#### ORIGINAL RESEARCH ARTICLE

# Factors Influencing the Use of Anemia Preventing Measures among Antenatal Clinic Attendees in the Kintampo North Municipality, Ghana

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#### Abstract

Anemia in pregnancy is a key public health problem worldwide. It results from a wide variety of causes. The World Health Organization (WHO) has recommended specific measures to help prevent anemia during pregnancy, which countries are required to integrate into their antenatal care. This study was designed to determine the factors influencing the use of anaemia preventing measures among antenatal clinic attendees in the Kintampo North Municipality, Ghana. A cross sectional study was conducted among pregnant women attending the clinics after 36 weeks of pregnancy. Demographic data and information on use of all interventions were obtained using a structured questionnaire. The factors associated with the use of the interventions were identified using multiple logistic regression. The use of all anemia preventing interventions among pregnant women was found to be 30%. The study identified that use of all anemia preventing measures among pregnant women is quite low. Provision of antihelmithics to pregnant women and their health education on the benefits of the use of anaemia preventing measures would help increase the usage of the interventions. (*Afr J Reprod Health 2019; 23[2]: 35-43*).

Keywords: Anemia in pregnancy, anemia prevention in pregnancy, Kintampo North, Ghana

#### Résumé

L'anémie pendant la grossesse est un problème majeur de santé publique dans le monde. Il résulte d'une grande variété de causes. L'Organisation mondiale de la santé (OMS) a recommandé certaines mesures pour aider à prévenir l'anémie pendant la grossesse, ce qui oblige les pays à intégrer leurs soins prénatals. Cette étude visait à déterminer les facteurs qui influent sur l'utilisation des mesures de prévention de l'anémie chez les préposés aux consultations prénatales de la municipalité de Kintampo du nord, au Ghana. Une étude transversale a été menée auprès des femmes enceintes à 36 semaines de gestation et au-dessus. Les données démographiques et les informations sur l'utilisation de toutes les interventions ont été obtenues à l'aide d'un questionnaire structuré. Les facteurs associés à l'utilisation des interventions ont été identifiés à l'aide d'une régression logistique multiple. L'utilisation de toutes les interventions de prévention de l'anémie chez les femmes enceintes s'est avérée être de 30%. L'étude a révélé que l'utilisation de toutes les mesures de prévention de l'anémie chez les femmes enceintes est assez faible. La fourniture d'anthelminthiques aux cliniques prénatales et l'éducation sanitaire sur les avantages de leur utilisation contribueraient à accroître l'utilisation des interventions. (*Afr J Reprod Health 2019*; 23[2]: 35-43).

Mots-clés: Anémie pendant la grossesse, prévention de l'anémie pendant la grossesse, Kintampo du nord, Ghana

#### Introduction

Anemia in pregnancy is a major public health problem that affects pregnant women in both developing and developed countries, but pregnant women in developing countries are mostly affected. An estimated 41.8% of pregnant women worldwide are anemic<sup>1</sup>. As compared to other regions of the world, prevalence of anemia in pregnancy is highest in Africa with 57.1% of pregnant women being anemic<sup>1</sup>. In Ghana, anemia in pregnancy prevalence in urban areas in Accra is

34%<sup>2</sup>. In 2015 and 2016, anemia in pregnancy prevalence in the Kintampo North Municipal, one of the Municipalities in Ghana was 16.4% and 21.3% respectively. The prevalence, however, is slightly higher in the 36 weeks gestation group; 24.0% in 2015 and 16.7% in 2016<sup>3</sup>.

Anemia in pregnancy results from a wide range of causes. Worldwide, the major cause of anemia in pregnancy is iron deficiency<sup>4</sup>. Iron deficiency is the cause of 50% of all cases of anemia during pregnancy. Iron requirements increases significantly during pregnancy, this is because iron is required to expand plasma volume, increase red cell mass and for the development of the placenta and the fetus. Iron deficiency during pregnancy causes hemoglobin concentration of the maternal blood to fall to an average of approximately 11.0 g/dl during the 36<sup>th</sup> week of gestation<sup>1,4</sup>.

