KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY,

KUMASI, GHANA

COLLEGE OF HEALTH SCIENCES

SCHOOL OF PUBLIC HEALTH

DEPARTMENT OF GLOBAL AND INTERNATIONAL HEALTH

MALARIA CONTROL IN PREGNANCY: AN EVALUATION OF THE EFFECTIVENESS OF IPTp POLICY ON MATERNAL AND NEONATAL HEALTH IN THE TAMALE METROPOLIS OF NORTHERN GHANA

BY

YAA NYARKO AGYEMAN

DECEMBER 2020

KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY,

KUMASI, GHANA

MALARIA CONTROL IN PREGNANCY: AN EVALUATION OF THE EFFECTIVENESS OF IPTp POLICY ON MATERNAL AND NEONATAL HEALTH IN THE TAMALE METROPOLIS OF NORTHERN GHANA

BY

YAA NYARKO AGYEMAN (PG 2393314)

B.Sc. Nursing, MPH.

A THESIS SUBMITTED TO DEPARTMENT OF GLOBAL AND INTERNATIONAL HEALTH, COLLEGE OF HEALTH SCIENCES, SCHOOL OF PUBLIC HEALTH, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN PUBLIC HEALTH

DECEMBER 2020

DECLARATION

I, Yaa Nyarko Agyeman hereby declare that, with the exception of references to other people's works and publications which have been duly acknowledged, this thesis is my original work and has not been presented for any other awards at the Kwame Nkrumah University of Science and Technology or any other learning institution.

YAA NYARKO AGYEMAN ……... ……..
(PG 2393314) SIGNATURE DATE

Certified by:

PROF. ELLIS OWUSU-DABO ……... ……
SIGNATURE DATE

Certified by:

PROF. SAM NEWTON …… ……
SIGNATURE DATE

Certified by:

PROF. EASMON OTUPRI ..……..... ……
SIGNATURE DATE

HEAD OF DEPARTMENT

PROF. SAM NEWTON …… ……
SIGNATURE DATE

DEDICATION

This thesis is dedicated to the memory of my mentor, father and pastor, the late Rev. Dr. Edmund Nii Laryea Browne.

ACKNOWLEDGEMENT

Firstly, I thank the Almighty God for His grace and mercies which saw me through this work. I am very grateful to Prof Ellis Owusu-Dabo, my primary supervisor for strengthening my research skills and knowledge; I appreciate his critical comments and suggestions, guidance, support, encouragement and above all the keen interest which he showed in this study. Indeed, I have really learnt a lot under his supervision and to Professors Sam Newton and Easmon Otupri, my secondary supervisors, thank you for critically reviewing the thesis and giving me valuable feedback.

I also wish to thank the Head of Department, Global and International Health, Prof. Sam Newton for his directions and support throughout the course of study and all the lecturers at the School of Public Health, KNUST.

My heartfelt gratitude goes to Dr. Jacob Mahama, Regional Director of Health Services, Ghana Health Service and Dr. Ali, the Metropolitan Director of Health Service Tamale, Northern Region, for their kind permission for this study to be conducted in the Metropolis and also for their support throughout the field work. Furthermore, I wish to thank Mr. Gaspard K. Dery, the Municipal Coordinating Director, Tamale Metropolitan Assembly, for assisting me with information on the classification of the towns into rural and urban. Again, I also want to thank the CEO of Tamale Teaching Hospital, Dr. Prosper Akambon, the Medical Superintendents of West and Central hospital as well as the Medical Director of the Seventh Day Adventist Hospital for the support throughout the period of data collection. I want to thank Mr. Bani Bannison, the Biomedical scientist at the Tamale Teaching Hospital who assisted me with the laboratory investigations and also my hardworking research assistants especially Rita Neindow and Alhassan Bukari. God bless you for the commitment and sacrifice you put in during the data collection. The technical assistance of the midwives

at all the data collection centers, the laboratory technicians and the staff of the health facilities involved in the study is gratefully acknowledged.

Special thanks go to the pregnant women who enrolled and participated to make this study possible.

