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What is the Link between Malaria Prevention in Pregnancy and Neonatal Survival in Nigeria?

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Abstract

Neonatal mortality has been recognized as a global public health challenge and Nigeria has the highest prevalence in Africa. Malaria during pregnancy jeopardizes neonatal survival through placental parasitaemia, maternal anaemia, and low birth weight. This study investigated association between the malaria prevention in pregnancy and neonatal survival using a nationally representative data - Nigeria Demographic Health Survey 2013. Child recode data was used and the outcome variable was neonatal death. The main independent variables were the use of at least 2 doses of intermittent preventive treatment in pregnancy with sulfadoxine-pyrimethamine (IPT-SP) and proportion of pregnant women who reported Insecticide Treated Net (ITN) use the night before the survey. Data were analyzed using Pearson Chi-square (x^2) test of association and survival analysis techniques. Total neonatal mortality rate was 38 per1000 live births. Cox proportional hazard model showed that low birth weight (HR 1.49, 95% CI (1.15 – 1.93 p=0.003) and adequate number of ANC visits (≥ 4 visits) (HR 0.68, 95% CI (0.53 – 0.93) were associated with neonatal survival. The use of at least 2 doses of IPT-SP was not an independent factor for neonatal survival (HR 0.72, 95% CI (0.53 – 1.15)**.** Malaria prevention in pregnancy is crucial for neonatal survival through the prevention of low birth weight. *(Afr J Reprod Health 2019; 23[1]: 139-149).*

Keywords: Malaria Prevention, Pregnancy, Intermittent Preventive Treatment in pregnancy with Sulfadoxine-Pyrimethamine, Insecticide Treated Net, Neonatal Mortality, Nigeria

Résumé

La mortalité néonatale a été reconnue comme un problème de santé publique mondial et le Nigéria connait la prévalence la plus élevée d'Afrique. Le paludisme pendant la grossesse compromet la survie néonatale par la parasitémie placentaire, l'anémie maternelle et l'insuffisance pondérale à la naissance. Cette étude a examiné l'association entre la prévention du paludisme pendant la grossesse et la survie néonatale à l'aide de données représentatives au niveau national - Enquête démographique sur la santé au Nigéria de 2013. Les données de recodage des enfants ont été utilisées. Les principales variables indépendantes étaient l'utilisation d'au moins 2 doses de traitement préventif intermittent pendant la grossesse par la sulfadoxine-pyriméthamine (IPT-SP) et la proportion de femmes enceintes qui avaient déclaré avoir utilisé une moustiquaire imprégnée d'insecticide (MII) la nuit précédant l'enquête. Les données ont été analysées à l'aide du test de Pearson sur le chi carré (x^2) des techniques d'analyse d'association et de survie. Le taux de mortalité néonatale total était de 38 pour 1 000 naissances vivantes. Le modèle de risque proportionnel de Cox a montré qu'un faible poids à la naissance (HR 1,49, IC à 95% (1,15 - 1,93 p = 0,003) et un nombre adéquat de visites ANC (≥ 4 visites) (HR 0,68, IC à 95% (0,53 - 0,93) étaient associés `a la survie néonatale. L'utilisation d'au moins deux doses d'IPT-SP n'est pas un facteur indépendant de la survie néonatale (HR 0,72, IC à 95% (0,53 - 1,15). La prévention du paludisme pendant la grossesse est cruciale pour la survie néonatale à travers la prévention du faible poids à la naissance. *(Afr J Reprod Health 2019; 23[1]: 139-149).*

Mots-clés: Prévention du paludisme, grossesse, traitement préventif intermittent par la sulfadoxine-pyriméthamine pendant la grossesse, moustiquaire imprégnée d'insecticide, mortalité néonatale, Nigéria

Introduction

Neonatal mortality (NNM) has been recognized as global public health challenge particularly in low and middle-income countries. Globally, it accounts for 41% of under-five mortality and an estimated 4 million deaths annually, caused primarily by neonatal infections, prematurity and birth asphyxia[1,2]. Nigeria contributes significantly to the global neonatal mortality figures (280,073) and has the highest prevalence in sub-Saharan Africa[3]. While Nigeria has made remarkable progress in under-five mortality reduction from 201 deaths per 1000 in 2003 to 128 per 1000 by 2013 (NDHS report 2013)[4], the decline in NNM rates within this time frame has been less remarkable. The NNM within this period has a marginal decrease from 48/1000 (2003) to 40/1000 (2008) to 37/1000 (2013). This persistence in NNM rates was one of the reasons for the failure to achieve the fourth Millennium Development Goal (MDG) in Nigeria[4].

While the causes of child mortality are easily identified and have been successfully tackled by interventions like immunization, breastfeeding, oral rehydration therapy and so on, factors that threaten neonatal survival are complex being closely associated with the maternal conditions during pregnancy, delivery and the early postpartum period. Consequently, Darmstadt *et al* identified 16 evidence-based cost-effective interventions that can improve neonatal survival across this continuum of care[5]. These included interventions like tetanus toxoid immunization, intermittent presumptive treatment in pregnancy with Sulphadoxine-Pyrimethamine (IPTp-SP) among others that can be provided during the antenatal period[5]. Doku and Neupane in a recent publication posited that interventions during the antenatal period may contribute significantly to neonatal mortality reduction in many low and middle-income countries where the coverage of skilled care at birth remains low[6].

