,4).

Estimates show that 50 million women living in malaria-endemic countries around the world become pregnant each year, and more than 50% of these live in tropical areas of Africa where there is a high transmission of *P. falciparum* (5,6). In sub-Sahara Africa, malaria is estimated to affect between 350 to 500 million people annually and accounts for 1 to 3 million deaths, 10,000 maternal and 200,000 neonatal deaths per year and one in four women have evidence of placental infection at the time of delivery (7–9). In Zambia, approximately 5.2 million malaria cases are reported per year with 98% of cases caused by P. falciparum. An estimated 200,000 pregnancies in Zambia are at risk of malaria each year (10).

Zambia National Malaria Elimination Centre (NMEC) in line with WHO strategic framework of malaria prevention and control during pregnancy has developed and is implementing a well-defined malaria in pregnancy (MiP) policy which includes the provision of free intermittent preventive treatment of malaria during pregnancy with sulfadoxine pyrimethamine (IPTp-SP), insecticide treated nets (ITNs) and prompt diagnosis and complete treatment of malaria (11). This malaria control package is implemented as part of antenatal care (ANC) (12). ANC provides a good platform for regular and close contact between pregnant women and skilled health personnel for improved service delivery and pregnancy monitoring. Zambia follows the 2016 WHO ANC model which recommends a minimum of 8 ANC contacts with the first contact scheduled to take place in the first trimester, two contacts in the second trimester and five contacts scheduled in the third trimester (12)

Administration of IPTp-SP is based on the assumption that every pregnant woman living in an area with high malaria transmission has malaria parasites. The parasites live in her blood or placenta, whether or not she has symptoms and signs of malaria (13). Recent findings with regards to placental malaria, characterized by the accumulation of *Plasmodium*-infected red blood cells in the placental intervillous space shows that it leads to adverse perinatal outcomes such as stillbirth, low birth weight, preterm birth, and small-for-gestational-age neonates (14). Further, low birth weight is highly associated with a marked increase in infant mortality (15,16). Results from more studies reviewed effects of malaria in pregnancy

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on child growth such as high rates of cognitive impairment, learning disability, and behavioural problems among children who were born with lower birth weight (17,18).

In Zambia, administration of two or more doses of IPTp-SP showed a decrease of low birthweight among paucigravid and multigravid women in Mansa district of Luapula province compared to one or less doses (19). In another study conducted in Mali, an addition of a third dose of ITPp-SP showed a halved risk of placental malaria, low birth weight and preterm births in all gravidae, compared with the standard two dose regimen (20). Based on the evidence from the two cited studies, the higher doses of IPTp-SP suggest to give better pregnancy outcomes than lower doses.

IPTp-SP involves administration of sulfadoxine pyrimethamine (SP) (comprising three tablets containing 500 mg/25 mg SP, giving the total required dosage of 1500 mg/75 mg SP) as direct observed therapy (DOT) to pregnant women. The first IPTp-SP dose is administered during the second trimester, 13-16 gestation weeks, followed by monthly doses until delivery for at least four doses.

In 2016, Zambia adopted the national malaria elimination strategy which includes uptake of four or more IPTp-SP doses (10). However, reports in the country have shown that the proportion of women receiving four or more doses of doses of IPTp-SP is low. The 2015 and 2018 malaria indicator survey (MIS) showed that only 5% of pregnant women took four or more doses of IPTp-SP (21). The reasons for the low coverage of IPTp-SP are not clear. Limited studies have been conducted on the predictors of the uptake of four or more doses of SP in Zambia Information.

Objectives

The aim of this study was to determine the prevalence and predictors of the uptake of four or more doses of IPTp-SP in Zambia. Information is required to inform policy and programming to improve uptake of SP in the country.

Methods

Study design

The present study is a secondary analysis of the 2018 Malaria indicator survey done in Zambia. It was a cross section survey conducted from April to May, 2018. The survey is periodically done to assess the malaria burden and coverages of key malaria interventions such as vector control, parasite clearance, health promotion, enhanced surveillance, monitoring, evaluation and research, health system capacity, financing and case management in the general population including MiP. The MIS 2018 was the latest

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comprehensive dataset that was representative of the whole country and readily accessible at the time of writing the manuscript.

Study site

The study used the 2018 MIS survey data which covered all the ten provinces of Zambia, making it nationally representative. The country is divided into ten provinces that are further divided into districts. For statistical purposes, each district is subdivided into census supervisory areas (CSAs) which are in turn subdivided into enumeration areas (EAs). The listing of EAs has information on the number of households and the populations.

Zambia is a sub-Saharan African country located in south-central Africa with a surface area of 752,614 square kilometres. Lusaka, the capital city, is located in the south-central part of the country. The topography is characterised by a high plateau, river valleys, and water bodies. The country derives its name from the Zambezi river, which drains all but a small northern part of the country (22). Zambia's population as of 8th September 2022 was 19,610,769. The male population was 9,603,056 and the female population was 10,007,713 (23). It has a tropical climate with the rainy season occurring during October to April. The climate is suitable for mosquito breeding and malaria transmission takes place throughout the year but peaks during the rainy season (24).

Study participants and procedures

Study participants were women of reproductive age who participated in the 2018 MIS. The country conducts MIS surveys every two to three years to provide updates on malaria interventions and disease burden in the country. A total of 3, 686 women of reproductive age who gave birth in the past five years participated in the 2018 MIS. From this sample, a total of 1, 381 were included in our analysis.

Inclusion criteria.

To be included in the study, participants needed to be:

- Pregnant women who were pregnant in the past two years and five months after the new 2016 policy on the fourth dose IPTp-SP was implemented
- All women aged between 15 to 49 years from all the ten provinces

Women who did not give consent and those who did not complete the individual questionnaires were not included in the analysis.

Sample size estimation

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The study participants in the main survey were selected using a two-stage cluster sampling technique which are based on a nationally representative sample of 4,177 households from 179 standard enumeration areas (SEAs) randomly selected from all ten provinces. Based on these criteria, at least 2,176 households were required in the rural domain. For further details on the 2018 MIS sampling technique and sample size determination see the 2018 MIS published report by the Zambian ministry of health.

Assumptions for the sample size determination were;

- 95% confidence interval
- 80% power
- design effect of 2.50
- Z-score of 1.96
- 10% relative standard error
- Margin of error of 2%
- 20% adjustment for non-response

The estimated minimum sample size in this study was determined by the formula below;

$$n=\frac{z^2 x\, p(1-p)(DEFF)}{d^2} = 1141 \text{ (25)}$$

Where: n is the calculated sample size, z =1.96 is the statistic that defines the level of confidence required, p=0.05 is a prevalence of uptake of IPTp-SP among pregnant women in Zambia, expressed as a proportion of that population

D=0.02 is the desired level of precision, DEFF=2.5 is the design effect (25).

Variables

The variables for the study were as follows:

- Outcome variable: uptake of four or more doses of IPTp-SP
- Predictor variables: sociodemographic variables (age, parity, place and province of residence, religion, educational level, wealth index)
- Basic knowledge about malaria
- Knowledge about malaria treatment

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The predictor variables were selected based on thorough literature review. In this study uptake means receiving any dosage of SP during pregnancy, with each dose being given at least 1 month apart starting from the second trimester of gestation, until the time of delivery as directly observed therapy.

Data sources and processing

The merged 2018 MIS dataset comprising women of reproductive age (15 to 49 years) was extracted into the Microsoft office excel sheet 2013 using the data extraction tool. We subset women 15 to 49 years of age who were eligible to complete the questionnaire. From the eligible women, we subsetted women who consented. Further, a subset of women who completed the questionnaire and delivered in 2016 or later (after the new IPTp policy) was done using the lubridate library in R Studio. This was determined by using the age of the youngest child (that is, if a child was less than 881 days).

Statistical analysis

Descriptive statistical analysis was carried out first on socio-demographics to obtain frequencies and proportions. The proportion of missing values on the outcome was calculated. The correlation among the predictor variables was explored. Thereafter, univariate logistic regression was carried out and explanatory variables whose p-values were less than 0.2 were presented in table 2. The estimators with a p-value level of 0.20 chose the adjusted estimate more frequently when confounding is present and so produced less bias than the estimators with a p-value level of 0.05 (26).

Then, a backward selection approach using stepwise method with a p-value of 0.2 threshold was used to select explanatory variables to be included in the multivariable logistic regression for further analysis of the association to obtain adjusted odds ratios. We also compared Akaike's Information Criteria (AIC), Bayesian Information Criteria (BIC) and Pseudo-R2 between the multivariable model which included all variables (full model) and the model after backward selection approach (reduced model) for model fit.

To account for the differences in sampling probabilities across the clusters and strata, sample weighting was used to adjust for the cluster sampling design using "svy" function in R studio and "svyset" command to match the multistage cluster sampling design method. Results from univariable and multivariable analysis were presented as crude and adjusted odds ratios along with their 95% CIs, respectively. A p-value of <0.05 was considered statistically significant for all analyses.

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The missing values were imputed using the multiple imputation by chain equation (MICE) methods. The study explored the proportions of missing values and compared the estimates from the full data models and the imputed models to see whether there was an observed difference. The multiple imputation was carried on multivariable analysis only (27). R-studio statistical software was used for all the analyses.

Patient and Public Involvement

The study design was determined by the research team. Participants and the public were not directly involved in the conceptualisation and design of the study. Selection of study participants for the 2018 MIS was done in collaboration with the provincial and district health managers. Permission for access to the dataset used for the current study was granted by the National Malaria Elimination centre in consultation with the Ministry of Health. A dissemination meeting was held and study findings shared with key stakeholders, including the Levy Mwanawasa Medical University School of Public Health, Ministry of Health and Zambia National Public Health Institute. A final report was also written and shared with the funding organization.

Results

Participants

A summary of the recruitment algorithm of study participants is shown below. A total of 4044 women of reproductive age were eligible to complete the questionnaire. Out of these, 3, 686 (91%) completed the questionnaire; 358 (9%) did not provide consent and were excluded from the study. A total of 1,381 (34%) participants comprising women who delivered after the new IPTp-SP policy was introduced were included into the final sample for analysis (**Supplementary figure 1).**

Demographic characteristics of respondents

Majority (68.9%) of study participants were in the age group 15-29 years; almost one third (30.8%) were in the age group 30-44 years and 0.3% were aged above 45 years. Close to half (48.9%) had completed primary education (48.9%), 28.2% had secondary school education and 2.8% had gone up to higher education. Most respondents (81.3%) lived in rural areas. With regard to province of residence, 19.1% were from Luapula, 18.0% from Eastern, 17.2% from Western and 4.1% from Copperbelt provinces. One fifth (21.9%) of the study participants were in lowest wealth quintile; 15.6% were in the middle quintile. Concerning religion, more than half (56.8%) of study participants were protestants followed by Catholics (22.2%); Muslims constituted 0.1% of the respondents. Majority (97.3%) attended ANC and most (77.9%) took less than four doses of IPTp-SP. Majority (71.3%) took three doses of IPTp-SP, 14.5% took two

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doses, 7.5% took IPTp-SP 4+ doses, 6.9% took only one dose. The proportions of IPTp-SP uptake increased from IPTp-SP 1 to IPTp-SP 3 and drastically dropped at IPTp-SP 4+. More than half (52.5%) of the study participants had three or more children and 22.2% had two children. Concerning knowledge on malaria prevention measures, most (76.4%) were knowledgeable and only 45.0% were exposed to media messages (**Table 1**).