I also want to thank Dr. Anthony Wemakor and Martin Adjuik, lecturers at the University for Development Studies and University of Health and Allied Sciences respectively, who tirelessly assisted me in the data analysis. I also wish to thank my father; Mr. Thomas Arthur who assisted in proof reading the thesis. God richly bless you all.

I also want to thank my husband, Rev. Dr Theophilus Adjeso and children; Kezia, Lois and Phoebe, for their support, love and sacrifice during the entire period of study.

Finally, my heartfelt gratitude goes to all my colleagues for their support and the various authors from whose work I extracted important information to make this study a success.

DEFINITION OF TERMS

Anaemia: defined as haemoglobin concentration less than 11.0g/dl

Fever: an axillary temperature equal to or greater than 37.7 degree Celsius

Gravidae: is the number of times a woman has been pregnant

Low Birth weight: less than 2.5kg /2500g (up to and including 2499g)

Maternal Clinical malaria: Acute onset of pyrexia, loss of appetite, vomiting, myalgia, headache and the presence of parasitaemia and in the absence of any comorbidity.

Malaria infection: the presence of asexual *P. Falciparum* parasite of any density in a blood smears detected by using thick microscopy.

Miscarriage: giving birth to a non-viable foetus either or before 28 weeks pregnancy

Multigravidae: a woman who has been pregnant for at least 3 times

Multiparous: a woman who has given birth two or more times

Nulliparous: a woman who has not delivered a child before

Parity: the number of times that a woman has delivered a foetus with a gestational age of 24-weeks or more, regardless of whether the baby was delivered alive or dead.

Prematurity: birth before the beginning of the 37^{th} weeks

Primigravidae: a woman becoming pregnant for the first time / one time

Primiparous: A woman who has given birth once before regardless of the outcome

Secundigravidae: a woman becoming pregnant for the second time

Stillbirth: delivery of a non-living foetus after 28 weeks of gestation

Sulphadoxine pyrimethamine: is a drug that is given to pregnant women from 16 weeks of gestation at 4 weeks' interval to prevent malaria in pregnancy

ABBREVIATIONS/ACRONYMS

ANC	Antenatal care
CRL	Crown Rump Length
DOT	Directly Observed treatment
ENAP	Every New-born Action Plan
GBD	Global Burden of Disease
GE	Gestational age
GHS	Ghana Health Service
HB	Haemoglobin level
HIV	Human Immunodeficiency Syndrome
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ITM	Insecticide Treated Material
ITN	Insecticide Treated Net
IPTp	Intermittent Preventive Treatment of Malaria in Pregnancy
LBW	Low Birth Weight
MIC	Multiple Indicator Cluster Survey
MiP	Malaria in Pregnancy
MOH	Ministry of Health
MPAC	Malaria Policy Advisory Committee
NMCP	National Malaria Control Programme
PM	Placental Malaria
PTB	Preterm baby
RDT	Rapid Diagnostic Test
SGA	Small for gestational age

SP	Sulphadoxine-Pyrimethamine
SMI	Submicroscopic Malaria Infection
UNICEF	United Nations International Children's Emergency Fund
WHO	World Health Organization

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF MAPS

LIST OF APPENDICES

ABSTRACT

Background: Malaria in pregnancy can have a negative impact on maternal and neonatal health, if not properly managed. One of the interventions for controlling the bad impact of unhealthy birth outcomes is through the use of Intermittent Preventive Treatment of Malaria (IPTp) using Sulphadoxine Pyrimethamine (SP). The World Health Organization (WHO) currently recommends the use of maximum five (5) doses of IPTp-SP during the second and third trimester of pregnancy at four weeks interval from 16 week to 38 weeks. However, no study has been done since its implementation in 2014. The aim of the study was to evaluate the effectiveness of IPTp policy on maternal and neonatal health in the Tamale Metropolis of Northern Ghana.