Malaria in pregnancy has significant impact on maternal and neonatal health, particularly in highly endemic areas like Nigeria[7,8]. Although, malaria in pregnancy may not be a direct cause of neonatal mortality, it has been indirectly linked to neonatal mortality through maternal anaemia and placental parasitaemia leading to intrauterine growth retardation (IUGR) and low birth weight. An estimated 11% of neonatal deaths in malaria endemic regions of Africa are due to low birthweight associated with *Plasmodium falciparum* infection during pregnancy[7]. The prevention of malaria in pregnancy in malaria endemic areas recommended by WHO involves the administration of at least two doses of IPTp-SP (in the second and third trimesters regardless of malaria parasitaemia status) and insecticide treated bed nets (ITN)[9]. IPTp-SP works by providing both treatment and prophylaxis; first by the intermittently clearing malaria parasites from the placenta, secondly the slow elimination of the drug from the body results in persistence of the drug and this prevents new malaria infections[10]. On the other hand, ITN works by preventing new infection through self-protection and prevention from person to person.

IPTp-SP and ITN are highly cost effective in reducing the impact of malaria related adverse pregnancy and birth outcomes[11,12]. Until recently, little research has been focused on the relationship between malaria prevention in pregnancy and neonatal mortality. Furthermore, this evidence is very scarce in Nigeria, which bears a huge burden of both malaria and neonatal mortality. Menendez *et al* in a randomized, placebo-controlled trial of IPT with SP among Mozambican pregnant women found that IPT use was associated with reduced NMM[13.] Eisele *et al* using a retrospective birth cohort from national cross-sectional datasets in 25 African countries from 2000 to 2010 found malaria prevention to be protective of neonatal mortality. Although Nigeria was included in the study, the pooled analysis may have masked the effect of this association among Nigerian women[14]. Hence the need for local evidence on association and link between malaria prevention in pregnancy and neonatal survival in Nigeria using the most recent Nigerian demographic and health survey data. The result of this study will serve as an advocacy tool for increasing the coverage and uptake of IPT-SP and ITN as one of the cost-

effective interventions necessary to halt NNM in Nigeria.

Methods

Study setting

A nationally representative data of women of reproductive age in Nigeria was used. This was conducted by the National Population Commission (NPC), Nigeria and the ICF International USA, in 36 states including the Federal Capital Territory[15]. Nigeria is made up of 6 geopolitical regions; North-East, North-West, North-Central, South-East, South-South, and South-West. The population in each of the geopolitical regions and States are relatively homogeneous and share similar socio-cultural characteristics. Also, health-related characteristics like access to health care, environment, housing system etc, are similar within the regions and States but differ significantly across regions[16].

Sources of data and sampling

Child recode data from the most current Nigeria Demographic and Household Survey was used (NDHS 2013)[15]. NDHS is a routine nationally representative survey and cross-sectional in design using a three-stage sampling technique to select the respondents. The survey uses three-stage sampling technique to select the respondents. First, Local Government Areas (LGA) are selected, then the Enumeration Areas (EA), which are the Primary Sampling Units (PSU) and referred to as clusters and lastly the selection of households within the selected EA. Primary information about households, sexual and reproductive health and history were collected from women aged 15-49 years within the selected households. Usually, the survey collects birth history of all women interviewed. More specifically, the survey collects information on all births to a woman. We, therefore, used the "child recode data" which contains all follow-up information on all children born to the interviewed women within five years preceding the survey.

Variables

The outcome variable is neonatal death. Neonatal mortality was defined as the death of a live born baby within the first 28 complete days after birth. Early neonatal mortality was defined as the death of a baby during the first seven days of life, while late neonatal mortality referred to deaths occurring between the 8^{th} and the 28^{th} completed days of life. The main independent variables were use of 2 doses of IPT-SP or more during ANC visit and proportion of pregnant women who reported ITN the night before the survey. The other co-variates were: maternal age, child's sex, geographical region, type of residence, maternal education, wealth index, ethnicity, religion, marital status, total children ever born, adequacy of ANC visits, source of anti-malarial drugs during pregnancy, number of tetanus injection before birth, maternal body mass index (BMI). These independent variables have been found to be associated with the outcome variable in earlier studies[17-21].

Statistical analysis

Among the 38,948 women who participated in 2013 surveys, a total of 31,482 children were born within five years preceding each of the surveys. All analyses in this study were therefore based on the survivorship of the 31,482 children within first 28 days of their life. Descriptive statistics were used to show the distribution of the children by the studied characteristics (Table 1). The early neonatal mortality rate (NMR) and late NMR were then computed as the number who died among a cohort of 1000 live births between 0-6.99 days and 7-28 days respectively using basic statistical proportions. The total NMR is the addition of the early and late NMR. Bivariate analyses were carried out to determine significant association between each of the outcome variables and the independent variables using Pearson Chi-square (x^2) test of association. Survival analysis technique was used to estimate the survivorship at every day the children were exposed to the risk of death. Any deaths on or before 28^{th} day of life were marked as "failure" while any living child who

had not lived up to 28 days as of the day of the survey or who survived the first 28 days were "censored" accordingly. The survival time is the number of days a child lived before "failure" while the censored survival time is the age of the surviving children as of the day of the survey. Cox proportional hazard regression models were fitted into the resulting data. The regression model was used to identify the predisposing factors to neonatal death, (Table 2). Sampling weights were applied and statistical significance was determined at 5%.