Table 1: Socio-demographic and clinical characteristics of the study participants (N=1381)

Variable	N (%)	Variable	N (%)
Age(years)		**Parity**	
15-24	678 (49.1)	1	348 (25.2)
25-34	497 (36.0)	2	307 (22.2)
35+	205 (14.8)	3+	725 (52.5)
Missing	1 (0.1)	Missing	1 (0.1)
Residence		**Got ANC**	
Rural	1123 (81.3)	Yes	1344 (97.3)
Urban	258 (18.7)	No	35 (2.5)
		Missing	2 (0.2)
Province			
Central	93 (6.7)	**IPTp-SP Uptake[a]**	
Copperbelt	56 (4.1)	1	80 (6.9)
Eastern	249 (18.0)	2	167 (14.4)
Luapula	264 (19.1)	3	829 (71.3)
Lusaka	87 (6.3)	4+	87 (7.5)
Muchinga	95 (6.9)		
North-Western	90 (6.5)	**Exposure to media message**	
Northern	120 (8.7)	No	759 (55.0)
Southern	90 (6.5)	Yes	622 (45.0)
Western	237 (17.2)	**Missing**	
Wealth quintile		**Knowledge about Malaria prevention**	
Low	578 (41.8)	Not knowledgeable	241 (17.5)
Middle	302 (21.9)	Knowledgeable	1055 (78.4)

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High	501 (36.3)	Missing	85 (6.1)
Education level		**Basic Malaria knowledge**	
Primary	675 (48.9)	Incorrect	351 (25.4)
Secondary+	428 (31.0)	Correct	945 (68.4)
Missing	278 (20.1)	Missing	85 (6.2)
Religion			
Christian	1092 (79.1)		
Non-christian	289 (20.9)		

[a] The proportions excludes the missing values

Predictors for the uptake of adequate doses of IPTp-SP (4+ doses)

The overall uptake of adequate (4+) doses of IPTp-SP was 7.5%. The uptake of 4+ doses of IPTp-SP decreased by level of education ranging from 9.2% for women with primary education to 4.6% for women with higher education. The same trend was observed across age group, i.e. decrease from 8.5 % in 15-24 years age group to 5.5% in age group of 35 and above years. The women from rural area had higher (7.6%) uptake of adequate doses compared to women from urban area (7.2 %). The uptake of adequate doses of SP was highest for women in the low wealth quintile (11.4 %). Also, women who were not exposed to media messages had higher uptake of SP (8.9%) compared to those who were exposed to media messages (5.9%) (Table 2).

The results of univariate logistic regression analysis (crude odds ratios) show that woman's education level, place of residence, province, wealth quintile, exposure to media messages and knowledge about malaria prevention were significantly associated with the adequate uptake of IPTp-SP. While age group showed no evidence of association with adequate uptake of IPTp-SP. The results in table 2 shows significant lower odds of taking an adequate IPTp-SP among women with at least secondary level of education (0.30, 95%CI 0.15-0.61, p-value=0.001) compared to those with primary level of education. Luapula and Muchinga provinces show significant higher odds of taking an adequate IPTp-SP (13.57, 95%CI 2.98-61.77, p-value=0.001 and 11.50, 95%CI 2.32-56.95, p-value=0.003, respectively) compared to those from Copperbelt.

Women in the middle and high wealth quintile show significant lower odds of taking an adequate IPTp-SP (0.35, 95%CI 0.17-0.72, p-value=0.005 and 0.10, 95%CI 0.10-0.20, p-value<0.001, respectively) compared to those in low wealth quintile. Women who were exposed to media messages had significant

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lower odds of taking an adequate IPTp-SP (0.49, 95%CI 0.28-0.85, p-value=0.011) compared to those who were not exposed. Women who had knowledge about malaria prevention had significant lower odds of taking an adequate IPTp-SP (0.44, 95%CI 0.23-0.86, p-value=0.016) compared to those who had none.

Using backward selection method with p-value threshold of 0.2, the reduced (final) model retained age group, education level, province and wealth quintile. Therefore, after adjusting for age group, education level and wealth quintile, Luapula and Muchinga provinces still showed significant higher (though reduced) odds of taking an adequate IPTp-SP (8.72, 95%CI 1.72-44.26, p-value=0.009 and 6.67, 95%CI 1.19-37.47, p-value=0.031, respectively) compared to those from Copperbelt. And after adjusting for age group, education level and province, only women in the higher wealth quintile had significant lower odds of taking an adequate IPTp-SP (0.32, 95%CI 0.13-0.79, p-value=0.014) compared to those in low wealth quintile.

Comparing AIC, BIC and Pseudo-R2 we have 417.7, 490.2 and 0.09 for the reduced model, and 436.7, 496.3 and 0.08 for the full model, respectively. This suggests that the reduced model is better fitted compared to the full model. This is because the AIC and BIC are lower, and Pseudo-R2 is higher for the reduced model compared to the full model. The proportion of missing values were highest under education level variable which accounted to 20.1%. Comparing estimates of full data model from multivariable analysis (appendix 3) and the imputed multivariable analysis, there is no much difference in the estimates apart from the fact that the 95% CI are narrower in some instances in imputed model compared to full data model. However, estimates from multiple imputation are only valid when data is at least missing at random (**Table 2).**

Table 2: Predictors for the adequate uptake of IPTp-SP (≥4 doses) during pregnancy in Zambia

Variable	n(weighted)	n(%)	cOR[a]	95% CI[b]	p-value	aOR[c]	95% CI	P-value
Overall	1163	87 (7.5)						
Age group (Years)								
15-24	542	46 (8.5)	1.00			1.00		
25-34	441	31 (7.0)	0.67	0.37-1.21	0.181	0.54	0.26-1.08	0.083

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35+	180	10 (5.5)	0.58	0.24-1.35	0.202	0.58	0.23-1.51	0.266
****Education level**								
Primary	542	50 (9.2)	1.00			1.00		
Secondary+	396	18 (4.6)	0.30	0.15-0.61	0.001*	0.55	0.27-1.11	0.093
Residence								
Rural	927	70 (7.6)	1.00					
Urban	219	17 (7.2)	0.22	0.11-0.44	<0.001*			
Province								
Copperbelt	44	2 (4.6)	1.00			1.00		
Central	89	3 (3.4)	2.15	0.28-16.78	0.463	2.03	0.27-15.48	0.493
Eastern	210	11 (5.2)	1.72	0.32-9.35	0.528	1.15	0.19-7.00	0.878
Luapula	196	36(18.4)	13.57	2.98-61.77	0.001*	8.72	1.72-44.26	0.009*
Lusaka	70	0 (0.0)	-	-	-	-	-	-
Muchinga	83	13(15.7)	11.50	2.32-56.95	0.003*	6.67	1.19-37.47	0.031*
North-western	84	4 (4.8)	2.32	0.38-14.08	0.359	2.08	0.32-13.34	0.441
Northern	111	16(14.4)	8.94	1.86-42.87	0.006	4.13	0.73-23.42	0.109
Southern	80	1 (1.3)	0.82	0.07-9.59	0.873	1.40	0.11-17.90	0.794
Western	196	1 (0.5)	0.53	0.05-6.13	0.608	-	-	-
Wealth quintile								
Low	438	50(11.4)	1.00			1.00		
Middle	259	16 (6.2)	0.35	0.17-0.72	0.005*	0.52	0.19-1.45	0.212
High	466	21 (4.5)	0.10	0.10-0.20	<0.001*	0.32	0.13-0.79	0.014*
Exposure to media messages								

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No	607	54 (8.9)	1.00					
Yes	556	33 (5.9)	0.49	0.28-0.85	0.011*			
****Knowledge about malaria prevention**								
Not knowledgeable	180	22(12.2)	1.00					
Knowledgeable	920	60 (6.5)	0.44	0.23-0.86	0.016*			

[a]cOR stands for Crude Odds ratio [b]CI stands for Confidence interval [c]aOR stands for adjusted odds ratio *significant at 5% level **The observations do not add up to the overall sample because the variables have missing values. Note: AIC, BIC and Pseudo-R2 are 417.7, 490.2 and 0.09 for the reduced model, and 436.7, 496.3 and 0.08 for the model which included all the variables (full model) in the table, respectively

Discussion

The study aimed to determine the predictors of IPTp-SP uptake for four or more doses in Zambia. Our findings show that uptake of four or more doses of IPTp-SP was low at 7.5% The place and province of residence were significantly associated with adequate uptake of IPTp-SP doses. Women who were residents of Luapula and Muchinga provinces had higher odds of taking adequate doses with reference to those in the Copperbelt province. Conversely, women in the highest wealth quintile were significantly less likely to receive IPTp-SP 4+ doses compared to those in the lowest quintile. Knowledge about malaria prevention and exposure to media messages was associated with low odds of adequate IPTp-SP uptake.

Our findings show an association between IPTp-SP uptake and place of residence. Women from rural provinces such as Muchinga and Luapula showed higher odds of IPTp-SP uptake than those from urban provinces of Copperbelt and Lusaka. The observed variation in the odds of IPTp-SP uptake between the urban and rural provinces could be due to differences in the malaria prevalence among these provinces. For example, Luapula province has a high malaria prevalence of 63% compared to 3% in Lusaka and Southern provinces. The province is rural with many water bodies, enhancing malaria transmission. These factors also make malaria transmission likely to be longer and more intense compared to other provinces. Thus, the province continues to report the largest malaria burden in the country.

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Women in provinces with low prevalence of malaria may not take adequate IPTp-SP due to low perceived risk (28). On the contrary, women from regions of high level of malaria transmission, may take adequate doses of IPTp-SP due to higher risk perception. In these regions, emphasis on SP uptake during awareness messages could be higher due to the higher risk of contracting malaria. This finding could reflect that women in rural areas may consider themselves at higher risk of contracting malaria compared to those in urban areas (29). Exploratory studies are required to investigate the reasons for the variations in uptake of IPTp-SP among different provinces.

These findings corroborate those from studies conducted in Tanzania and Uganda which showed that variations in IPTp_SP uptake were related to differences in malaria transmission in the regions. The study in Tanzania showed that residents of the Central, Eastern, Southern, Lake regions, Southern highlands and South west highlands were significantly associated with the optimal uptake of SP doses compared to the residents of Zanzibar and Northern zones where malaria transmission was low. Similarly, the Uganda study showed that pregnant women residing in Eastern and Coastal regions had higher odds of optimal uptake of SP (30).

Our findings showed no significant association between education level and uptake of IPTp-SP. However, univariate analysis showed that women who attained secondary education had less odds of taking four or more doses of IPTp-SP compared with those who attained primary education. None of the women who attained higher education took four or more doses of IPTp-SP. Our findings contract previous studies and surveys. Literally, one would expect that having higher educational level may be of influence on the uptake of the recommended doses of IPTp-SP compared to women with a lower education level. A study which compared Malaria Indicators Survey of 12 countries in sub-Saharan Africa (30) found that women with higher education had higher odds of reporting receiving three or more doses of IPTp-SP. The differences in the findings could be as a result of using different methods. Furthermore, the findings in our study show that a large proportion of women who took four or more doses resided in rural areas and that many people from the rural areas with low educational level (31).

This study found that women in the highest and middle wealth quintile had less odds of taking four or more doses of IPTp-SP compared to those in the lowest wealth quintile. This finding contradicts previous studies which revealed that wealth index has a significant effect on uptake of IPTp-SP. These studies showed that the chances of completing the recommended dose of IPTp-SP increased with increase in wealth index (32). A study done in Senegal found that women in richer or middle wealth quintile were more likely to use the recommended doses of IPTp-SP (33). The reason for the difference between our findings and these studies could be due to confounding by place of residence. Our findings show that

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most study participants who took four or more doses of IPTp-SP were from the rural areas who are mostly in the low wealth quintile. The other reason is the fact that IPTp-SP is provided for free in Zambia.

Our findings show that participants who had knowledge about malaria prevention and exposure to media messages had less odds of receiving adequate IPTp-SP doses. These findings contradict the literature which has shown that effective uptake of IPTp-SP could be realized when pregnant women are adequately and properly informed about malaria interventions. Studies conducted in Zambia and Ghana (34) showed that maternal knowledge on IPTp-SP positively influenced the uptake of the intervention. The difference in findings could be that our study did not assess specifically the knowledge about IPTp-SP and its benefits. Rather, the study focused on knowledge about malaria prevention in general. Studies show that women who understand the benefits of IPTp-SP and know the recommended SP doses are more likely to receive the adequate dosage. This calls for more awareness on malaria interventions in general and in particular about the recommended doses of IPTp-SP during pregnancy.

Regarding teenage mothers, there were no significant associations noted in taking four or more doses of IPTp-SP. However, the highest proportion of women who took four or more doses of IPTp-SP was noted among teenage mothers. This maybe due to the fact that the majority of our study participants were from the rural areas and that teenage pregnancy in rural areas is high in Zambia (35).

Literature reveals that younger women may lack adequate access to information and communication channels used for IPTp-SP promotion and this may impact negatively on the uptake of IPTp-SP. More attention is needed to this age group as reported in a study conducted in Ghana where low uptake of the recommended dose was seen among this population group (36). Teenagers often hide their pregnancies and delay in ANC attendance and are therefore not able to take the recommended doses before they deliver (36).

This study further reports that the uptake of four or more doses of IPTp-SP during pregnancy is still low at 7.5% compared to the recommended coverage of 80% by the WHO and Roll Back Malaria (RBM) benchmark target. The highest proportion of women took up to the third dose of IPTp-SP during pregnancy. This finding could be due lack of awareness about the fourth dose. More emphasis is still being placed on taking at least three or more doses of IPTp-SP. Health messages should focus on and emphasise the new policy on four or more doses in the country.