Methods and Materials: The study was a Prospective Cohort with a quantitative approach from the four selected hospitals (Seventh Day Adventist (SDA), Tamale Teaching Hospital (TTH), Central and West hospitals) within the Tamale Metropolis from September, 2016 to August 2017. A cross-section of pregnant women who attended ANC were recruited at 16 weeks of gestation and also at quickening of the baby though the pregnancy may not be up to 16 weeks (at quickening) from the four selected health facilities. The register at the facilities served as a sampling frame and respondents were randomly sampled out of the numbers of pregnant women available during each clinic visit to obtain the predetermined sample size. Microscopy was used to check malaria parasitaemia at 36 weeks of gestation, however, haemoglobin level estimation was extracted from the Maternal Health Book at registration (booking) and at 36 weeks of gestation. Validated weighing scales were used to weigh the babies within 6 hours of delivery and the birth outcome recorded immediately after delivery. Chi-square and logistic regression were used to determine the odds association between the independent variable (IPTp-SP) and the dependent outcomes (maternal malaria infection, haemoglobin, low birth weight and and stiibirth)

Statistical significance was set at $p< 0.05$.

Results: A total pf 1181 participants were used in the final analysis. Almost half of the pregnant women (42.4%) reported uptake of ≥3 doses of SP up to the revised WHO acceptable doses. The prevalence of malaria (16.9%), anaemia (54.1%) LBW (7.1%) and stillbirth (7.4%) were high among the pregnant women who reported usage of ≥3 doses of SP. Pregnant women who reported uptake of ≥3 doses were 56% less likely of having malaria (aOR 0.44; CI 0.27-0.70; p=0.001) and 63% less likely to give birth to babies with low weight (aOR 0.37; CI 0.21-0.68; p=0.001). However, the effect of taking three or more doses did not translate into protection against maternal anaemia (aOR 0.89; CI 0.55-1.45; p=0.65) and stillbirth delivery (aOR 1.15; CI 0.55-2.42; p=0.71). A laboratory-based content analysis was performed on the 23 SP samples. A significant proportion of the drugs contained the right amount of Sulphadoxine but inadequate amount of the pyrimethamine.

Conclusion: The revised WHO IPTp-SP policy of taking at least 3 doses of SP was associated with reduced odds of peripheral malaria parasitaemia and low birth weight but this effect did not translate into the benefits on maternal anaemia and stillbirths. It is highly recommended that, the Ministry of Health should find innovative ways to help increase the usage of IPTp 3 and above. Further research is required to provide answers to the deficiencies related with intervention use and the increased risk of anaemia during late gestation.

CHAPTER ONE

1.0 INTRODUCTION

Chapter one entails the background information, problem statement, conceptual framework, the study objectives, the scope of the study and the organization of the study.

1.1 Background Information

Malaria is a parasitic disease that affects people living in the tropical and subtropical regions of the world. The most affected group are pregnant women and children under 5 years of age. Most maternal deaths and miscarriages have resulted because of malaria infection. The disease is caused by a protozoan of the genus Plasmodium and transmitted through the bite of an infective female Anopheles mosquito. There are five species of Plasmodium parasites that cause malaria in humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale and Plasmodium knowlesi* (Dfid, 2010).

The various Plasmodium species demonstrate differential risk, severity and gravidity effects in pregnant women because of dissimilar pathologies and distinctive immunity. *P. falciparum*, often interact with placenta receptors so infections largely increase the magnitude of adverse birth outcomes like low birth weight (LBW) and stillbirth (McLean *et al.*, 2015).

Since 2010, 125 million pregnancies in *P. falciparum*-endemic areas of the world, suffer a yearly malaria-related infant mortalities in the region of 75 000 and 200 000 (Steketee & Campbell, 2010). In Sub-Saharan Africa, the main infecting parasite is *P. falciparum* and is responsible for 99% of all Malaria in Pregnancy (MiP) cases (World Malaria Report, 2017). In areas where the parasite transmission is stable, over 20 million pregnancies annually are at risk (WHO, 2014; Desai *et al.*, 2007; Guyatt and Snow, 2004). According to a meta-analysis report, the mortalities are because of limitations in the effective detection and management of malaria cases in pregnant women and the further risk of anaemia in the mothers. Thus,

malaria-related anaemia affects maternal health status and induces LBW in the foetus, which catalyses infant death. MiP induced low birth weight causes 100 000 infant deaths in Africa each year (WHO, 2013; Desai *et al.*, 2007).