Results

Table 1 describes the occurrence of early, late and total neonatal mortality and neonatal survival rates per 1000 live births by the socio-demographic and selected maternal characteristics of 38,948 women of reproductive age who had live births in the five years preceding the survey. Total mortality and early neonatal mortality rates were 38 per1000 live births and 30 per 1000 live births respectively, early neonatal deaths accounted for most of the deaths in neonatal period. Neonatal deaths were significantly higher among adolescent mothers (61/1000) compared with mothers within 25-34 age bracket (33/1000), mothers without formal education (48.4/1000), male neonates (43/1000) compared to females (25/1000), low birth weight (60/1000) compared with normal weight neonates (35/1000), rural (41/1000) compared with urban (30/1000) dwellers, Hausa/Fulani women (40/1000) compared with other tribes (34/1000), grand multiparous women (≥ 5 children). The results revealed majority of women (90%) did not have IPT-SP during pregnancy and this was significantly associated with neonatal mortality (38/1000) compared with those who had. No significant difference was found in the neonatal mortality experience of women who used or did not use bed nets the night before the survey was conducted.

Table 2 shows the results of bivariate and multivariate Cox hazard regression modelswith the unadjusted and adjusted hazard ratios and their 95 percent confidence intervals. It shows the associations between neonatal mortality, having at least 2 doses of SP as main explanatory variable and other characteristics associated with neonatal survival. The unadjusted model shows that those who had 2 doses of SP (HR 0.69, 95% CI (0.53 – 0.89) had a 31% lower risk of neonatal death than those who did not receive SP. The risk of neonatal death was also 30% lower among those who had a minimum of 4 ANC visits (HR 0.70, 95% CI (0.57 – 0.86) compared to those who did not have at all. The hazard ratios were significantly higher among low birth weight babies (HR 1.73, 95% CI (1.46 – 2.06) compared with normal weight babies, rural dwellers (HR 1.37, 95% CI (1.18 – 1.59), grand multiparous women (HR 1.21, 95% CI (1.03 – 1.42) and male neonates (HR 1.38, 95% CI (1.2 – 1.57), Muslims (HR 1.20, 95% CI (1.05 – 1.38), poor women and those with a lower level of education.

The multivariate model showed that those who obtained an adequate number of antenatal visits had a significantly lower risk of neonatal mortality after adjusting for other important co-variates (HR 0.70, 95% CI (0.57 – 0.86) compared with those who did not. Similarly, low birth weight babies had 49% higher risk of neonatal death (HR 1.49, 95% CI (1.15 – 1.93) compared with normal weight babies after adjusting for important covariates. Although, obtaining at least 2 doses of SP remained protective while controlling for other factors with a 28% lower hazard of neonatal death (HR 0.72, 95% CI (0.53 – 1.15), it was not statistically significant.

Figures 1 and 2 show the neonatal survivorship curves by selected socio-demographic, maternal and child characteristics. The survival experience was better in neonates whose mothers were within the age bracket of 25-34 years, had post-secondary education, belonged to households in upper wealth quintiles and were urban dwellers. Rate of neonate survival was also higher among female neonates and those whose

Table 1: Early, late and total neonatal mortality and neonatal survival rates per 1000 live births in Nigeria by selected socio-demographic and maternal characteristics

			Rates per 1000 live-births				
Characteristics	**Number**	**Proportion***	**Early neonatal Mortality**	**Late neonatal mortality**	**Total neonatal Mortality**	**Neonatal survival**	**p-value**
Overall	31482	100	30	8	38	962	
Net used last night							
No net	25316	80.4	29	8	37	963	0.358
treated nets	6166	19.6	28	9	37	963	
Mothers age							
15-19	1543	4.9	48	13	61	939	<0.001
20-24	6127	19.5	33	7	40	960	
25-34	15626	49.6	25	8	33	968	
35-49	8186	26.0	32	8	40	961	
Gender							
Male	15953	50.7	35	8	43	957	<0.001
Female	15529	49.3	25	8	33	967	
Baby weight at birth							
Above average	13225	42.8	21	6	27	973	<0.001
Average	12992	42.1	27	8	35	965	
Below average	4656	15.1	48	12	60	940	
Geographical Zone							
North Central	4452	14.1	25	7	32	968	<0.001
North East	6633	21.1	33	6	39	961	
North West	10420	33.1	30	11	41	959	
South East	2670	8.5	30	7	37	963	
South South	3598	11.4	26	4	30	970	
South West	3708	11.8	29	7	36	965	
Residence							
Urban	10178	32.3	24	6	30	970	<0.001
Rural	21304	67.7	32	9	41	960	
Education							
No education	15222	48.4	30	9	39	960	<0.001
Primary	6330	20.1	31	9	40	960	
Secondary	8087	25.7	27	5	32	968	
Higher	1843	5.9	23	2	25	975	
Wealth Quintiles							
Poorest	7387	23.5	32	9	41	959	<0.001
Poorer	7428	23.6	32	10	42	957	
Middle	6186	19.7	27	7	34	966	
Richer	5760	18.3	28	6	34	966	
Richest	4719	15.0	24	5	29	971	
Ethnicity							
Hausa/Fulani	13180	41.9	30	10	40	960	0.019
Yoruba	3299	10.5	30	7	37	963	
Igbo/Ibibio	3205	10.2	29	7	36	964	
Others	11798	37.5	28	6	34	967	
Religion							
Christianity	12099	38.4	29	6	35	965	0.054