The study findings are similar to other studies in the sub-Saharan Africa which reported the low uptake of the recommended doses of IPTp-SP (37). This may suggest that many countries in sub–Saharan Africa are still struggling to reach their recommended IPTp service coverage. Hence, the urgent need for strategies to increase IPTp-SP coverage for improved maternal and newborn health outcomes. This

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may contribute to the ambitious sustainable development goals (SDG) and target of reducing maternal mortality rate (MMR) from 319 to 70 per 100,000 live births (38-42).

Study limitations

This study has potential limitations. First, we did not collect the data, but used secondary data from the 2018 MIS. This prevented the team from having any control over the measurement and selection of the variables. Some important variables that would have been of interest such as distance from the health facility to the communities where people live, stocks of SP, timing of ANC and number of times the woman attended ANC were not contained in the data set and thus could not be analysed. Further, the MIS data were cross-sectional, the associations in this study cannot guarantee any causation or directionality.

Despite these limitations, we believe our findings have provided important information on the low coverage of four or more doses of IPTp-SP and the associated factors. In addition, use of a nationally presentative data from the 2018 MIS that covered all the provinces increases the generalisability of our findings.

Conclusion

These findings confirm low uptake of four or more doses of IPTp-SP in Zambia at 7.5%. Various factors including province and place of residence, wealth quintile, knowledge about malaria prevention and exposure to media messages are significantly associated with IPTp-SP uptake. Strategies and interventions aimed at improving uptake and coverage of IPTp-SP must focus on women in high wealth quintile from urban areas with low malaria transmission in the country. Interventions should include health messages with emphasis on the new policy of four or more doses of IPTp-SP. Messages should also stress the benefits of strengthening the linkage between IPTp-SP program with ANC services for optimal uptake of IPTp-SP.

Figure Legend/Caption

Figure 1 : Participant recruitment algorithm

Authors' Contribution

DS, CS, and NM contributed to the conception of the study and literature search. DS conducted the extraction, analysis and drafted the manuscript. CS, NM, BH LSM and HM contributed to the coordination study activities. CS, NM, BH contributed to the revision of the manuscript. All authors read and approved the manuscript.

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Competing Interests

All authors declare that they have no conflicting interests in this work

Ethics approval

Ethical approval and waiver of consent was given by ERES converge IRB (Ref No. 2021-Nov-004). Permission to conduct the study and access to the 2018 MIS dataset was granted by the National Health Research Authority (NRFA) Ref No. NHRA000023/04/03/2022) and Ministry of Health, respectively. The dataset was then secured as soft copy in the computer. No information regarding names of study participants was obtained and used; the dataset was only used for the purpose of this study and it was not given to any other person or organization. No harm was inflicted to the participants, the study used secondary data and there was no direct contact with study participants.

Data Sharing

Data are available upon reasonable request from the corresponding author and with permission of the ERES ethics review board.

Costs and payments

N/A

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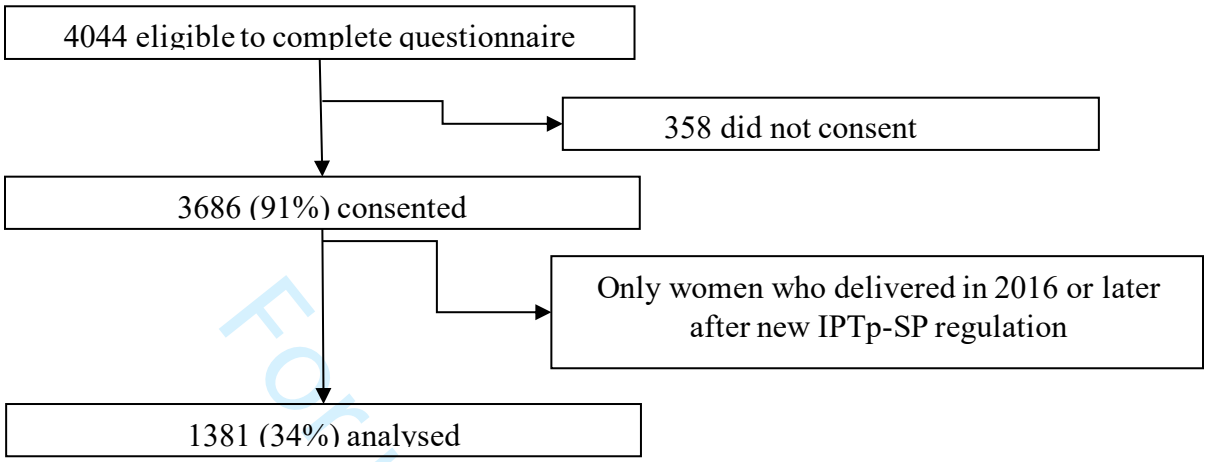
Figure 1: Flow diagram for participant selection



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STROBE Statement—Checklist of items that should be included in reports of descriptive studies

Item	Recommendation	Page
Title and abstract	Indicate the study's design with a commonly used term in the title or the abstract	1
	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction		
Background/rationale	Explain the scientific background and rationale for the investigation being reported	4
Objectives	State specific objectives, including any pre-specified hypotheses	5
Methods		
Study design	Present key elements of study design early in the paper	5
Setting	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
Study size	Explain how the study size was arrived at	7
Variables	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Statistical methods	Describe all statistical methods, including those used to control for confounding	8
	If applicable, explain how loss to follow-up was addressed	
Patient and public involvement		8
Results		
Participants	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage Participants (c) Consider use of a flow diagram	9
Descriptive statistics	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Descriptive data (b) Indicate number of participants with missing data for each variable of interest	9
Main results		10
Discussion		14

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Uptake of Four or More Doses of Sulfadoxine Pyrimethamine for Intermittent Preventive Treatment of Malaria during Pregnancy in Zambia: Findings from the 2018 Malaria in Pregnancy Survey

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Keywords:	EPIDEMIOLOGY, Health Services Accessibility, PUBLIC HEALTH, Maternal medicine < OBSTETRICS

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Uptake of Four or More Doses of Sulfadoxine Pyrimethamine for Intermittent Preventive Treatment of Malaria during Pregnancy in Zambia: Findings from the 2018 Malaria in Pregnancy Survey

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Abstract

Objective: To determine the prevalence and predictors of the uptake of four or more doses of sulfadoxine pyrimethamine (IPTp-SP 4+) in Zambia.

Design: A cross-sectional study using secondary data from the malaria in pregnancy survey (MIS) dataset conducted from April to May 2018.

Setting: The primary survey was conducted at community level and covered all the ten provinces of Zambia.

Participants: A total of 3, 686 women of reproductive age (15 to 45 years) who gave birth within the five years before the survey.

Primary outcome: Proportion of participants with four or more doses of IPTp-SP

Statistical analysis: All analyses were conducted using R-studio statistical software version 4.2.1. Descriptive statistics were computed to summarise participant characteristics and IPTp-SP uptake. Univariate logistic regression was carried out to determine association between the explanatory and outcome variables. Explanatory variables with a p-value less than 0.20 on univariate analysis were included in the multivariable logistic regression model and crude and adjusted odds ratios (AORs) along with their 95% confidence intervals (CIs) were computed ($p<0.05$).

Results: Of the total sample of 1,163, only 7.5% of participants received IPTp-SP 4+. Province of residence and wealth tertile were associated with uptake of IPTp-SP doses; participants from Luapula (aOR=8.72, 95%CI [1.72—44.26, p=0.009]) and Muchinga (aOR=6.67, 95%CI [1.19—37.47, p=0.031]) provinces were more likely to receive IPTp-SP 4+ compared to those from Copperbelt province. Conversely, women in the highest wealth tertile were less likely to receive IPTp-SP 4+ doses compared to those in the lowest quintile (aOR=0.32; 95%CI [0.13—0.79, p=0.014])

Conclusion: These findings confirm a low uptake of four or more doses of IPTp-SP in the country. Strategies should focus on increased coverage of IPTp-SP in provinces with much higher malaria burden where the risk is greatest and the ability to afford health care lowest.

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Word count: 295

Key words: Malaria in Pregnancy, Intermittent Preventive Treatment, Uptake, Policy, Zambia.

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Strengths and weakness

- Use of large dataset from the 2018 malaria in pregnancy (MIP) survey with a nationally representative sample reduced selection bias and increased external validity and generalisability of the findings .
- Use of multi-stage random sampling technique reduced selection bias and increased validity of the findings
- Inclusion into analysis only women of reproductive age who gave birth after the new IPTp-SP policy was introduced reduced information bias and increased internal validity of the study
- Use of secondary data limited the choice of variables to be included in the analysis
- Exclusion of participants with incomplete data could have reduced the power of the study

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Introduction

Globally, there are an estimated 247 million cases of malaria reported from 84 malaria-endemic countries, with the majority (95%) being reported from the world health organisation (WHO) African Region. Sub-Sahara Africa is disproportionately affected, accounting for an estimated 350 to 500 million cases, 1 to 3 million deaths, 10,000 maternal and 200,000 neonatal deaths per year [1,2]. With an estimated 125 million pregnant women being at risk of contracting malaria globally, malaria in pregnancy (MIP) remains an important preventable cause of adverse maternal, neonatal health outcomes worldwide [3-5]. Out of an estimated 50 million annual pregnancies in malaria-endemic countries around the world each year, more than 50% of these live in the tropical areas of Africa where there is a high transmission of *P. falciparum [*6,7*]* .

Malaria is a parasitic disease caused by a protozoon of the genus Plasmodium. Although there are species of malaria that infect humans— *Plasmodium falciparum*, *P. malariae, P.ovale*, *P.vivax and P. knowlesi*— two main species*, P. falciparum and P. vivax,* pose the greatest risk and contribute to adverse outcomes. *P. falciparum* is the deadliest malaria parasite and the most prevalent on the African continent [7,8]. Malaria parasites contribute to adverse pregnancy and birth outcomes due to their preferential accumulation in placental intervillous spaces, putting pregnant women and their babies at an increased risk. MIP is associated with anaemia, miscarriage, premature birth, stillbirth, congenital infection, low birth weight (lbw), maternal, foetal and perinatal death; one in four women have evidence of placental infection at the time of delivery (7–9). Moreover, evidence from previous studies shows that lbw is associated with a marked increase in infant mortality, high rates of cognitive impairment, learning disability, and behavioural problems [9-12].

Zambia is a sub-Saharan African country with a high malaria burden with an approximate 5.2 million annual malaria cases and an estimated 200,000 pregnancies being at risk of malaria [13]. The Zambia National Malaria Elimination Centre (NMEC) in line with WHO strategic framework of malaria prevention and control during pregnancy has developed and is implementing an MIP policy which includes the provision of four or more doses of intermittent preventive treatment of malaria during pregnancy with sulfadoxine pyrimethamine (IPTp-SP) [14]. Other interventions are insecticide treated nets (ITNs), in-door residual spraying (IRS) and case management.

IPTp-SP and ITN interventions are being implemented as part of antenatal care (ANC) services [15] and involves administration of sulfadoxine pyrimethamine (SP) (comprising three tablets containing 500 mg/25 mg SP, giving the total required dosage of 1500 mg/75 mg SP) as direct observed therapy (DOT) to pregnant women. The first IPTp-SP dose is administered during the second trimester, 13-16 gestation

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weeks, followed by monthly doses until delivery for at least four doses. ANC has been identified to provide a good platform for regular and close contact between pregnant women and skilled health personnel for improved service delivery and monitoring. Zambia follows the 2016 WHO ANC model which recommends a minimum of 8 ANC contacts with the first contact scheduled to take place in the first trimester, two contacts in the second trimester and five contacts scheduled in the third trimester [15, 16].

Administration of IPTp-SP is based on the assumption that every pregnant woman living in a high malaria transmission area has malaria parasites. The parasites live in blood or placenta, whether or not she has symptoms and signs of malaria [17,18]. Previous studies in Zambia and elsewhere have provided evidence on the effectiveness of IPTp-SP on improved maternal and new-born health outcomes. In Zambia, administration of two or more doses of IPTp-SP showed a decrease in low birthweight among paucigravid and multigravid women compared to one dose [19]. A study conducted in Mali [20] showed that addition of a third dose of ITPp-SP led to a reduced risk of placental malaria, low birth weight and preterm births in all gravidae, compared with the standard two dose regimen. A systematic review and meta-analysis on Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa by Kayentao and colleagues [21] showed that three or more doses were associated with a 3.3% reduction in low birth weight, 3.1% reduction in placental malaria and 1.4% reduction in moderate to severe maternal anaemia.