According to the Global Burden of Diseases (GBD) report, 2017, the global stillbirth rates have declined by 47% since 1990 however, 2.6 million third-trimester stillbirths still occur annually. The reductions, especially beyond the year 2000, were as a result of improvements in access to antenatal care and the resolution of known maternal risks for stillbirth. Nevertheless, gaps in the utilisation of antenatal care, inadequate detection and treatment of maternal conditions such as malaria during pregnancy, were increasing the rates in Sub-Saharan Africa (~29 stillbirths per 1000 births), and Southern Asia (~26 stillbirths per 1000 births) (Global Burden of Disease Study 2017, 2017; S. M. Taylor & Kuile, 2017). *Plasmodium falciparum* associated MiP account for 4.5% of all stillbirths (in excess of one million) in Asia and the Oceania regions. Similarly, in Africa, over 200,000 stillbirths are due to falciparum MiP (Moore *et al.*, 2017; Aminu *et al.*, 2014).

Fundamentally, the commencement of pregnancy alters the immunological pattern of mothers to reduce foetal rejection and accommodate maternal transfer of antibodies to the foetus. Nonetheless, the immunological changes and the presence of the placenta (serving as a sequestration site for malaria parasites), modify the susceptibility to falciparum infections by 3-fold (McLean *et al.*, 2015; Sappenfield, Jamieson and Kourtis, 2013; Huynh *et al.*, 2011). Classically, *Plasmodium falciparum* infected red blood cells (RBCs) often sequester in the intervillous spaces of the placenta to hide from splenic clearance and cause acute, chronic or past placental malaria (PM) infections. The risk for PM is higher in pregnant women with symptomatic malaria, primigravidae (women pregnant for the first time) and pregnant women living in rural settings (Lufele *et al.*, 2017). However, women in endemic areas such as

Ghana, develop high levels of immunity after infection. Yet, the immunity reduces parasite densities and clinical symptoms rather than protecting women against subsequent infections. Therefore, future infections are sub-microscopic and asymptomatic. Thus, women do not experience fever or other commonly known malaria symptoms to facilitate detection and initiate prompt treatment (McLean *et al.*, 2015).

Since, placental malaria are sub-microscopic, asymptomatic and undetectable by diagnostic microscopes, they subsequently transform into symptomatic infections or serve as a repository for parasite transmission (Chen, Clarke, Gosling, Hamainza, & Killeen, 2016). Accordingly, the WHO has recommended three interventions for implementation in member countries to control MiP. These are (i) effective case management of malaria, (ii) the use of Insecticide Treated Nets (ITNs) and (iii) Intermittent Preventive Treatment (IPT) using Sulphadoxine-Pyrimethamine (SP) (WHO, 2004). Conventionally, Artemisinin Combination Therapies (ACTs) and Quinine are available antimalarials for treating MiP and are of bearable toxic effects, safety and efficacy outcomes (WHO, 2015). However, the ineffectiveness of antimalarial drugs provided to patients with malaria affect the overall management of the disease. The total parasite load in not effectively cleared because treatment is not effective. Thus, a resultant 16% of uncomplicated and 50% of severe malaria cases remain untreated (World Malaria Report, 2017). Additionally, the absence of safe and effective viable methods for active detection of early pregnancy infections are impeding the efforts to prevent MiP through effective case management (Rijken *et al.*, 2014).

Thus, the interventions that protect pregnant women against malaria infection before their first ANC visit continue to fail. Pregnant women acquire PM through pre-antenatal infections of the peripheral blood and have submicroscopic and asymptomatic infections prior to their first enrolment at the ANC. Further, women are also at risk of developing malaria infections

in-between scheduled antenatal visits, after the first ANC contact (Cohee *et al.,* 2014). Hence, health planners have to implement operative measures that control malaria infections throughout the period of pregnancy in order to reduce the risk of malaria-related adverse birth outcomes like LBW and stillbirth. In as much as treatment does not eliminate MiP, preventative methods such as ITN and IPTp-SP have become important in stable transmission areas (Moore *et al.,* 2017). In Ghana, the government provides free antenatal care and pregnant women have access to ITNs and IPT with SP (the programme drug providing prophylaxis against malaria) (Owusu-Boateng & Anto, 2017).