The leading cause of iron deficiency among pregnant women includes increase iron requirements due to pregnancy, poor absorption of iron from diets, and low intake of iron<sup>4</sup>. Hemolysis because of malaria, congenital hereditary defects in hemoglobin synthesis and glucose-6-phosphate dehydrogenase deficiency are also causes of anemia during pregnancy<sup>2</sup>. Other causes are; blood loss associated with schistosomiasis, hookworm infestation and nutritional deficiency such as vitamin B12 and folic acid<sup>4</sup>.

Studies have shown that, maternal anemia leads to antepartum and postpartum hemorrhage, spontaneous abortion and maternal mortality. Additionally, maternal anemia leads to preterm delivery, low birth weigth, congenital anomalies and fetal death<sup>5-8</sup>.

Anemia in pregnancy due to iron hemolysis deficiency, because of malaria helminthic infection, and infestation preventable causes<sup>9</sup>. The WHO has recommended a package of measures to help prevent these causes of anemia during pregnancy for countries to integrate into their antenatal care. Ghana is one of the countries that have integrated this policy into its antenatal care. The interventions are: daily iron supplementation throughout pregnancy, use of insecticide treated bed nets (ITNs) throughout pregnancy, use of sulphadoxine pyrimethamine (SP) as intermittent preventive treatment in pregnancy (IPTp) and antihelminthics in the second trimester of pregnancy. Because the causes of anemia for which these interventions target coexist, the WHO recommends that these interventions should not be done in isolation since they are known to significantly prevent anemia in pregnancy if not done separately<sup>4</sup>.

Worldwide, numerous studies have been done on the usage of these individual interventions including their effectiveness and factors that may be influencing the intervention usage among pregnant women, but not much is known about the use of all the interventions and the factors that influence their use among pregnant women. Information on the usage of all the interventions among pregnant women in the Kintampo North Municipality is not available.

Consequently, this study was conducted to estimate the proportion of pregnant women using anemia preventing interventions and determine the factors influencing the use of these interventions.

#### Methods

### Study design and setting

A cross-sectional design was used. The study was conducted in seven antenatal clinics (ANC) among pregnant women in the Kintampo North Municipality (KNM). The municipality has 17 health facilities that provide antenatal care. During the study, ANC attendants were assessed to determine the proportion that have had all interventions to prevent anemia during pregnancy and the factors that influenced the use of these interventions. The entire duration of the study was six (6) months and fieldwork was done for a period of four weeks between 1st and 30th May 2017. The area is predominantly rural, and majority of people are subsistence farmers living in small, scattered settlements. The KNM has one municipal hospital that serves as a referral point for 4 health centres, 2 private clinics, and 19 Community-based Health Planning and Services

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(CHPS) compounds offering basic health care manned by 2 doctors, 30 midwives, and 46 community health nurses/officers (CHNs/CHOs).

#### Study variables

#### Dependent variable

The use of anaemia preventing interventions during pregnancy was the outcome variable. These included:

- 1. Daily iron supplementation throughout pregnancy.
- 2. Use of insecticide treated bed nets (ITNs) throughout pregnancy.
- 3. Use of sulphadoxine pyrimethamine (SP) as intermittent preventive treatment in pregnancy (IPTp).
- 4. Use of antihelminthics in the second trimester of pregnancy.

These interventions were used to construct a binary variable as follows: 1 for women who received all the 4 interventions and 0 otherwise (i.e. <4 interventions)

### Independent variables

These were parity of mother, gestational age of mother at first ANC visit, frequency of subsequent visits, knowledge of pregnant women about interventions and availability of interventions at health facility. Other variables included educational level of mother, maternal age, occupation and marital status.

#### Sample size estimation

Sample size for the study was determined using the formula  $n = (z^2 pq)/d^2$  where

N = sample size

Z = z value for 95% confidence interval = 1.96

P = estimated proportion = 21% = 0.21

Q = 1-p = 1 - 0.21 = 0.79

D = distance on either side of the mean in confidence interval = 5% = 0.05

 $N = (1.96^2 \times 0.21 \times 0.79)/0.05^2$ 

Factors Influencing Anemia Preventing Measures

N = 254 + 10%

N = 279

10% of the calculated sample was added to the sample size to cater for refusals and non-respondents. Therefore, the total sample size would be 279.

Assumption on estimated proportion: per the WHO guidelines, if interventions are followed correctly, by the time mother is due for her fourth dose of SP, she would have had all interventions (including required minimum of 3<sup>rd</sup> dose of SP) to prevent anemia during pregnancy<sup>10</sup>. The average annual SP4 coverage of Kintampo North which is 21%<sup>3</sup> was used as the estimated proportion.