However, the 2018 MIS report [22] shows that the proportion of pregnant women receiving four or more doses of doses of IPTp-SP is low at 5%. The reasons for the low coverage of IPTp-SP are not clear. Limited studies have been conducted on the predictors of the uptake of four or more doses of SP in Zambia. The reasons for the low coverage of IPTp-SP are not clear. Limited studies have been conducted on the predictors of the uptake of four or more doses of SP in Zambia.

Objectives

The aim of this study was to determine the prevalence and predictors of the uptake of four or more doses of IPTp-SP in Zambia. Information is required to inform policy and programming to improve uptake of SP in the country.

Methods

Study design

The present study is a secondary analysis of the 2018 Malaria indicator survey done in Zambia. It was a cross section survey conducted from April to May, 2018. The survey is periodically done to assess the malaria burden and coverages of key malaria interventions such as vector control, parasite clearance,

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health promotion, enhanced surveillance, monitoring, evaluation and research, health system capacity, financing and case management in the general population including MIP. The MIS 2018 was the latest comprehensive dataset that was representative of the whole country and readily accessible at the time of writing the manuscript.

Study site

The study used the 2018 MIS survey data which covered all the ten provinces of Zambia, making it nationally representative. The country is divided into ten provinces that are further divided into districts. For statistical purposes, each district is subdivided into census supervisory areas (CSAs) which are in turn subdivided into enumeration areas (EAs). The listing of EAs has information on the number of households and the populations. Zambia is a sub-Saharan African country located in south-central Africa with a surface area of 752,614 square kilometres. Lusaka, the capital city, is located in the south-central part of the country [23]. The topography is characterised by a high plateau, river valleys, and water bodies. The country derives its name from the Zambezi River, which drains all but a small northern part of the country. It has a tropical climate with the rainy season occurring during October to April. The climate is suitable for mosquito breeding and malaria transmission takes place throughout the year but peaks during the rainy season [24,25]. Zambia's population as of 8th September 2022 was 19,610,769. The male population was 9,603,056 and the female population was 10,007,713 [26].

Study participants and procedures

Study participants were women of reproductive age who participated in the 2018 MIS. The country conducts MIS surveys every two to three years to provide updates on malaria interventions and disease burden in the country. A total of 3, 686 women of reproductive age who gave birth in the past five years participated in the 2018 MIS. From this sample, a total of 1, 381 were included in our analysis.

Inclusion criteria.

To be included in the study, participants needed to be:

- Pregnant women who were pregnant in the past two years and five months after the new 2016 policy on the fourth dose IPTp-SP was implemented
- All women aged between 15 to 49 years from all the ten provinces

Women who did not give consent and those who did not complete the individual questionnaires were not included in the analysis.

Sample size estimation

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The study participants in the main survey were selected using a two-stage cluster sampling technique which are based on a nationally representative sample of 4,177 households from 179 standard enumeration areas (SEAs) randomly selected from all ten provinces. Based on these criteria, at least 2,176 households were required in the rural domain. For further details on the 2018 MIS sampling technique and sample size determination see the 2018 MIS published report by the Zambian ministry of health.

Assumptions for the sample size determination were;

- 95% confidence interval
- 80% power
- design effect of 2.50
- Z-score of 1.96
- 10% relative standard error
- Margin of error of 2%
- 20% adjustment for non-response

The estimated minimum sample size in this study was determined by the formula below;

$$n=\frac{z^2 x\, p(1-p)(DEFF)}{d^2} = 1141 \ (25)$$

Where: n is the calculated sample size, z =1.96 is the statistic that defines the level of confidence required, p=0.05 is a prevalence of uptake of IPTp-SP among pregnant women in Zambia, expressed as a proportion of that population

D=0.02 is the desired level of precision, DEFF=2.5 is the design effect [27].

Variables

The variables for the study were as follows:

- Outcome variable: uptake of four or more doses of IPTp-SP
- Predictor variables: sociodemographic variables (age, parity, place and province of residence, religion, educational level, wealth index)
- Basic knowledge about malaria
- Knowledge about malaria treatment

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The predictor variables were selected based on thorough literature review. In this study uptake means receiving any dosage of SP during pregnancy, with each dose being given at least 1 month apart starting from the second trimester of gestation, until the time of delivery as directly observed therapy.

Data sources and processing

The merged 2018 MIS dataset comprising women of reproductive age (15 to 49 years) was extracted into the Microsoft office excel sheet 2013 using the data extraction tool. We subset women 15 to 49 years of age who were eligible to complete the questionnaire. From the eligible women, we subsetted women who consented. Further, a subset of women who completed the questionnaire and delivered in 2016 or later (after the new IPTp policy) was done using the lubridate library in R Studio. This was determined by using the age of the youngest child (that is, if a child was less than 881 days).

Statistical analysis

R-studio statistical software version 4.2.1. was used for all the analyses. Descriptive statistical analysis was carried out first on socio-demographics to obtain frequencies and proportions. The proportion of missing values on the outcome was calculated. The correlation among the predictor variables was explored. Thereafter, univariate logistic regression was carried out and explanatory variables whose p-values were less than 0.2 were presented in table 2. The estimators with a p-value level of 0.20 chose the adjusted estimate more frequently when confounding is present and so produced less bias than the estimators with a p-value level of 0.05 [28]. Then, a backward selection approach using stepwise method with a p-value of 0.2 threshold was used to select explanatory variables to be included in the multivariable logistic regression for further analysis of the association to obtain adjusted odds ratios. We also compared Akaike's Information Criteria (AIC), Bayesian Information Criteria (BIC) and Pseudo-R2 between the multivariable model which included all variables (full model) and the model after backward selection approach (reduced model) for model fit. To account for the differences in sampling probabilities across the clusters and strata, sample weighting was used to adjust for the cluster sampling design using "svy" function in R studio and "svyset" command to match the multistage cluster sampling design method. Results from univariable and multivariable analysis were presented as crude and adjusted odds ratios along with their 95% CIs, respectively (p-value <0.05).

The missing values were imputed using the multiple imputation by chain equation (MICE) methods. The study explored the proportions of missing values and compared the estimates from the full data models

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and the imputed models to see whether there was an observed difference. The multiple imputation was carried on multivariable analysis only [28]

Patient and Public Involvement

The study design was determined by the research team. Participants and the public were not directly involved in the conceptualisation and design of the study. Selection of study participants for the 2018 MIS was done in collaboration with the provincial and district health managers. The public were involved in the participant recruitment for the primary survey. However, since the study used secondary data from the 2018 MIS, patients and the public were not directly involvement in the selection of the variables to be included in the analysis. Rather, the team from Levy Mwanawasa Medical university and National Malaria Elimination Centre decided and agreed on the variables to be included in the analysis. Consequently, permission for access to the dataset used for the analysis was granted by the National Malaria Elimination centre in consultation with the Ministry of Health. After analysis and report writing, the research team held a dissemination meeting and study findings were shared with key stakeholders, including the Levy Mwanawasa Medical University School of Public Health, Ministry of Health and Zambia National Public Health Institute. A final report was also written and shared with the funding organization.

Results

Participants

A summary of the recruitment algorithm of study participants is shown below. A total of 4044 women of reproductive age were eligible to complete the questionnaire. Out of these, 3, 686 (91%) completed the questionnaire; 358 (9%) did not provide consent and were excluded from the study. A total of 1,381 (34%) participants comprising women who delivered after the new IPTp-SP policy was introduced were included into the final sample for analysis (**Supplementary figure 1).**

Demographic characteristics of respondents

Majority (68.9%) of study participants were in the age group 15-29 years; almost one third (30.8%) were in the age group 30-44 years and 0.3% were aged above 45 years. Close to half (48.9%) had completed primary education, 28.2% had secondary school education and 2.8% had gone up to higher education. Most respondents (81.3%) lived in rural areas. With regard to province of residence, 19.1% were from Luapula, 18.0% from Eastern, 17.2% from Western and 4.1% from Copperbelt provinces. One fifth (21.9%) of the study participants were in lowest wealth tertile; 15.6% were in the middle tertile. Concerning religion, more than half (56.8%) of study participants were protestants followed by Catholics

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(22.2%); Muslims constituted 0.1% of the respondents. Majority (97.3%) attended ANC and most (92.5%) took less than four doses of IPTp-SP. Majority (71.3%) took three doses of IPTp-SP, 14.5% took two doses, 7.5% took IPTp-SP 4+ doses, 6.9% took only one dose. The proportions of IPTp-SP uptake increased from IPTp-SP 1 to IPTp-SP 3 and drastically dropped at IPTp-SP 4+. More than half (52.5%) of the study participants had three or more children and 22.2% had two children. Concerning knowledge on malaria prevention measures, most (76.4%) were knowledgeable and only 45.0% were exposed to media messages (**Table 1**).

Table 1: Socio-demographic and clinical characteristics of the study participants (N=1381)

Variable	N (%)
Age(years)	
15-24	678 (49.1)
25-34	497 (36.0)
35+	205 (14.8)
Missing	1 (0.1)
Residence	
Rural	1123 (81.3)
Urban	258 (18.7)
Province	
Central	93 (6.7)
Copperbelt	56 (4.1)
Eastern	249 (18.0)
Luapula	264 (19.1)
Lusaka	87 (6.3)
Muchinga	95 (6.9)
North-Western	90 (6.5)
Northern	120 (8.7)
Southern	90 (6.5)
Western	237 (17.2)
Wealth tertile	
Low	578 (41.8)
Middle	302 (21.9)
High	501 (36.3)
Education level	
Primary	675 (48.9)
Secondary+	428 (31.0)
Missing	278 (20.1)
Religion	
Christian	1092 (79.1)
Non-christian	289 (20.9)

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Parity	
1	348 (25.2)
2	307 (22.2)
3+	725 (52.5)
Missing	1 (0.1)
Got ANC	
Yes	1344 (97.3)
No	35 (2.5)
Missing	2 (0.2)
IPTp-SP Uptake[a]	
1	80 (6.9)
2	167 (14.3)
3	829 (71.3)
4+	87 (7.5)
Exposure to media message	
No	759 (55.0)
Yes	622 (45.0)
Missing	
Knowledge about Malaria prevention	
Not knowledgeable	241 (17.5)
Knowledgeable	1055 (78.4)
Missing	85 (6.1)
Basic Malaria knowledge	
Incorrect	351 (25.4)
Correct	945 (68.4)
Missing	85 (6.2)

[a] The proportions excludes the missing values

Predictors for the uptake of adequate doses of IPTp-SP (4+ doses)

The overall uptake of adequate (4+) doses of IPTp-SP was 7.5%. The uptake of 4+ doses of IPTp-SP decreased by level of education ranging from 9.2% for women with primary education to 4.6% for women with higher education. The same trend was observed across age group, i.e. decrease from 8.5% in 15-24 years age group to 5.5% in age group of 35 and above years. The women from rural area had higher (7.6%) uptake of adequate doses compared to women from urban area (7.2 %). The uptake of adequate doses of SP was highest for women in the low wealth tertile (11.4 %). Also, women who were not exposed to media messages had higher uptake of SP (8.9%) compared to those who were exposed to media messages (5.9%) (Table 2).

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The results of univariate logistic regression analysis (crude odds ratios) show that woman's education level, place of residence, province, wealth tertile, exposure to media messages and knowledge about malaria prevention were significantly associated with the adequate uptake of IPTp-SP. While age group showed no evidence of association with adequate uptake of IPTp-SP. The results in table 2 shows significant lower odds of taking an adequate IPTp-SP among women with at least secondary level of education (0.30, 95%CI 0.15-0.61, p-value=0.001) compared to those with primary level of education. Luapula and Muchinga provinces show significant higher odds of taking an adequate IPTp-SP (13.57, 95%CI 2.98-61.77, p-value=0.001 and 11.50, 95%CI 2.32-56.95, p-value=0.003, respectively) compared to those from Copperbelt. However, this may be due to chance given the low sample size in Copperbelt province which is a reference. This is evidenced by the wide 95% confidence interval, which increases uncertainty.