However, evidence from reviewed documents indicates diminishing efficacy and effectiveness of SP under IPT (Yeboah, Afoakwah, Nwaefuna, Verner, & Boampong, 2016). Therefore, the Evidence Review Group (ERG) of the WHO now recommends that SP be took under Directly Observed Therapy (DOT), from the second trimester (first ANC visit) and also at subsequent visits separated by a month interval until delivery. The new policy however, increases the number of SP doses to three and above. But this new policy does not refer to a specific number of doses, thus, providing an avenue for variation between WHO target countries (WHO, 2013).

Ghana initiated the new WHO IPTp-SP recommendation in 2014, and pregnant women were expected to take a minimum of three doses of SP and a maximum of five doses, with each dose took under the direct observation of a health worker. The first dose is taken at the first ANC enrolment in the second trimester and the remaining doses scheduled to be taken during regular monthly antenatal visits until delivery (‘President's Malaria Iniyiative, Ghana Malaria Operational Plan FY 2014’, 2014; National Malaria Control Programme, 2013). The revised policy has been scaled up to all the regions of Ghana including the 26 districts of the Northern Region but its effectiveness in reducing maternal malaria parasitaemia, maternal

anaemia, LBW and stillbirth after implementation remain unknown. Analysed data of ITN users in the country revealed that Ghana has the highest (48%) prevalence of MiP in the sub-region both in the wet (59%) and in the dry seasons (41%). Therefore, ITN use is not protecting women since MiP prevalence is increasingly high among bed net users (Berry *et al.*, 2018). Besides, primigravidae were at an uncontrollable risk of recording higher prevalence of malaria-related adverse birth outcomes like LBW and stillbirth after the review of existing MiP chemoprophylaxis programmes. According to Igboeli *et al.*, (2018), pregnant women have become more liable to malaria infection after the review of chemoprophylaxis prevention in Nigeria. The authors reported that national programme coverage depreciated and prevalence as low as 13% usually accompany such reviews. Meanwhile, lower IPTp-SP coverage significantly increases the prevalence of LBW deliveries in all gravidities (Igboeli *et al.*, 2018).

Notwithstanding, West Africa is generally witnessing improvements few years after the implementation of the new WHO IPTp-SP policy. Comparably, in Ghana, 41% of women are attending their first ANC in the first trimester and SP stock levels in health facilities remain optimal, four years after implementation. Again, the majority of women (87%) are still satisfying the requirement of not less than four visits before delivery, as per the erstwhile WHO policy on ANC visits (Owusu-Boateng & Anto, 2017). Yet, the new IPTp-SP is partially effective against submicroscopic infections and does not prevent new infections. Subsequently, the risk of recurrent malaria is increased and the last episode is often detectable in the third trimester. Moreover, submicroscopic parasitaemia have been reported to have strong association with PM, which increase the burden of LBW and stillbirth. Therefore, it is important to design studies that link antenatal infections with definite delivery and birth outcomes such as LBW and stillbirth. In that, such studies are capable of detecting

sub-microscopic infections, therefore making it possible to evaluate the effectiveness of MiP preventive strategies like the reviewed IPTp-SP programme (Moore *et al.*, 2017; Cohee *et al.*, 2014).

Importantly, the antimalarial and prophylactic properties of SP depend on drug dose, pharmacokinetic properties, and level of parasite resistance. However, the clinical effectiveness of SP under IPTp is dependent on acquired antimalarial immunity. Therefore, in settings with established immunity and low parasite resistance like Ghana, administering quality SP under increased dosages limits malaria-related adverse birth outcomes (Odongo, Odida, Wabinga, Obua, & Byamugisha, 2016). Since, pregnant women who take IPTp-SP still have high parasitaemia in their peripheral blood detectable by conventional diagnostic methods such as RDTs and microscopes. Consistently, high parasitaemia is associated with LBW especially among non-ITN users. Similarly, awareness and usage of ITNs have dropped and most pregnant women are not using bed nets to protect themselves against malaria infections. In Ghana, the prevalence of LBW in women who take IPTp-SP and do not use ITNs is 14% in the Bekwai district of the Ashanti region (Darko, Prince, Jonathan, & Kd, 2018).