#### Study population and sampling procedure

The study was conducted among pregnant women at 36 weeks gestation and above attending ANC in selected seven (7) health facilities providing ANC services in the Kintampo North Municipality. Pregnant women at 36 weeks gestation and above who did not take sulphonamides due to medical conditions and all pregnant women below 36 weeks gestation were not included in the study. facilities were purposively selected. Facilities with an average attendance of four and above for pregnant women at 36 weeks gestation and above in a month were used for the study. Although the estimated sample size was 279, a total of 171 respondents were enrolled because the number of the targeted respondents for the period allocated for data collection was lower than expected. Respondents were enrolled into the study (if they provide consent) as and when they report to the facility for the entire duration of data collection. The number of respondents per study site is as shown in Table 1.

#### Data collection and quality control

A structured questionnaire made up of open and closed ended questions was administered by trained research assistants from the 1<sup>st</sup> to the 31<sup>st</sup> of May 2017. The questionnaire captured the following information; demographic background of respondents, use of anemia preventing measures

during pregnancy andfactors affecting use of anemia preventing measures. The principal investigator supervised the data collection process. Each questionnaire was pre-labelled with a unique respondent identification number for easy identification and retrieval. Questionnaires were cross-checked daily by the study team after data collection to determine the completeness of the data and to make corrections where possible. Data was thoroughly cleanedbefore analysis. Data from completed questionnaires were keyed in to both Microsoft Access and Microsoft Excel 2013 by two (2) different data entry clerks to check for data entry error.

### Statistical analysis

Descriptive analysis was performed to show the background characteristics of the respondents. Frequencies and percentages were generated to describe the distribution covariates and coverage of interventions for all participants. Multiple logistic regression was used to estimate associations between each independent variable and the dependent variable. Prior to fitting the multivariable model, potential multi-collinearity among independent variables were assessed using tolerance and variance inflation factor cut points of 0.1 and 4.0. The models were built using backward procedure. elimination stepwise Factors significantly associated with study outcome at pvalue< 0.20 or that were hypothesized to be associated with study outcome were retained. The final model assessed the effect of the independent variables on the intervention uptake. A two-sided p-value of 0.05 was considered statistically significant. **STATA** software version (StataCorp. LP, College Station, USA) was used to perform all analysis.

#### Results

#### Background characteristics of respondents

A total of 171 questionnaires were administered, they were all used for analysis because they did not contain any errors or missing values. The ages of respondents were between 15 and 45 years with

a mean of 27.4  $\pm 6.4$  years. Teenagers (15-19 years) constituted 9.9% (17) of the respondents. Average monthly income for employed respondents was between GHS 86.00 (USD 17.8) and GHS 6450.00 (USD 1343.8). Most of the respondents, 98.8% (169) resided within the municipality whiles 1.2% (2) resided outside the municipality. More than half, 62.6% (107) resided within Kintampo Township. Table 1 gives a detailed description of the respondents.

# Proportion of respondents using interventions

The proportion of respondents who had all four anemia preventing interventions was 29.8% (51), the remaining 70.2% (73) had less than the four interventions. Uptake of SP1 was 36.8% (63) while SP2 was 26.3% (45). Uptake of SP3 was 17.5% (30), SP4 and SP5 was 9.9% (17) and 9.4% (16) and, respectively. All the respondents were on iron supplements which they took daily. Majority of the respondents 94.2% (161) owned an ITN of which about 81.9% (140) obtained it free of charge from the health facility. Tables 3 and 4 show the use of interventions among respondents.

# Multiple logistic regression of factors associated with use of interventions

The unadjusted analysis showed an association between parity and the use of anemia preventing interventions during pregnancy. Women with a parity of two or three had 1.68 the odds of using all interventions compared to women with a parity of zero or one (uOR = 1.68; 95% CI 1.05 - 2.68). After adjusting for the other factors in the model, the association between parity and use of the interventions remained significant (aOR = 3.54; 95% CI 1.97 - 6.37). Women who had junior high school education had 1.96 times the odds of using the interventions compared to women who had no education (uOR = 1.96; 95% CI 1.18 - 3.24). Compared to employed women, the use of the interventions during pregnancy unemployed women was over two times better (uOR = 2.17; 95% CI 1.09 - 4.3) in the crude analysis and remained significant in the adjusted