Women in the middle and high wealth tertile show significant lower odds of taking adequate IPTp-SP (0.35, 95%CI 0.17-0.72, p-value=0.005 and 0.10, 95%CI 0.10-0.20, p-value<0.001, respectively) compared to those in low wealth tertile. Women who were exposed to media messages had significant lower odds of taking an adequate IPTp-SP (0.49, 95%CI 0.28-0.85, p-value=0.011) compared to those who were not exposed. Women who had knowledge about malaria prevention had significant lower odds of taking an adequate IPTp-SP (0.44, 95%CI 0.23-0.86, p-value=0.016) compared to those who had none.

Using backward selection method with p-value threshold of 0.2, the reduced (final) model retained age group, education level, province and wealth quintile. Therefore, after adjusting for age group, education level and wealth quintile, Luapula and Muchinga provinces still showed significant higher (though reduced) odds of taking an adequate IPTp-SP (8.72, 95%CI 1.72-44.26, p-value=0.009 and 6.67, 95%CI 1.19-37.47, p-value=0.031, respectively) compared to those from Copperbelt. And after adjusting for age group, education level and province, only women in the higher wealth tertile had significant lower odds of taking an adequate IPTp-SP (0.32, 95%CI 0.13-0.79, p-value=0.014) compared to those in low wealth tertile.

Comparing AIC, BIC and Pseudo-R2 we have 417.7, 490.2 and 0.09 for the reduced model, and 436.7, 496.3 and 0.08 for the full model, respectively. This suggests that the reduced model is better fitted compared to the full model. This is because the AIC and BIC are lower, and Pseudo-R2 is higher for the reduced model compared to the full model. The proportion of missing values were highest under education level variable which accounted to 20.1%. Comparing estimates of full data model from multivariable analysis and the imputed multivariable analysis, there is no much difference in the estimates

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apart from the fact that the 95% CI are narrower in some instances in imputed model compared to full data model. However, estimates from multiple imputation are only valid when data is at least missing at random (**Table 2).**

Table 2: Predictors for the adequate uptake of IPTp-SP (≥4 doses) during pregnancy in Zambia

Variable	n(weighted)	n(%)	cOR[a]	95% CI[b]	p-value	aOR[c]	95% CI	P-value
Overall	1163	87 (7.5)						
Age group (Years)								
15-24	542	46 (8.5)	1.00			1.00		
25-34	441	31 (7.0)	0.67	0.37-1.21	0.181	0.54	0.26-1.08	0.083
35+	180	10 (5.5)	0.58	0.24-1.35	0.202	0.58	0.23-1.51	0.266
****Education level**								
Primary	542	50 (9.2)	1.00			1.00		
Secondary+	396	18 (4.6)	0.30	0.15-0.61	0.001*	0.55	0.27-1.11	0.093
Residence								
Rural	927	70 (7.6)	1.00					
Urban	219	17 (7.2)	0.22	0.11-0.44	<0.001*			
Province								
Copperbelt	44	2 (4.6)	1.00			1.00		
Central	89	3 (3.4)	2.15	0.28-16.78	0.463	2.03	0.27-15.48	0.493
Eastern	210	11 (5.2)	1.72	0.32-9.35	0.528	1.15	0.19-7.00	0.878
Luapula	196	36(18.4)	13.57	2.98-61.77	0.001*	8.72	1.72-44.26	0.009*
Lusaka	70	0 (0.0)	-	-	-	-	-	-
Muchinga	83	13(15.7)	11.50	2.32-56.95	0.003*	6.67	1.19-37.47	0.031*

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North-western	84	4 (4.8)	2.32	0.38-14.08	0.359	2.08	0.32-13.34	0.441
Northern	111	16(14.4)	8.94	1.86-42.87	0.006	4.13	0.73-23.42	0.109
Southern	80	1 (1.3)	0.82	0.07-9.59	0.873	1.40	0.11-17.90	0.794
Western	196	1 (0.5)	0.53	0.05-6.13	0.608	-	-	-
Wealth tertile								
Low	438	50(11.4)	1.00			1.00		
Middle	259	16 (6.2)	0.35	0.17-0.72	0.005*	0.52	0.19-1.45	0.212
High	466	21 (4.5)	0.10	0.10-0.20	<0.001*	0.32	0.13-0.79	0.014*
Exposure to media messages								
No	607	54 (8.9)	1.00					
Yes	556	33 (5.9)	0.49	0.28-0.85	0.011*			
****Knowledge about malaria prevention**								
Not knowledgeable	180	22(12.2)	1.00					
Knowledgeable	920	60 (6.5)	0.44	0.23-0.86	0.016*			

[a]cOR stands for Crude Odds ratio [b]CI stands for Confidence interval [c]aOR stands for adjusted odds ratio *significant at 5% level **The observations do not add up to the overall sample because the variables have missing values. Note: AIC, BIC and Pseudo-R2 are 417.7, 490.2 and 0.09 for the reduced model, and 436.7, 496.3 and 0.08 for the model which included all the variables (full model) in the table, respectively

Discussion

The study aimed to determine the predictors of IPTp-SP uptake for four or more doses in Zambia. Our findings show that uptake of four or more doses of IPTp-SP was low at 7.5% The place and province of residence were significantly associated with adequate uptake of IPTp-SP doses. Women who were residents of Luapula and Muchinga provinces had higher odds of taking adequate doses with reference

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to those in the Copperbelt province. Conversely, women in the highest wealth tertile were significantly less likely to receive IPTp-SP 4+ doses compared to those in the lowest tertile.

Our findings show an association between IPTp-SP uptake and place of residence. Women from rural provinces such as Muchinga and Luapula showed higher odds of IPTp-SP uptake than those from urban provinces of Copperbelt and Lusaka. The observed variation in the odds of IPTp-SP uptake between the urban and rural provinces could be due to differences in the malaria prevalence among these provinces. For example, Luapula province has a high malaria prevalence of 63% compared to 3% in Lusaka and Southern provinces. The province is rural with many water bodies, enhancing malaria transmission. These factors also make malaria transmission likely to be longer and more intense compared to other provinces. Thus, the province continues to report the largest malaria burden in the country. Women in provinces with low prevalence of malaria may not take adequate IPTp-SP due to low perceived risk [29,30]. On the contrary, women from regions of high level of malaria transmission, may take adequate doses of IPTp-SP due to higher risk perception. In these regions, emphasis on SP uptake during awareness messages could be higher due to the higher risk of contracting malaria. This finding suggests that women in rural areas may consider themselves at higher risk of contracting malaria compared to those in urban areas. Exploratory studies are required to investigate the reasons for variations in uptake of IPTp-SP among different provinces. These findings corroborate those from studies conducted in Uganda [30] and Tanzania [31,32] which showed that variations in IPTp-SP uptake were related to differences in malaria transmission in the regions. The study in Tanzania showed that residents of the Central, Eastern, Southern, Lake regions, Southern highlands and Southwest highlands were significantly associated with the optimal uptake of SP doses compared to the residents of Zanzibar and Northern zones where malaria transmission was low. Similarly, the Uganda study showed that pregnant women residing in Eastern and Coastal regions had higher odds of optimal uptake of SP.

Our findings show that participants who had knowledge about malaria prevention and exposure to media messages had less odds of receiving adequate IPTp-SP doses. These findings contradict the study conducted by Muntayi et al [33] which showed that maternal knowledge on IPTp-SP positively influenced the uptake of the intervention in Tanzania, Cameroon, Zambia and Ghana. The difference between these findings and the current study could be that our study did not assess specifically the knowledge about IPTp-SP and its benefits. Rather, the study focused on knowledge about malaria prevention in general. This calls for more awareness on malaria interventions in general and about the recommended doses of IPTp-SP during pregnancy.

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Moreover, our findings showed no significant association between education level and uptake of IPTp-SP. However, unadjusted analysis showed that women who had secondary level education and above had less odds of taking four or more doses of IPTp-SP compared with those who attained primary education. Our findings contrast previous studies and surveys. Literally, one would expect that having secondary educational level or higher may be of influence on the uptake of the recommended doses of IPTp-SP compared to women with a lower education level. A study which compared MIS results of 12 countries in sub-Saharan Africa [34] found that women with higher education had higher odds of reporting receiving three or more doses of IPTp-SP. The differences in the findings could be as a result of using different methods. It could also be due to selection bias; a large proportion of our study participants were those with primary level education who mainly resided in rural areas.

This study found that women in the highest and middle wealth tertile had less odds of taking four or more doses of IPTp-SP compared to those in the lowest wealth quintile. This finding contradicts previous studies [35,36] which revealed that wealth index has a significant effect on uptake of IPTp-SP. These studies showed that the chances of completing the recommended dose of IPTp-SP increased with increase in wealth index [36]. For example, a study conducted in Senegal found that women in richer or middle wealth tertile were more likely to use the recommended doses of IPTp-SP [36]. The reason for the difference between our findings and these studies could be due to confounding by place of residence. Our findings show that most study participants who took four or more doses of IPTp-SP were from the rural areas who are mostly in the low wealth tertile. The other reason could be the fact that IPTp-SP is provided for free in Zambia.

There was no significant associations noted between age and taking four or more doses of IPTp-SP. However, the adjusted analysis showed that, compared to the youthful mothers (15 to 24 years), those aged between 25 and 34 years were less likely to take four or more doses of IPTp-SP. This finding contradicts previous studies [36,37] which revealed that younger women are less likely to use health services due to inadequate access to information and communication channels used for IPTp-SP promotion which are necessary for the uptake of IPTp-SP. For example, a study conducted in Ghana [37] reported low uptake of the recommended dose of IPTp-SP among the youth. Many youth often hide their pregnancies and start their ANC late, when they cannot take the recommended doses before delivery.

This study further reports that the uptake of four or more doses of IPTp-SP during pregnancy is still low at 7.5%. Most women (71.3%) took up to the third dose of IPTp-SP during pregnancy. This finding could be due to lack of awareness about the new guidelines on the fourth dose. More emphasis is needed on

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the new guidelines and taking at least three or more doses of IPTp-SP. Health messages should focus on and emphasise the new policy on four or more doses in the country. This finding is similar to other studies in sub-Saharan Africa which reported low uptake of the recommended doses of IPTp-SP [38] and suggests an urgent need for strategies to increase IPTp-SP coverage for improved maternal and newborn health outcomes in the region. This may contribute to the achievement of the ambitious sustainable development goals (SDG) and the target of reducing maternal mortality rate (MMR) from 319 to 70 per 100,000 live births [38-44].

Study limitations

This study has potential limitations. First, we did not collect the data, but used secondary data from the 2018 MIS. This prevented the team from having any control over the measurement and selection of the variables. Some important variables that would have been of interest such as distance from the health facility to the communities where people live, stocks of SP, timing of ANC and number of times the woman attended ANC were not contained in the data set and thus could not be analysed. Further, the MIS data were cross-sectional, the associations in this study cannot guarantee any causation or directionality.

Despite these limitations, we believe our findings have provided important information on the low coverage of four or more doses of IPTp-SP and the associated factors. In addition, use of a nationally presentative data from the 2018 MIS that covered all the provinces increases the generalisability of our findings.

Conclusion

These findings confirm low uptake of four or more doses of IPTp-SP in Zambia at 7.5% and that province and place of residence and wealth tertile affect IPTp-SP uptake. Strategies and interventions should focus on increased coverage of IPTp-SP from the current very low levels, with emphasis on provinces with much higher malaria burden where the risk is greatest and the ability to afford health care lowest. Interventions should include dissemination messages on the new policy of four or more doses of IPTp-SP and the benefits of strengthening the linkage between IPTp-SP program with ANC services.

Figure Legend/Caption

Figure 1 : Participant recruitment algorithm

Authors' Contribution

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DS, CS, and NM contributed to the conception of the study and literature search. DS conducted the extraction, analysis and drafted the manuscript. CS, NM, BH LSM and HM contributed to the coordination study activities. CS, NM, BH contributed to the revision of the manuscript. All authors read and approved the manuscript.

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Competing Interests

All authors declare that they have no conflicting interests in this work

Ethics approval

Ethical approval and waiver of consent was given by ERES converge IRB (Ref No. 2021-Nov-004). Permission to conduct the study and access to the 2018 MIS dataset was granted by the National Health Research Authority (NRFA) Ref No. NHRA000023/04/03/2022) and Ministry of Health, respectively. The dataset was then secured as soft copy in the computer. No information regarding names of study participants was obtained and used; the dataset was only used for the purpose of this study and it was not given to any other person or organization. No harm was inflicted to the participants, the study used secondary data and there was no direct contact with study participants.

Data Sharing

Data are available upon reasonable request from the corresponding author and with permission of the ERES ethics review board.