Islam	18932	60.1	29	9	38	962	
Others	451	1.4	34	10	44	956	
Marital Status							
Single	583	1.9	38	12	50	949	0.128
Married	30039	95.4	29	8	37	964	
Widowed	861	2.7	33	12	45	955	
Children Ever Born							
1-2	8927	28.4	28	7	35	965	0.043
3-4	9529	30.3	27	7	34	966	
5+	13025	41.4	31	9	40	960	
Adequacy of ANC visits							
None	6916	34.5	24	7	31	969	0.071
Inadequate	2528	12.6	25	5	30	970	
Adequate	10628	53	20	5	25	975	
Source of antimalarials							
Homes	44	0.1	17	0	17	983	0.817
Public HF	3645	11.5	19	5	24	976	
Private HF	583	1.8	14	3	17	983	
Others	137	0.4	6	0	6	995	
None	27097	86.1	31	8	39	961	
When SP/Fansidar was taken							
1st Trimester	85	0.3	9	0	9	991	0.022
2nd Trimester	1053	3.5	28	4	32	968	
3rd Trimester	1966	6	16	6	22	977	
None	28378	90.1	30	8	38	962	
Tetanus injection obtained during pregnancy							
None	8098	40.5	22	6	28	972	0.059
1	2144	10.7	23	9	32	969	
2	6854	34.3	20	4	24	976	
3	2539	12.7	21	5	26	974	
4	207	1	11	18	29	971	
5+	144	0.7	5	0	5	995	
Mothers BMI							
Under Weight (<18.5)	2763	8.9	24	8	32	967	0.200
Normal (18.5-24.9)	20631	66.2	29	8	37	963	
Over Weight(25.0-29.9)	5681	18.2	31	7	38	962	
Obese (30.0+)	2095	6.7	36	7	43	958	

**percentages adds column wise to 100*

mothers had received at least 2 doses of SP, had adequate number of ANC visits, and had completed 5 doses of TT vaccine.

Discussion

Nigeria bears an intersecting burden of malaria and neonatal mortality with the highest numbers of neonatal deaths in sub-Saharan Africa. WHO recommendation of at least two doses of IPTp-SP and ITN have been highly cost effective in reducing the burden and adverse outcomes of malaria in pregnancy. We investigated the association between the malaria prevention in pregnancy and neonatal survival using a nationally representative data of mothers in Nigeria.

We found that the use of at least 2 doses of IPTp-SP in mothers reduced the risk of neonatal death by 31% in bivariate Cox analysis. Although, it remained protective on multivariate analysis (AHR = 0.72) it was no longer statistically significant (p=0.108). This however does not

Table 2: Unadjusted and adjusted hazard ratios with 95% confidence intervals of factors associated with neonatal mortalit in Nigeria