Table 1: Distribution of sample size by study facility

Name of Health Facility	Total number of
	respondents enrolled
Kintampo Municipal Hospital	88
(urban)	
Glory Prince of Peace Maternity	40
Home (urban)	
Yizura Hospital (urban)	6
New Longoro Health Center	3
(rural)	
Dawadawa Health Center (rural)	14
Kunsu Health Center (rural)	13
Gulumpe CHPS (rural)	7
Total	171

**Table 2:** Background Characteristics of pregnant women in Kintampo North Municipality, Ghana (n=171)

Variables	Number	%
	Number	/0
Age group	60	25.1
15 – 24	60	35.1
25 - 29	51	29.8
30 - 34	36	21.1
35 +	24	14.0
Parity		
None or once	68	39.8
Twice or three times	75	43.9
Four or more	28	16.4
Marital status		
Unmarried	41	24.0
Married	130	76.0
Education level		
None	54	31.6
Primary	22	12.9
JHS	68	39.8
Secondary+	27	15.8
Employment status		
Employed	133	77.8
Unemployed	38	22.2
Monthly income (GH¢)		
≤100 (≤USD 20.83)	139	81.3
>100 (>USD 20.83)	32	18.7

analysis (aOR = 5.51; 95% CI 2.32 - 13.09). Women who made their first visit to the ANC in their second trimester had 0.35 odds of using the interventions as compared to those who made the first visit in their first trimester (uOR = 0.65; 95% CI 0.42 - 0.99). After adjusting for the other factors, the association was still significant (aOR = 0.28; 95% CI 0.14 - 0.59) (Table 6).

#### **Discussion**

The study revealed that about 30% of pregnant women use all interventions to prevent anemia during pregnancy. Even though this coverage is low considering the 21.3% prevalence of anemia among pregnant women in the study area<sup>3</sup>, there are no similar studies to compare these findings with. The proportion of pregnant women using individual anemia preventing measures have been well documented in studies conducted all over the world. Generally, use of iron supplements during pregnancy has a high coverage, while 92% coverage is reported for Ghana<sup>11</sup>, 99% coverage is reported for Akaki Kality Sub-city in Ethiopia 12. In this study, use of iron supplement among pregnant women was 100%; this is like what has been reported in other studies.

ITN use among pregnant women in this study was 73.1%, even though this finding is in line with a study conducted in Western Kenya<sup>13</sup> which reported 85% it contradicts National Malaria Control Programme<sup>14</sup> which reports use of ITN among pregnant women in Ghana as 33%. The reason for the high usage recorded in this study could be increase in ITN ownership due to free distribution of ITNs in ANCs and child welfare clinics in the country since 2013.

There is some amount of disparity in use of IPTp with SP among pregnant women across studies worldwide. A descriptive cross-sectional study conducted among pregnant women in Simiyu Region in Tanzania<sup>15</sup> indicated that 62% of the women had one dose, 27% had two doses and 11% had three doses of IPTp with SP. Nganda et al<sup>16</sup>, reported that 57% of women had one dose whiles 12% had two doses. However, results of this study revealed that 36.8% of the women had one dose, 26.3% had two doses and 17.5% had 3 doses of IPTp with SP. The differences observed could be because of country specific policy regarding use of IPTp with SP during pregnancy and the difference in methods employed in the various studies. Use of antihelminthic among pregnant women was found to be 39% in Ghana<sup>11</sup>.

**Table 3:** Proportion of pregnant women in Kintampo North Municipality, Ghana on anti-anemia interventions (n=171)

Variable		Number	%
Sulphadoxine	Pyrimethamine		
dose			
<3		46	26.9
3+		125	73.1
Insecticide Treat	ted Net use		
No		46	26.9
Yes		125	73.1
Iron supplement	intake		
No		0	0.0
Yes		171	100.0
Antihelminthic	taken in 2nd		
trimester			
No		120	70.2
Yes		51	29.8

Similarly, this study recorded 29.8% usage. The low usage of antihelminthic observed in this study and other studies is possibly due to lack of staff understanding of the benefits of the management of worm infestation in anemia prevention and because antihelminthics are not provided free of charge to ANC as the other interventions. For instance, in Gulumpe Health Centre (H/C), antihelminthics were available but none of the respondents interviewed there were given some. Kunsu H/C did not have any antihelminthic in stock and respondents did not know that the use of antihelminthic was one of the measures of anemia prevention during pregnancy. Kintampo municipal hospital, the main referral facility in the municipality did not have any antihelminthics at the ANC. Kintampo North Municipal has a hookworm prevalence of 45% <sup>17</sup> and per the WHO guidelines antihelminthic treatment should be done in the second trimester in areas where hookworm prevalence is greater than 20%<sup>9</sup>.