Costs and payments

N/A

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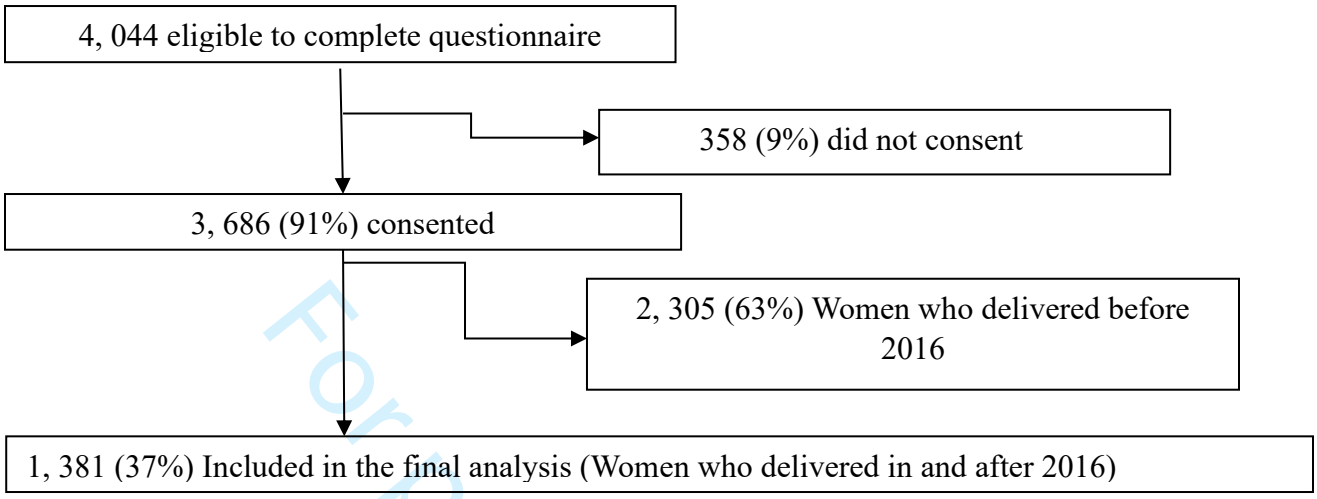
Figure 1: Participant recruitment algorithm



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STROBE Statement—Checklist of items that should be included in reports of descriptive studies

Item	Recommendation	Page
Title and abstract	Indicate the study's design with a commonly used term in the title or the abstract	1
	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction		
Background/rationale	Explain the scientific background and rationale for the investigation being reported	4
Objectives	State specific objectives, including any pre-specified hypotheses	5
Methods		
Study design	Present key elements of study design early in the paper	5
Setting	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
Study size	Explain how the study size was arrived at	7
Variables	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Statistical methods	Describe all statistical methods, including those used to control for confounding	8
	If applicable, explain how loss to follow-up was addressed	
Patient and public involvement		8
Results		
Participants	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage Participants (c) Consider use of a flow diagram	9
Descriptive statistics	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Descriptive data (b) Indicate number of participants with missing data for each variable of interest	9
Main results		10
Discussion		14

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Uptake of Four or More Doses of Sulfadoxine Pyrimethamine for Intermittent Preventive Treatment of Malaria during Pregnancy in Zambia: Findings from the 2018 Malaria in Pregnancy Survey

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Uptake of Four or More Doses of Sulfadoxine Pyrimethamine for Intermittent Preventive Treatment of Malaria during Pregnancy in Zambia: Findings from the 2018 Malaria in Pregnancy Survey

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Abstract

Objective: To determine the prevalence and predictors of the uptake of four or more doses of sulfadoxine pyrimethamine (IPTp-SP 4+) in Zambia.

Design: A cross-sectional study using secondary data from the malaria in pregnancy survey (MIS) dataset conducted from April to May 2018.

Setting: The primary survey was conducted at community level and covered all the ten provinces of Zambia.

Participants: A total of 3, 686 women of reproductive age (15 to 45 years) who gave birth within the five years before the survey.

Primary outcome: Proportion of participants with four or more doses of IPTp-SP

Statistical analysis: All analyses were conducted using R-studio statistical software version 4.2.1. Descriptive statistics were computed to summarise participant characteristics and IPTp-SP uptake. Univariate logistic regression was carried out to determine association between the explanatory and outcome variables. Explanatory variables with a p-value less than 0.20 on univariate analysis were included in the multivariable logistic regression model and crude and adjusted odds ratios (AORs) along with their 95% confidence intervals (CIs) were computed ($p<0.05$).

Results: Of the total sample of 1,163, only 7.5% of participants received IPTp-SP 4+. Province of residence and wealth tertile were associated with uptake of IPTp-SP doses; participants from Luapula (aOR=8.72, 95%CI [1.72—44.26, p=0.009]) and Muchinga (aOR=6.67, 95%CI [1.19—37.47, p=0.031]) provinces were more likely to receive IPTp-SP 4+ compared to those from Copperbelt province. Conversely, women in the highest wealth tertile were less likely to receive IPTp-SP 4+ doses compared to those in the lowest quintile (aOR=0.32; 95%CI [0.13—0.79, p=0.014])

Conclusion: These findings confirm a low uptake of four or more doses of IPTp-SP in the country. Strategies should focus on increased coverage of IPTp-SP in provinces with much higher malaria burden where the risk is greatest and the ability to afford health care lowest.

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Word count: 295

Key words: Malaria in Pregnancy, Intermittent Preventive Treatment, Uptake, Policy, Zambia.

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Strengths and weakness

- Use of large dataset from the 2018 malaria in pregnancy (MIP) survey with a nationally representative sample reduced selection bias and increased external validity and generalisability of the findings .
- Use of multi-stage random sampling technique reduced selection bias and increased validity of the findings
- Inclusion into analysis only women of reproductive age who gave birth after the new IPTp-SP policy was introduced reduced information bias and increased internal validity of the study
- Use of secondary data limited the choice of variables to be included in the analysis
- Exclusion of participants with incomplete data could have reduced the power of the study

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Introduction

Globally, there are an estimated 247 million cases of malaria reported from 84 malaria-endemic countries, with the majority (95%) being reported from the world health organisation (WHO) African Region. Sub-Sahara Africa is disproportionately affected, accounting for an estimated 350 to 500 million cases, 1 to 3 million deaths, 10,000 maternal and 200,000 neonatal deaths per year [1,2]. With an estimated 125 million pregnant women being at risk of contracting malaria globally, malaria in pregnancy (MIP) remains an important preventable cause of adverse maternal, neonatal health outcomes worldwide [3-5]. Out of an estimated 50 million annual pregnancies in malaria-endemic countries around the world each year, more than 50% of these live in the tropical areas of Africa where there is a high transmission of *P. falciparum [*6,7*]* .

Malaria is a parasitic disease caused by a protozoon of the genus Plasmodium. Although there are species of malaria that infect humans— *Plasmodium falciparum*, *P. malariae, P.ovale*, *P.vivax and P. knowlesi*— two main species*, P. falciparum and P. vivax,* pose the greatest risk and contribute to adverse outcomes. *P. falciparum* is the deadliest malaria parasite and the most prevalent on the African continent [7,8]. Malaria parasites contribute to adverse pregnancy and birth outcomes due to their preferential accumulation in placental intervillous spaces, putting pregnant women and their babies at an increased risk. MIP is associated with anaemia, miscarriage, premature birth, stillbirth, congenital infection, low birth weight (lbw), maternal, foetal and perinatal death; one in four women have evidence of placental infection at the time of delivery [7-9]. Moreover, evidence from previous studies shows that lbw is associated with a marked increase in infant mortality, high rates of cognitive impairment, learning disability, and behavioural problems [9-12].

Zambia is a sub-Saharan African country with a high malaria burden with an approximate 5.2 million annual malaria cases and an estimated 200,000 pregnancies being at risk of malaria [13]. The Zambia National Malaria Elimination Centre (NMEC) in line with WHO strategic framework of malaria prevention and control during pregnancy has developed and is implementing an MIP policy which includes the provision of four or more doses of intermittent preventive treatment of malaria during pregnancy with sulfadoxine pyrimethamine (IPTp-SP) [14]. Other interventions are insecticide treated nets (ITNs), in-door residual spraying (IRS) and case management.

IPTp-SP and ITN interventions are being implemented as part of antenatal care (ANC) services [15] and involve administration of sulfadoxine pyrimethamine (SP) (comprising three tablets containing 500 mg/25 mg SP, giving the total required dosage of 1500 mg/75 mg SP) as direct observed therapy (DOT) to pregnant women. The first IPTp-SP dose is administered during the second trimester, 13-16 gestation

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weeks, followed by monthly doses until delivery for at least four doses. ANC has been identified to provide a good platform for regular and close contact between pregnant women and skilled health personnel for improved service delivery and monitoring. Zambia follows the 2016 WHO ANC model which recommends a minimum of 8 ANC contacts with the first contact scheduled to take place in the first trimester, two contacts in the second trimester and five contacts scheduled in the third trimester [15, 16].

Administration of IPTp-SP is based on the assumption that every pregnant woman living in a high malaria transmission area has malaria parasites. The parasites live in blood or placenta, whether or not she has symptoms and signs of malaria [17,18]. Previous studies in Zambia and elsewhere have provided evidence on the effectiveness of IPTp-SP on improved maternal and new-born health outcomes. In Zambia, administration of two or more doses of IPTp-SP showed a decrease in low birthweight among paucigravid and multigravid women compared to one dose [19]. A study conducted in Mali [20] showed that addition of a third dose of IPTp-SP led to a reduced risk of placental malaria, low birth weight and preterm births in all gravidae, compared with the standard two dose regimen. A systematic review and meta-analysis on Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa by Kayentao and colleagues [21] showed that three or more doses were associated with a 3.3% reduction in low birth weight, 3.1% reduction in placental malaria and 1.4% reduction in moderate to severe maternal anaemia.

However, the 2018 MIS report [22] shows that the proportion of pregnant women receiving four or more doses of doses of IPTp-SP is low at 5%. The reasons for the low coverage of IPTp-SP are not clear. Limited studies have been conducted on the predictors of the uptake of four or more doses of SP in Zambia. The reasons for the low coverage of IPTp-SP are not clear. Limited studies have been conducted on the predictors of the uptake of four or more doses of SP in Zambia.

Objectives

The aim of this study was to determine the prevalence and predictors of the uptake of four or more doses of IPTp-SP in Zambia. Information is required to inform policy and programming to improve uptake of SP in the country.

Methods

Study design

The present study is a secondary analysis of the 2018 Malaria indicator survey done in Zambia. It was a cross section survey conducted from April to May, 2018. The survey is periodically done to assess the malaria burden and coverages of key malaria interventions such as vector control, parasite clearance,

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health promotion, enhanced surveillance, monitoring, evaluation and research, health system capacity, financing and case management in the general population including MIP. The MIS 2018 was the latest comprehensive dataset that was representative of the whole country and readily accessible at the time of writing the manuscript.

Study site

The study used the 2018 MIS survey data which covered all the ten provinces of Zambia, making it nationally representative. The country is divided into ten provinces that are further divided into districts. For statistical purposes, each district is subdivided into census supervisory areas (CSAs) which are in turn subdivided into enumeration areas (EAs). The listing of EAs has information on the number of households and the populations. Zambia is a sub-Saharan African country located in south-central Africa with a surface area of 752,614 square kilometres. Lusaka, the capital city, is located in the south-central part of the country [23]. The topography is characterised by a high plateau, river valleys, and water bodies. The country derives its name from the Zambezi River, which drains all but a small northern part of the country. It has a tropical climate with the rainy season occurring during October to April. The climate is suitable for mosquito breeding and malaria transmission takes place throughout the year but peaks during the rainy season [24,25]. Zambia's population as of 8th September 2022 was 19,610,769. The male population was 9,603,056 and the female population was 10,007,713 [26].

Study participants and procedures

Study participants were women of reproductive age who participated in the 2018 MIS. The country conducts MIS surveys every two to three years to provide updates on malaria interventions and disease burden in the country. A total of 3, 686 women of reproductive age who gave birth in the past five years participated in the 2018 MIS. From this sample, a total of 1, 381 were included in our analysis.

Inclusion criteria.

To be included in the study, participants needed to be:

- Pregnant women who were pregnant in the past two years and five months after the new 2016 policy on the fourth dose IPTp-SP was implemented
- All women aged between 15 to 49 years from all the ten provinces

Women who did not give consent and those who did not complete the individual questionnaires were not included in the analysis.