Characteristics	Crude HR (95% CI)	Adjusted HR (95% CI)
Had 2 doses of SP		
Yes	0.69 (0.53 - 0.89)*	0.72 (0.53 – 1.15)
No	1.00	
Net used last night		
No net	1.02 (0.87 - 1.21)	
treated nets	1.00	
Mothers age		
15-19	1.48 (1.13 - 1.93)*	1.27 (0.794- 2.01)
20-24	1.02 (0.85 - 1.24)	0.79 (0.53 - 1.15)
25-34	0.79 (0.67 - 0.92)*	0.82 (0.63 - 1.05)
35-49	1.00	
Gender		
Male	1.38 (1.20 - 1.57)*	**1.52(1.25 - 1.86)***
Female	1.00	
Baby weight at birth		
Above average	0.77 (0.65-0.901)*	0.80 (0.64-1.01)
Average	1.00	
Below average	1.73 (1.46-2.06)*	**1.49 (1.15-1.93)***
Zone		
North Central	0.63 (0.50 - 0.78)*	**0.67 (0.46 - 0.98)***
North East	0.73 (0.61 - 0.88)*	0.83 (0.62 - 1.10)
North West	1.00	
South East	0.77 (0.60 - 0.99)	0.96 (0.57 – 1.56)
South South	0.59 (0.46 - 0.76)	0.71 (0.44 - 1.12)
South West	0.82 (0.66 - 1.01)	0.84 (0.54 - 1.30)
Region		
Urban	1.00	
Rural	1.37 (1.18 - 1.59)*	1.26 (0.95 - 1.65)
Education		
No education	2.23 (1.51 - 3.28)*	1.34 (0.73 - 2.45)
Primary	2.25 (1.51 - 3.36)*	1.72 (0.97 – 3.04)
Secondary	1.74 (1.17 - 2.6)*	1.33 (0.77 - 2.24)
Higher	1.00	
Wealth Quintiles		
Poorest	1.48 (1.17 – 1.86)*	0.75 (0.46 – 1.24)
Poorer	1.60 (1.27 – 2.00)*	1.04 (0.66 – 1.63)
Middle	1.25 (0.98 – 1.59)	1.00 (0.67 – 1.51)
Richer	1.18 (0.92 – 1.51)	0.95 (0.65 – 1.39)
Richest	1.00	
Ethnicity		
Hausa/Fulani	1.11 (0.89 - 1.38)	
Yoruba	1.00	
Igbo/Ibibio	0.88 (0.66 - 1.17)	
Others	0.85 (0.68 - 1.07)	
Religion		
Islam	1.20 (1.05 - 1.38)*	0.83 (0.60 - 1.14)
Christianity	1.00	
Others	1.33 (0.81 - 2.21)	0.88 (0.38 - 2.03)
Marital Status		
Never married	1.00	
Married	0.84 (0.54 - 1.31)	
Widowed	1.12 (0.64 - 1.96)	
Children Ever Born		
1-2	1.00	
3-4	1.01 (0.85 - 1.21)	0.83 (0.63 - 1.14)
5+	1.21 (1.03 - 1.42)	0.93 (0.67 - 1.30)
Adequacy of ANC visits		
None	1.00	
Inadequate	0.89 (0.66 - 1.21)	0.25 (0.66 - 1.28)
Adequate	0.70 (0.57 - 0.86)*	**0.68(0.53 - 0.93)***
Source of antimalarial		
Homes	1.00	
Public HF	0.59 (0.46 - 0.76)*	0.49 (0.70 - 1.27)
Private HF	0.48 (0.25 - 0.93)*	0.84 (0.43 - 1.66)
Others	0.24 (0.03 - 1.74)	0.43 (0.06 - 2.99)
Tetanus injection in pregnancy		
none	1.00	
1	1.03 (0.75 - 1.41)	
2	0.81 (0.64 - 1.02)	
3	0.82 (0.59 - 1.12)	
4	1.17 (0.52 - 2.65)	
5+	0.26 (0.04 - 1.87)	
Mothers BMI		
Underweight (<18.5)	1.00	
Normal	1.18 (0.92 - 1.53)	
Overweight	1.16 (0.87 - 1.54)	
Obese	1.38 (0.99 - 1.93)	

obliterate the clinical relevance of the finding, which suggest that the use of at least 2 doses of SP during pregnancy may remain a cost-effective intervention in preventing neonatal mortality in malaria endemic countries like Nigeria. The protective effect of IPTp-SP on neonatal survival has been corroborated by earlier studies[13,14,22-24]. Menendez *et al*, in a randomized, placebo-controlled trial of intermittent preventive treatment (IPTp-SP) in 1030 Mozambican pregnant women who use a ITN, found a 60% reduction in neonatal mortality in the intervention group compared with the control group[13.] Although, the mechanism was not fully understood, the authors suggested that improved neonatal survival might be attributed to the reduction of malaria complications in pregnancy (particularly low birth weight) as well as the antibiotic effect of SP[13]. Expectedly, neonates with low birth weight had