# Factors associated with use of anemia preventing measures

Use of anemia preventing measures is known to be associated with factors such as high socio-economic status, frequent periodic shortage and late clinic attendance. Other factors include frequency of subsequent visit, parity, gestational age at first visit, educational background, type of

facility and health education<sup>16,18,19</sup>. Even though this study did not include all the above-mentioned factors, the association between the factors studied and the outcome variable were similar to previous studies. This study, however, had a different outcome variable, use of all anemia preventing measures, which captures aspects of outcome variables in previous studies.

Although Nganda *et al*<sup>16</sup>, reported an association between use of IPTp with SP and maternal age, it indicated that there was no association between use of ITNs and maternal age. This current study's finding confirms that there is no association between maternal age and the use of all the interventions. The reason for the lack of association was not clear in this study, further studies are needed to ascertain the reason for this.

The findings of this study demonstrated that there was an association between parity and the use of anemia preventing measures. This is consistent with Hill et al18, and Kiwuwa and Mutubenga<sup>19</sup> which identified parity as a key determinant to use of the interventions. It was noted in this study and previous studies that primigravidaes were more likely to use the interventions compared to multigravidaes, lack of previous pregnancy experience could possibly be a reason for this. Contrary to Hill et al. 18, which recorded a strong association between marital status and use of ITN, the findings of this study did not reveal any association. This seems to suggest that the use of ITN is not necessarily a function of marital status but interventions targeting ITN use among pregnant women should encouraged regardless of marital status.

In the unadjusted analysis, there was an association between women who had Junior Secondary education and use of interventions. This finding contradicts that of Ngimuh *et al.*<sup>19</sup> which reported no association between educational background and use of ITNs and IPTp with SP. Employment status is known to be associated with use of anemia preventing measures among pregnant women in most studies<sup>18,20,21</sup>, the results of this study are similar to that of these previous studies. Possible reason for this association could be because employment is linked with income

**Table 4:** Comparison of proportion of pregnant women who used <4 Interventions and all the 4 interventions (n=171)

Variable	<4 interventions	4 interventions	Total
	n(%)	n(%)	n((%)
Age group			
15 - 24	22(36.7)	38(63.3)	60(35.01)
25 - 29	24(47.1)	27(52.9)	51(29.8)
30 - 34	16(44.4)	20(55.6)	36(21.1)
35 +	11(48.3)	13(54.2)	24(14.0)
Parity			
None or once	34(50.0)	34(50.0)	68(39.8)
Twice or three times	28(37.3)	47(62.7)	75(43.9)
Four or more	11(39.3)	17(60.7)	28(16.4)
Marital Status			
Single	16(39.0)	25(61.0)	41(24.0)
Married	57(43.8)	73(56.2)	130(76.0)
Education level			
None	27(50.0)	27(50.0)	54(31.6)
Primary	11(50.0)	11(50.0)	22(12.9)
JHS	23(33.8)	45(66.2)	68(39.8)
Secondary+	12(44.4)	15(55.6)	27(15.8)
Employment status			
Employed	61(45.9)	72(54.1)	133(77.8)
Unemployed	12(31.6)	26(68.4)	38(22.2)
Gestational age at first A	NC visit		
1-13weeks	16(20.8)	61(79.2)	77(45.0)
14-26weeks	54(60.7)	35(39.3)	89(52.1)
27-40weeks	3(60.0)	2(40.0)	5(2.9)
Frequency of ANC visit			
4 visits +	68(41.5)	96(58.5)	164(95.9)
< 4 visits	5(71.4)	2(28.6)	7(4.1)
Yes	59(39.6)	90(60.4)	149(87.1)
No	14(63.6)	8(36.4)	22(12.9)

**Table 5:** Availability of interventions at the health facility

Variable	Number (%)
Availability of Antihelminthic at facility	
Yes	73 (42.7)
No	98 (57.3)
Availability of Iron at facility	
Yes	171(100)
No	0(0.0)
Availability of SP at facility	
Yes	171(100)
No	0(0.0)
Availability of SP at facility	
Yes	171(100)
No	0(0.0)

generation which partly eliminates the problem of accessibility to health facilities.