Sample size estimation

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The study participants in the main survey were selected using a two-stage cluster sampling technique which are based on a nationally representative sample of 4,177 households from 179 standard enumeration areas (SEAs) randomly selected from all ten provinces. Based on these criteria, at least 2,176 households were required in the rural domain. For further details on the 2018 MIS sampling technique and sample size determination see the 2018 MIS published report by the Zambian ministry of health.

Assumptions for the sample size determination were;

- 95% confidence interval
- 80% power
- design effect of 2.50
- Z-score of 1.96
- 10% relative standard error
- Margin of error of 2%
- 20% adjustment for non-response

The estimated minimum sample size in this study was determined by the formula below;

$$n=\frac{z^2 x\, p(1-p)(DEFF)}{d^2} = 1141 \ (25)$$

Where: n is the calculated sample size, z =1.96 is the statistic that defines the level of confidence required, p=0.05 is a prevalence of uptake of IPTp-SP among pregnant women in Zambia, expressed as a proportion of that population

D=0.02 is the desired level of precision, DEFF=2.5 is the design effect [27].

Variables

The variables for the study were as follows:

- Outcome variable: uptake of four or more doses of IPTp-SP
- Predictor variables: sociodemographic variables (age, parity, place and province of residence, religion, educational level, wealth index)
- Basic knowledge about malaria
- Knowledge about malaria treatment

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The predictor variables were selected based on thorough literature review. In this study uptake means receiving any dosage of SP during pregnancy, with each dose being given at least 1 month apart starting from the second trimester of gestation, until the time of delivery as directly observed therapy.

Data sources and processing

The merged 2018 MIS dataset comprising women of reproductive age (15 to 49 years) was extracted into the Microsoft office excel sheet 2013 using the data extraction tool. We subset women 15 to 49 years of age who were eligible to complete the questionnaire. From the eligible women, we subsetted women who consented. Further, a subset of women who completed the questionnaire and delivered in 2016 or later (after the new IPTp policy) was done using the lubridate library in R Studio. This was determined by using the age of the youngest child (that is, if a child was less than 881 days).

Statistical analysis

R-studio statistical software version 4.2.1. was used for all the analyses. Descriptive statistical analysis was carried out first on socio-demographics to obtain frequencies and proportions. The proportion of missing values on the outcome was calculated. The correlation among the predictor variables was explored. Thereafter, univariate logistic regression was carried out and explanatory variables whose p-values were less than 0.2 were presented in table 2. The estimators with a p-value level of 0.20 chose the adjusted estimate more frequently when confounding is present and so produced less bias than the estimators with a p-value level of 0.05 [28]. Then, a backward selection approach using stepwise method with a p-value of 0.2 threshold was used to select explanatory variables to be included in the multivariable logistic regression for further analysis of the association to obtain adjusted odds ratios. We also compared Akaike's Information Criteria (AIC), Bayesian Information Criteria (BIC) and Pseudo-R2 between the multivariable model which included all variables (full model) and the model after backward selection approach (reduced model) for model fit. To account for the differences in sampling probabilities across the clusters and strata, sample weighting was used to adjust for the cluster sampling design using "svy" function in R studio and "svyset" command to match the multistage cluster sampling design method. Results from univariable and multivariable analysis were presented as crude and adjusted odds ratios along with their 95% CIs, respectively (p-value <0.05).

The missing values were imputed using the multiple imputation by chain equation (MICE) methods. The study explored the proportions of missing values and compared the estimates from the full data models

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and the imputed models to see whether there was an observed difference. The multiple imputation was carried on multivariable analysis only [28]

Patient and Public Involvement

The study design was determined by the research team. Participants and the public were not directly involved in the conceptualisation and design of the study. Selection of study participants for the 2018 MIS was done in collaboration with the provincial and district health managers. The public were involved in the participant recruitment for the primary survey. However, since the study used secondary data from the 2018 MIS, patients and the public were not directly involved in the selection of the variables to be included in the analysis. Rather, the team from Levy Mwanawasa Medical university and National Malaria Elimination Centre decided and agreed on the variables to be included in the analysis. Consequently, permission for access to the dataset used for the analysis was granted by the National Malaria Elimination centre in consultation with the Ministry of Health. After analysis and report writing, the research team held a dissemination meeting and study findings were shared with key stakeholders, including the Levy Mwanawasa Medical University School of Public Health, Ministry of Health and Zambia National Public Health Institute. A final report was also written and shared with the funding organization.

Results

Participants

A summary of the recruitment algorithm of study participants is shown below. A total of 4044 women of reproductive age were eligible to complete the questionnaire. Out of these, 3, 686 (91%) completed the questionnaire; 358 (9%) did not provide consent and were excluded from the study. A total of 1,381 (34%) participants comprising women who delivered after the new IPTp-SP policy was introduced were included into the final sample for analysis (**Supplementary figure 1).**

Demographic characteristics of respondents

Majority (68.9%) of study participants were in the age group 15-29 years; almost one third (30.8%) were in the age group 30-44 years and 0.3% were aged above 45 years. Close to half (48.9%) had completed primary education, 28.2% had secondary school education and 2.8% had gone up to higher education. Most respondents (81.3%) lived in rural areas. With regard to province of residence, 19.1% were from Luapula, 18.0% from Eastern, 17.2% from Western and 4.1% from Copperbelt provinces. One fifth (21.9%) of the study participants were in lowest wealth tertile; 15.6% were in the middle tertile. Concerning religion, more than half (56.8%) of study participants were protestants followed by Catholics

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(22.2%); Muslims constituted 0.1% of the respondents. Majority (97.3%) attended ANC and most (92.5%) took less than four doses of IPTp-SP. Majority (71.3%) took three doses of IPTp-SP, 14.5% took two doses, 7.5% took IPTp-SP 4+ doses, 6.9% took only one dose. The proportions of IPTp-SP uptake increased from IPTp-SP 1 to IPTp-SP 3 and drastically dropped at IPTp-SP 4+. More than half (52.5%) of the study participants had three or more children and 22.2% had two children. Concerning knowledge on malaria prevention measures, most (76.4%) were knowledgeable and only 45.0% were exposed to media messages (**Table 1**).

Table 1: Socio-demographic and clinical characteristics of the study participants (N=1381)

Variable	N (%)
Age(years)	
15-24	678 (49.1)
25-34	497 (36.0)
35+	205 (14.8)
Missing	1 (0.1)
Residence	
Rural	1123 (81.3)
Urban	258 (18.7)
Province	
Central	93 (6.7)
Copperbelt	56 (4.1)
Eastern	249 (18.0)
Luapula	264 (19.1)
Lusaka	87 (6.3)
Muchinga	95 (6.9)
North-Western	90 (6.5)
Northern	120 (8.7)
Southern	90 (6.5)
Western	237 (17.2)
Wealth tertile	
Low	578 (41.8)
Middle	302 (21.9)
High	501 (36.3)
Education level	
Primary	675 (48.9)
Secondary+	428 (31.0)
Missing	278 (20.1)
Religion	
Christian	1092 (79.1)
Non-Christian	289 (20.9)

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Parity	
1	348 (25.2)
2	307 (22.2)
3+	725 (52.5)
Missing	1 (0.1)
Got ANC	
Yes	1344 (97.3)
No	35 (2.5)
Missing	2 (0.2)
IPTp-SP Uptake[a]	
1	80 (6.9)
2	167 (14.3)
3	829 (71.3)
4+	87 (7.5)
Exposure to media message	
No	759 (55.0)
Yes	622 (45.0)
Missing	
Knowledge about Malaria prevention	
Not knowledgeable	241 (17.5)
Knowledgeable	1055 (78.4)
Missing	85 (6.1)
Basic Malaria knowledge	
Incorrect	351 (25.4)
Correct	945 (68.4)
Missing	85 (6.2)

[a] The proportions excludes the missing values

Predictors for the uptake of adequate doses of IPTp-SP (4+ doses)

The overall uptake of adequate (4+) doses of IPTp-SP was 7.5%. The uptake of 4+ doses of IPTp-SP decreased by level of education ranging from 9.2% for women with primary education to 4.6% for women with higher education. The same trend was observed across age group, i.e. decrease from 8.5% in 15-24 years age group to 5.5% in age group of 35 and above years. The women from rural area had higher (7.6%) uptake of adequate doses compared to women from urban area (7.2 %). The uptake of adequate doses of SP was highest for women in the low wealth tertile (11.4 %). Also, women who were not exposed to media messages had higher uptake of SP (8.9%) compared to those who were exposed to media messages (5.9%) (Table 2).

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The results of univariate logistic regression analysis (crude odds ratios) show that woman's education level, place of residence, province, wealth tertile, exposure to media messages and knowledge about malaria prevention were significantly associated with the adequate uptake of IPTp-SP. While age group showed no evidence of association with adequate uptake of IPTp-SP. The results in table 2 shows significant lower odds of taking an adequate IPTp-SP among women with at least secondary level of education (0.30, 95%CI 0.15-0.61, p-value=0.001) compared to those with primary level of education. Luapula and Muchinga provinces show significant higher odds of taking an adequate IPTp-SP (13.57, 95%CI 2.98-61.77, p-value=0.001 and 11.50, 95%CI 2.32-56.95, p-value=0.003, respectively) compared to those from Copperbelt. However, this may be due to chance given the low sample size in Copperbelt province which is a reference. This is evidenced by the wide 95% confidence interval, which increases uncertainty.

Women in the middle and high wealth tertile show significant lower odds of taking adequate IPTp-SP (0.35, 95%CI 0.17-0.72, p-value=0.005 and 0.10, 95%CI 0.10-0.20, p-value<0.001, respectively) compared to those in low wealth tertile. Women who were exposed to media messages had significant lower odds of taking an adequate IPTp-SP (0.49, 95%CI 0.28-0.85, p-value=0.011) compared to those who were not exposed. Women who had knowledge about malaria prevention had significant lower odds of taking an adequate IPTp-SP (0.44, 95%CI 0.23-0.86, p-value=0.016) compared to those who had none.

Using backward selection method with p-value threshold of 0.2, the reduced (final) model retained age group, education level, province and wealth quintile. Therefore, after adjusting for age group, education level and wealth quintile, Luapula and Muchinga provinces still showed significant higher (though reduced) odds of taking an adequate IPTp-SP (8.72, 95%CI 1.72-44.26, p-value=0.009 and 6.67, 95%CI 1.19-37.47, p-value=0.031, respectively) compared to those from Copperbelt. And after adjusting for age group, education level and province, only women in the higher wealth tertile had significant lower odds of taking an adequate IPTp-SP (0.32, 95%CI 0.13-0.79, p-value=0.014) compared to those in low wealth tertile.

Comparing AIC, BIC and Pseudo-R2 we have 417.7, 490.2 and 0.09 for the reduced model, and 436.7, 496.3 and 0.08 for the full model, respectively. This suggests that the reduced model is better fitted compared to the full model. This is because the AIC and BIC are lower, and Pseudo-R2 is higher for the reduced model compared to the full model. The proportion of missing values were highest under education level variable which accounted to 20.1%. Comparing estimates of full data model from multivariable analysis and the imputed multivariable analysis, there is no much difference in the estimates

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apart from the fact that the 95% CI are narrower in some instances in imputed model compared to full data model. However, estimates from multiple imputation are only valid when data is at least missing at random (**Table 2).**

Table 2: Predictors for the adequate uptake of IPTp-SP (≥4 doses) during pregnancy in Zambia

Variable	n(weighted)	n(%)	cOR[a]	95% CI[b]	p-value	aOR[c]	95% CI	P-value
Overall	1163	87 (7.5)						
Age group (Years)								
15-24	542	46 (8.5)	1.00			1.00		
25-34	441	31 (7.0)	0.67	0.37-1.21	0.181	0.54	0.26-1.08	0.083
35+	180	10 (5.5)	0.58	0.24-1.35	0.202	0.58	0.23-1.51	0.266
****Education level**								
Primary	542	50 (9.2)	1.00			1.00		
Secondary+	396	18 (4.6)	0.30	0.15-0.61	0.001*	0.55	0.27-1.11	0.093
Residence								
Rural	927	70 (7.6)	1.00					
Urban	219	17 (7.2)	0.22	0.11-0.44	<0.001*			
Province								
Copperbelt	44	2 (4.6)	1.00			1.00		
Central	89	3 (3.4)	2.15	0.28-16.78	0.463	2.03	0.27-15.48	0.493
Eastern	210	11 (5.2)	1.72	0.32-9.35	0.528	1.15	0.19-7.00	0.878
Luapula	196	36(18.4)	13.57	2.98-61.77	0.001*	8.72	1.72-44.26	0.009*
Lusaka	70	0 (0.0)	-	-	-	-	-	-
Muchinga	83	13(15.7)	11.50	2.32-56.95	0.003*	6.67	1.19-37.47	0.031*