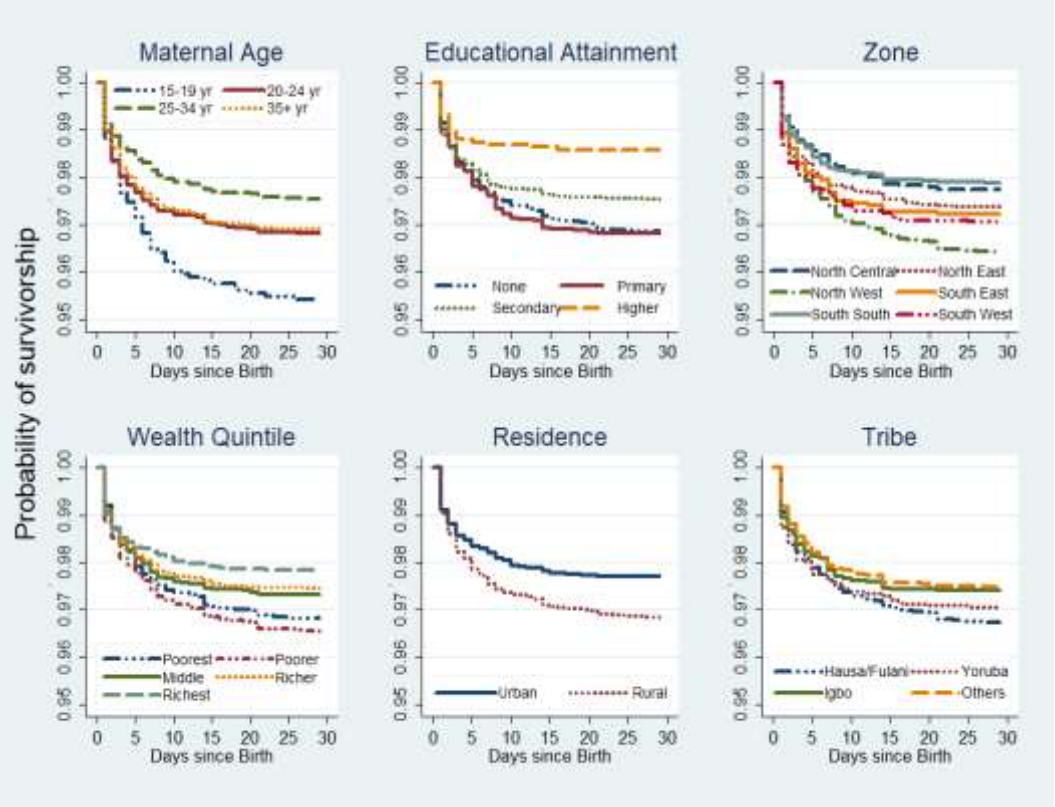

Figure 1: Neonate survivorship curves by mother's background characteristics

higher hazards (HR=1.49) for neonatal mortality. The association between low birth weight due to prematurity or intrauterine growth retardation and NNM is well established in literature[22-24]. The causes of low birth weight are multifactorial which include maternal age, maternal nutrition (measured by maternal height, pre-pregnancy weight, and gestational weight gain), socio-economic status, birth intervals, multiple pregnancies, cigarette smoking, alcohol consumption and maternal infections[25-26]. Malaria infestation is distinct because it is the most important preventable cause of LBW during pregnancy in malaria endemic areas[27]. This association has been partly attributed to placenta parasitaemia which elicits an immune response that affects maternal – fetal transfer of nutrients across the placenta[28]. Eisele *et al*, in their meta-analysis of malaria prevention in pregnancy and neonatal mortality in 32 African countries, found that malaria prevention in pregnancy through IPTp with sulfadoxine–pyrimethamine or ITNs was associated with a 21% reduction in low birthweight[14]. Our results showed no significant association between ITN use and neonatal mortality (HR=1.02). This may be partly explained by the low uptake of bed nets. Generally, the uptake is malaria prevention in pregnancy is low among Nigerian women. We noted that only 19.6% mothers reported the use of bed nets while 9.9% reported the used of IPTp-SP. Hence, there is the need to continue to promote the use of both IPTp-SP, long-lasting insecticide treated nets and other protective measures like personal protective measures among pregnant women through health communication and promotion activities. Fortunately, antenatal care