The strong association observed between gestational age at first visit and use of the

interventions is in line with Hill *et al*<sup>18</sup>, which reported similar findings. Early initiation of ANC attendance means that there will be high number of subsequent visits which make a woman more likely to receive the interventions. Both the unadjusted and adjusted analysis showed no association between the availability of antihelminthics in the facility and use of the intervention. The association between frequency of subsequent visit and the use of the intervention reported in Kiwuwa and Mutubenga<sup>19</sup> is like the findings of this study.

#### **Ethical Consideration**

Ethical clearance was obtained from the Ghana Health Service Ethical Review Committee (Approval Number: GHS-ERC: 29/12/2016).

**Table 6:** Multiple Logistic Regression of Factors Associated with use of Interventions

Variable	Univariate	Multivariate			
	uOR(95%CI)	aOR(95%CI)			
Age group					
15-24	1	-			
25 - 29	1.12(0.65 - 1.95)	-			
30 – 34	1.25(0.65 - 2.42)	-			
35 +	1.18(0.53 - 2.64)				
Parity					
None or once	1				
Twice or					
three	1.68(1.05 - 2.68)*	3.54(1.97 - 6.37)**			
Four or more	1.55(0.72 - 3.31)	4.57(1.76 -11.89)**			
Marital					
status					
Unmarried	1				
Married	1.28(0.9 - 1.81)	-			
Education					
None	1				
Primary	1(0.43 - 2.31)	-			
Junior					
Secondary	1.96(1.18 - 3.24)*	-			
Secondary+	1.25(0.58 - 2.68)	-			
Employment stat	us				
Employed	1				
Unemployed	2.17(1.09 - 4.3)*	5.51(2.32 -13.09)**			
Gestational age a	Gestational age at 1st ANC visit				
1-13weeks	1				
14-26weeks	0.65(0.42 - 0.99)*	0.28(0.14 - 0.59)**			
27-40weeks	0.67(0.11 - 4.01)	0.20(0.03 - 1.26)			
Knowledge on Ar	naemia prevention				
Yes	1				
No	0.57(0.24 - 1.37)	-			
Availability of Antihelmintic					
Yes	1				
No	0.88(0.59 - 1.32)	0.69(0.35 - 1.34)			
Frequency of ANC visit					
4 visits +	1				
< 4 visits	0.4(0.08 - 2.07)	0.18(0.04 - 0.92)*			

\*\*p-value < 0.001 \*p-value <0.05; CI: Confidence Interval; aOR: Adjusted Odd Ratio; uOR: Unadjusted Odd Ratio

Approval was also sought from the Kintampo North Municipal Health Directorate and all heads of facility as well as unit heads in the study sites. Informed consent was obtained from all respondents and their confidentiality was assured before the interview.

#### **Conclusion**

The use of anemia preventing measures among pregnant women in the Kintampo North Municipality in this study was quite low. Factors

that significantly influenced the use of all anemia preventing measures among pregnant women were parity, employment status and gestational age at first ANC. Others include frequency of subsequent visits and availability of antihelminthic in the health facility. The findings of this study reveal that the underlisted strategies can help increase the usage of the interventions among pregnant women.

- 1. Antihelminthics used in pregnancy should be made available to all antenatal clinics.
- 2. In addition to giving out the intervention, health education targeting especially multigravidaes should be reinforced on the importance of their use. Public health authorities and actors can undertake mass awareness campaign to educate mothers on early initiation and continual attendance of ANC
- 3. Regular refresher training on the benefits and timing of the interventions should be conducted for all ANC staff.

## **Conflict of Interest**

The authors declare no conflict of interest regarding this research.

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#### **Contribution of Authors**

The study was conceptualized by OL and the initial protocol was developed by OL and RMA. OL coordinated the research implementation activities. FD and OL coded the questionnaire into the data management software system and led the statistical analysis. The manuscript was drafted by OL with inputs from RMA and FD. All the authors reviewed and approved the manuscript.

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