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North-western	84	4 (4.8)	2.32	0.38-14.08	0.359	2.08	0.32-13.34	0.441
Northern	111	16(14.4)	8.94	1.86-42.87	0.006	4.13	0.73-23.42	0.109
Southern	80	1 (1.3)	0.82	0.07-9.59	0.873	1.40	0.11-17.90	0.794
Western	196	1 (0.5)	0.53	0.05-6.13	0.608	-	-	-
Wealth tertile								
Low	438	50(11.4)	1.00			1.00		
Middle	259	16 (6.2)	0.35	0.17-0.72	0.005*	0.52	0.19-1.45	0.212
High	466	21 (4.5)	0.10	0.10-0.20	<0.001*	0.32	0.13-0.79	0.014*
Exposure to media messages								
No	607	54 (8.9)	1.00					
Yes	556	33 (5.9)	0.49	0.28-0.85	0.011*			
****Knowledge about malaria prevention**								
Not knowledgeable	180	22(12.2)	1.00					
Knowledgeable	920	60 (6.5)	0.44	0.23-0.86	0.016*			

[a]cOR stands for Crude Odds ratio [b]CI stands for Confidence interval [c]aOR stands for adjusted odds ratio *significant at 5% level **The observations do not add up to the overall sample because the variables have missing values. Note: AIC, BIC and Pseudo-R2 are 417.7, 490.2 and 0.09 for the reduced model, and 436.7, 496.3 and 0.08 for the model which included all the variables (full model) in the table, respectively

Discussion

The study aimed to determine the predictors of IPTp-SP uptake for four or more doses in Zambia. Our findings show that uptake of four or more doses of IPTp-SP was low at 7.5% The place and province of residence were significantly associated with adequate uptake of IPTp-SP doses. Women who were residents of Luapula and Muchinga provinces had higher odds of taking adequate doses with reference

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to those in the Copperbelt province. Conversely, women in the highest wealth tertile were significantly less likely to receive IPTp-SP 4+ doses compared to those in the lowest tertile.

Our findings show an association between IPTp-SP uptake and place of residence. Women from rural provinces such as Muchinga and Luapula showed higher odds of IPTp-SP uptake than those from urban provinces of Copperbelt and Lusaka. The observed variation in the odds of IPTp-SP uptake between the urban and rural provinces could be due to differences in the malaria prevalence among these provinces. For example, Luapula province has a high malaria prevalence of 63% compared to 3% in Lusaka and Southern provinces. The province is rural with many water bodies, enhancing malaria transmission. These factors also make malaria transmission likely to be longer and more intense compared to other provinces. Thus, the province continues to report the largest malaria burden in the country. Women in provinces with low prevalence of malaria may not take adequate IPTp-SP due to low perceived risk [29,30]. On the contrary, women from regions of high level of malaria transmission, may take adequate doses of IPTp-SP due to higher risk perception. In these regions, emphasis on SP uptake during awareness messages could be higher due to the higher risk of contracting malaria. This finding suggests that women in rural areas may consider themselves at higher risk of contracting malaria compared to those in urban areas. Exploratory studies are required to investigate the reasons for variations in uptake of IPTp-SP among different provinces. These findings corroborate those from studies conducted in Uganda [30] and Tanzania [31,32] which showed that variations in IPTp-SP uptake were related to differences in malaria transmission in the regions. The study in Tanzania showed that residents of the Central, Eastern, Southern, Lake regions, Southern highlands and Southwest highlands were significantly associated with the optimal uptake of SP doses compared to the residents of Zanzibar and Northern zones where malaria transmission was low. Similarly, the Uganda study showed that pregnant women residing in Eastern and Coastal regions had higher odds of optimal uptake of SP.

Our findings show that participants who had knowledge about malaria prevention and exposure to media messages had less odds of receiving adequate IPTp-SP doses. These findings contradict the study conducted by Muntayi et al [33] which showed that maternal knowledge on IPTp-SP positively influenced the uptake of the intervention in Tanzania, Cameroon, Zambia and Ghana. The difference between these findings and the current study could be that our study did not assess specifically the knowledge about IPTp-SP and its benefits. Rather, the study focused on knowledge about malaria prevention in general. This calls for more awareness on malaria interventions in general and about the recommended doses of IPTp-SP during pregnancy.

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Moreover, our findings showed no significant association between education level and uptake of IPTp-SP. However, unadjusted analysis showed that women who had secondary level education and above had less odds of taking four or more doses of IPTp-SP compared with those who attained primary education. Our findings contrast previous studies and surveys. Literally, one would expect that having secondary educational level or higher may be of influence on the uptake of the recommended doses of IPTp-SP compared to women with a lower education level. A study which compared MIS results of 12 countries in sub-Saharan Africa [34] found that women with higher education had higher odds of reporting receiving three or more doses of IPTp-SP. The differences in the findings could be as a result of using different methods. It could also be due to selection bias; a large proportion of our study participants were those with primary level education who mainly resided in rural areas.

This study found that women in the highest and middle wealth tertile had less odds of taking four or more doses of IPTp-SP compared to those in the lowest wealth tertile. This finding contradicts previous studies [35,36] which revealed that wealth index has a significant effect on uptake of IPTp-SP. These studies showed that the chances of completing the recommended dose of IPTp-SP increased with increase in wealth index [36]. For example, a study conducted in Senegal found that women in richer or middle wealth tertile were more likely to use the recommended doses of IPTp-SP [36]. The reason for the difference between our findings and these studies could be due to confounding by place of residence. Our findings show that most study participants who took four or more doses of IPTp-SP were from the rural areas who are mostly in the low wealth tertile. The other reason could be the fact that IPTp-SP is provided for free in Zambia.

There was no significant association noted between age and taking four or more doses of IPTp-SP. However, the adjusted analysis showed that, compared to the youthful mothers (15 to 24 years), those aged between 25 and 34 years were less likely to take four or more doses of IPTp-SP. This finding contradicts previous studies [36,37] which revealed that younger women are less likely to use health services due to inadequate access to information and communication channels used for IPTp-SP promotion which are necessary for the uptake of IPTp-SP. For example, a study conducted in Ghana [37] reported low uptake of the recommended dose of IPTp-SP among the youth. Many youth often hide their pregnancies and start their ANC late, when they cannot take the recommended doses before delivery.

This study further reports that the uptake of four or more doses of IPTp-SP during pregnancy is still low at 7.5%. Most women (71.3%) took up to the third dose of IPTp-SP during pregnancy. This finding could be due to lack of awareness about the new guidelines on the fourth dose. More emphasis is needed on

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the new guidelines and taking at least three or more doses of IPTp-SP. Health messages should focus on and emphasise the new policy on four or more doses in the country. This finding is similar to other studies in sub-Saharan Africa which reported low uptake of the recommended doses of IPTp-SP [38] and suggests an urgent need for strategies to increase IPTp-SP coverage for improved maternal and newborn health outcomes in the region. This may contribute to the achievement of the ambitious sustainable development goals (SDG) and the target of reducing maternal mortality rate (MMR) from 319 to 70 per 100,000 live births [38-44].

Study limitations

This study has potential limitations. First, we did not collect the data, but used secondary data from the 2018 MIS. This prevented the team from having control over the measurement and selection of the variables. Some important variables that would have been of interest such as distance from the health facility to the communities where people live, stocks of SP, timing of ANC and number of times the woman attended ANC were not contained in the data set and thus could not be analysed. Further, the MIS data were cross-sectional, the associations in this study cannot guarantee causation or directionality.

Despite these limitations, we believe our findings have provided important information on the low coverage of four or more doses of IPTp-SP and the associated factors. In addition, use of a nationally representative data from the 2018 MIS that covered all the provinces increases the generalisability of our findings.

Conclusion

These findings confirm low uptake of four or more doses of IPTp-SP in Zambia at 7.5% and that province and place of residence and wealth tertile affect IPTp-SP uptake. Strategies and interventions should focus on increased coverage of IPTp-SP from the current very low levels, with emphasis on provinces with much higher malaria burden where the risk is greatest and the ability to afford health care lowest. Interventions should include dissemination messages on the new policy of four or more doses of IPTp-SP and the benefits of strengthening the linkage between IPTp-SP program with ANC services.

Figure Legend/Caption

Supplementary figure 1 : Participant recruitment algorithm

Authors' Contribution

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DS, CS, and NM contributed to the conception of the study and literature search. DS conducted the extraction, analysis and drafted the manuscript. CS, NM, BH LSM and HM contributed to the coordination study activities. CS, NM, BH contributed to the revision of the manuscript. All authors read and approved the manuscript.

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Competing Interests

All authors declare that they have no conflicting interests in this work

Ethics approval

Ethical approval and waiver of consent was given by ERES converge IRB (Ref No. 2021-Nov-004). Permission to conduct the study and access to the 2018 MIS dataset was granted by the National Health Research Authority (NRFA) Ref No. NHRA000023/04/03/2022) and Ministry of Health, respectively. The dataset was then secured as soft copy in the computer. No information regarding names of study participants was obtained and used; the dataset was only used for the purpose of this study and it was not given to any other person or organization. No harm was inflicted to the participants, the study used secondary data and there was no direct contact with study participants.

Data Sharing

Data are available upon reasonable request from the corresponding author and with permission of the ERES ethics review board.

Costs and payments

N/A

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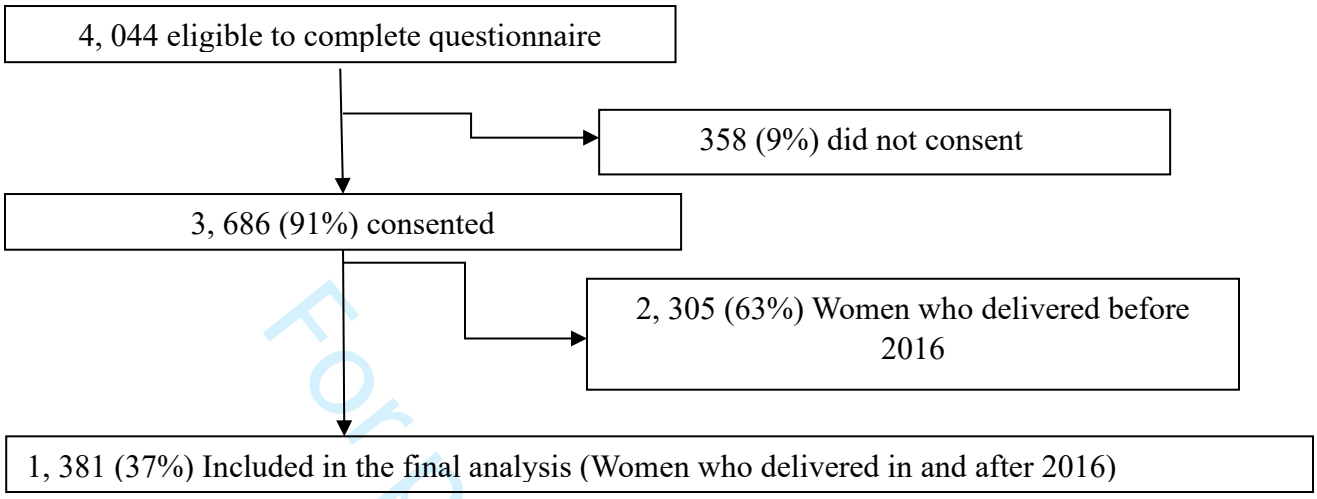
Figure 1: Participant recruitment algorithm



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STROBE Statement—Checklist of items that should be included in reports of descriptive studies

Item	Recommendation	Page
Title and abstract	Indicate the study's design with a commonly used term in the title or the abstract	1
	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction		
Background/rationale	Explain the scientific background and rationale for the investigation being reported	4
Objectives	State specific objectives, including any pre-specified hypotheses	5
Methods		
Study design	Present key elements of study design early in the paper	5
Setting	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
Study size	Explain how the study size was arrived at	7
Variables	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Statistical methods	Describe all statistical methods, including those used to control for confounding	8
	If applicable, explain how loss to follow-up was addressed	
Patient and public involvement		8
Results		
Participants	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage Participants (c) Consider use of a flow diagram	9
Descriptive statistics	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Descriptive data (b) Indicate number of participants with missing data for each variable of interest	9
Main results		10
Discussion		14

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