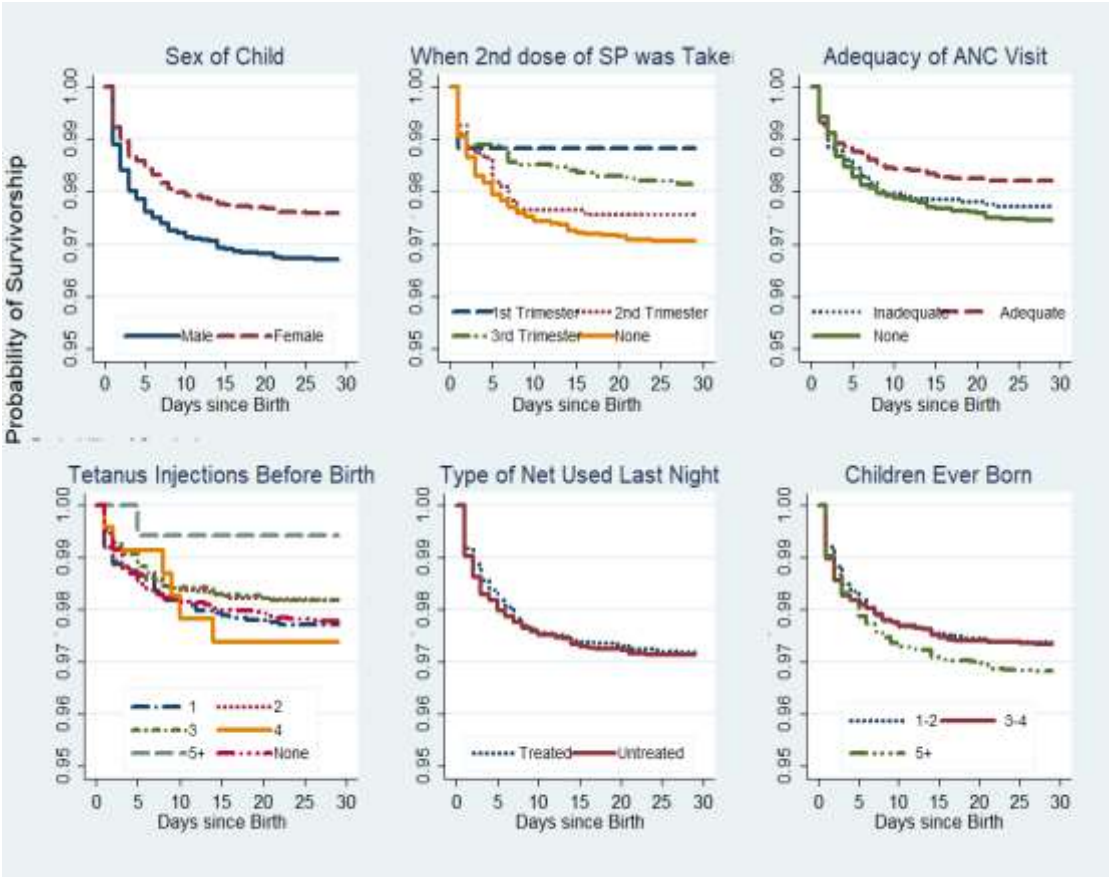

Figure 2: Neonate survivorship curves by selected maternal and child characteristics

provides the platform for such health promotional activities.

Adequate ANC visits were significantly associated with reduced likelihood of neonatal mortality both with univariate and multivariate Cox analysis. Adequate antenatal care visits have been associated with improved maternal and neonatal outcomes [18 -22]. This offers the opportunity to provide interventions like tetanus immunization, calcium supplementation for prevention of pre-eclampsia and eclampsia and IPT-SP that can improve neonatal survival. For instance, we found in this study that mothers who had completed the 5 doses of TT recommended for women in the reproductive age had 4 times improved neonatal survival compared to those who had not received any at all. The association between tetanus immunization and neonatal survival is well established, especially in environments where tetanus infection is important. Doku and Neupanne, in a recent article on the survival analysis of the association between antenatal care attendance and neonatal mortality in 57 low and middle-income countries, found a 51% lower risk of neonatal mortality among women who had at 4 antenatal care visits after adjusting for potential confounding factors. They showed that having adequate antenatal care is important for neonatal survival in low and middle-income countries like Nigeria[6].

In conclusion, our study supports the crucial role of IPTp-SP in neonatal survival in Nigeria although it was not found to an independent protective factor for NNM. However, it remains a cost-effective intervention for preventing NNM by preventing low birth weight

which is the most important cause of NNM. We found that adequate antenatal care was an independent factor for neonatal survival. It is also critical for the prevention of NNM as it creates the platform for the provision of important interventions and health promotional activities for the increased uptake of malaria prevention in pregnancy.

Despite these findings, our study had certain limitations. The first being the low proportion of women who experienced the primary independent variables (IPTp-SP and ITN). This may explain the reason for the lack of statistical association. The study is also subject to recall bias because information was elicited by a retrospective report from the study participants. Residual confounding is also likely to affect our estimates because the use of secondary data is associated with incomplete variables and data. It is difficult to establish causal relationships because of the cross-sectional study design used. For future research primary data that captures all necessary variables is suggested.

Ethical Consideration

The Institutional Review Board (IRB) of the National Institute of Medical Research, Nigeria approved the study protocol, survey instrument, and materials prior to the commencement of the survey.

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Contribution of Authors

IAA conceived and designed the study. FAA analyzed the data. Both discussed the results, contributed to the draft and approved the final manuscript.

References

1. Lawn JE, Cousen S and Zupan J. Four million neonatal deaths: when? Where? Why? Lancet 2005; 365:891 - 900.
2. UNICEF and WHO levels and trends in child mortality. 2015. Report 2015 http://www.who.int/maternal_child_adolescent/documents/levels_trends_child_mortality_2015.pdf?ua=1 (accessed Mar 2017).
3. Lawn J, Kerber K, Enweronu-Laryea C and Massee Bateman O. Newborn survival in low resource settings—are we delivering? BJOG 2009;16 (Suppl. 1):49–59.
4. Ezeh OK. Trends and population-attributable risk estimates for predictors of early neonatal mortality in Nigeria, 2003–2013: a cross sectional analysis. BMJ Open 2017;7: e013350. doi:10.1136/bmjopen-2016-013350
5. Darmstadt GL, Bhutta, ZA, Cousens S, Adam T, Walker N and de Bernis L, Evidence-based, cost-effective interventions: how many newborn babies can we save? www.thelancet.com.2005 ; 365:9463:977-988. DOI:https://doi.org/10.1016/S0140-6736(05)71088-6
6. Doku DT and Neupane S. Survival analysis of the association between antenatal care attendance and neonatal mortality in 57 low and middle-income countries International Journal of Epidemiology;2017, 1668–16771–10 doi: 10.1093/ije/dyx125.
7. Guyatt HLand Snow RW. Malaria in pregnancy as an in direct cause of infant mortality in sub-Saharan Africa. Trans R. Soc Trop Med Hyg; 2001 (95)569-76.
8. Desai M, terKuile, FO, Nosten F, McGready R, Asamoa K, Brabin B. and Newman R D. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis 2007; 7:93-104.
9. World Health Organization Regional Office for Africa: A strategic framework for malaria prevention and control during pregnancy in the African region. WHO/AFRO. AFR/MAL/04/01. Brazzaville (Congo). http://www.afro.who.int/en/clusters-a-programmes/dpc/malaria/mal-publications.html
10. O. terKuile F, van Eijk MA and Filler SJ. Effect of sulphadoxine-pyrimethamine resistance on the efficacy of intermittent preventive therapy for malaria control during pregnancy. A systematic review. JAMA. 2007; 297:2603-2616
11. Orobaton N, Austin AM, Abegunde D, Ibrahim M, Mohammed Z, Abdul-Azeez J , Ganiyu H , Nanbol Z , Fapohunda B and Beal K. Scaling-up the use of sulfadoxine-pyrimethamine for the preventive treatment of malaria in pregnancy: results and lessons on scalability, costs and programme impact from three local government areas in Sokoto State, Nigeria. Malar J.; 2016 (15):533
12. Falade CO, Yusuf B, Fadero FF, Mokuolu OA, Hamer DH and Salako LA. Intermittent preventive treatment with sulphadoxine-pyrimethamine is effective in preventing maternal and placental

malaria in Ibadan, southwestern Nigeria. Malaria Journal 2007, 6(88).

13. Menéndez C, Bardaji A, Sigauque B, Sergi Sanz S, John J, Aponte JJ, Mabunda S, Pedro L and Alonso PL Malaria Prevention with IPTp during Pregnancy Re duces Neonatal Mortality. PLoS ONE. 2010; Vol. 5 , Issue 2.
14. Eisele TP, David A, Larsen DA, Philip A, Anglewicz PA, Keating J, Yukich J, Bennett A, Hutchinson P and Steketee R W. Malaria prevention in pregnancy, birthweight, a nd neonatal mortality; a meta-analysis of 32 national crosssectional datasets in Afr ica. Lancet Infect Dis 2012; (12) 942–49
15. National Population Commission (NPC) [Nigeria] and ICF International. Nigeria Demographic and Health Survey 2013. Abuja, Nigeria, and Rockville, Maryland, USA: NPC and ICF International 2014.
16. Fagbamigbe A F, Bamgboye EA, Yusuf BO, Akinyemi JO, Issa BK, Ngige E and Abatta, E. The Nigeria wealth distribution and health seeking behaviour: evidence from the 2012 national HIV / AIDS and reproductive health survey. Health Economics Review (2015); 5(5), e1–e10. https://doi.org/10.1186/s13561-015-0043-9
17. UNICEF and WHO levels and trends in child mortality. Report 2015 http://www.who.int/maternal_child_adolescent/doc uments/levels_trends_child_mortality_2015.pdf?ua =1 (accessed Mar 2018).
18. Adeoye I, Quadri G and Adedini SA. Maternal health care utilization and neonatal mortality in Nigeria: looking beyond the micro-level pathway of influence African Population Studies 2017; Vol. 31, No. 1,(Supp.),
19. Ezeh O K, Agho K E, Dibley M,Hall J and Page AN. Determinants of neonatal mortality in Nigeria: evidence from the 2008 Demographic and Health Survey BMC Public Health 2014, 14:521
20. Kayode GA, Ansah E, Agyepong IA, Amoakoh-Coleman M, Grobbee DE and Klipstein-Grobusch K. Individual and community determinants of neonatal mortality in Ghana: a multi-level analysis BMC Pregnancy and Childbirth 2014, 14:165.
21. Singh A, Pallikadavath S, Ram F and Alagarajan M. Do antenatal care interventions improve neonatal survival in India? Health Policy Plan 2014 29 (7): 842-848. DOI: https://doi.org/10.1093/heapol/czt066
22. Tongo OO, Orimadegun AE and Akinyinka OO. Utilization of malaria preventive measures during pregnancy and birth outcomes in Ibadan, Nigeria BMC Pregnancy and Childbirth 2011,11:60 http://www.biomedcentral.com/1471-2393/11/60.
23. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. New England Journal of Medicine, 1985, 312: 82–90.
24. Yasmin S, Osrin D, Paul E and Costello A. Neonatal mortality of low-birth-weight infants in Bangladesh. Bulletin of the World Health Organization, 2001, 79: 608–614.
25. United Nations Children's Fund and World Health Organization, Low Birthweight: Country, regional and global estimates. UNICEF, New York, 2004.
26. Kramer MS. Determinants of Low Birth Weight: methodological assessment and meta-analysis. Bulletin of the World Health Organization. 1987;65(5):663–737.
27. Steketee RW, Wirima JJ, Hightower AW, Slutzker L, Heymann DL, and Breman JG. The effect of malaria and malaria prevention in pregnancy on offspring birthweight, prematurity, and intrauterine growth retardation in rural Malawi. 1996. Am. J. Trop. Med. Hyg.55**:**33-41
28. Rogerson SJ, Brown HC, Pollina E, Abrams ET, Tadesse E, Lema VM and Molyneux ME. Placental Tumor Necrosis Factor Alpha but Not Gamma Interferon Is Associated with Placental Malaria and Low Birth Weight in Malawian Women Infection and Immunity, Jan. 2003, Vol. 71, No. 1 p. 267–270.