However, scientists and researchers into malaria are inconclusive on the importance of using RDTs to assess the effectiveness of malaria control programmes implemented to reduce malaria-related adverse pregnancy outcomes (Medina *et al.*, 2018).

In this light, the current study used microscopes (the gold standard) to examine peripheral blood smears of pregnant women to investigate the effectiveness of the revised IPTp-SP in protecting women against malaria parasitaemia. The different SP doses available under the new programme were assessed to determine the dose under which protection against LBW and stillbirth is attained if the right quality of IPTp-SP is dispensed at the ANC to pregnant

women. With this in place, ongoing efforts aimed at improving the quality of IPTp-SP services and the scaling-up of SP as well as ITN coverage towards universal levels can avert the significant adversities of malaria in pregnancy (Hill *et al.*, 2014).

1.2 Problem Statement

Malaria in pregnancy is a major public health problem, with substantial risks for the mother, her foetus and the new-born. According to the Ghana Health Service (GHS), malaria is the leading cause of morbidity in Ghana. In 2012, malaria accounted for 16.8% of pregnant women hospital admissions and 3.4% maternal mortalities (NMCP, 2013; Akotsen-Mensah, 2014). Since 2013, the frequency of Malaria in Pregnancy (MiP) in the Northern Region is increasing, that is 13,423 in 2011, 15,954 in 2012, 16,547 in 2013, 21,864 in 2015, over 25,000 in 2016 and almost 30,000 in 2017 (NMCP, 2013; NMCP, 2016; GHS, 2018). Contrary, malaria-related maternal deaths in the Northern Region was reported to be 144 in 2011 and 122 in 2013. Within the same period, the national rates of malaria attributable LBW marginally declined from 8.7% in 2011 to 8.3% (49,338 births) in 2013 but stillbirth rates remained comparably lower, 1.8% representing 10 700 births (Reproductive and Child Health Report, 2013). Comparably, the global stillbirth cases have also declined from 4·0 million in 1990 to 2·1 million as reported by the Global Burden of Disease (GBD) in 2017 (Global Burden of Disease Study, 2017). In absolute terms, stillbirth rates are dropping from 28 per 1000 live births to 15 per 1000 live births. However, among the 10 regions of Ghana, the Northern Region rates remain higher. The region recorded LBW rates of 9.4%, though higher than the national average of 8.3%. With respect to stillbirth, the region ranked second to the Western region with a rate of 2.2% and 2.3% respectively, compared to the national rate of 1.8% (A. Report, 2013). For the Tamale metropolis where this study was conducted, the percentage stillbirth and LBW were 3.4% and 10.1% respectively, once again higher than

the national and regional rates (Reproductive and Child Health Report, 2013). Therefore, it is unclear whether the observable drops in LBW and stillbirth are linked to implemented malaria control interventions or not.

The drug that is used to mitigate the effect of malaria in pregnancy is Sulphadoxine Pyrimethamine. The IPTp-SP in Ghana generally contains the right active ingredients (Sulphadoxine and pyrimethamine), but the amount available for absorption after ingestion is less and renders it ineffective due to the low dose. The situation is magnifying the susceptibility of pregnant women to malaria infections and defeating the aim of the new IPTp-SP revision in the Central Region of Ghana. Poor quality SP accounts for persistent malaria infections in pregnant women living in the Cape-Coast Metropolis who were enrolled in the reviewed IPTp-SP programme implemented in the country. The gap identified was whether the persistence exposure to malaria infection due to the ineffective treatment and protection of the IPTp-SP, was aggravating the consequences of MiP (LBW and stillbirth) (Yeboah *et al.,* 2016). According to a 2014 report, taking a single SP dose protected pregnant women in Kumasi, Ghana, better than multiple dosing (Asundep *et al.,* 2014). Once again, questioning the basis for the policy review in the first place. However, Yeboah *et. al.*, reported that taking less than three doses of SP has been identified to provide weaker protection against malaria infection among pregnant women in Central region of Ghana (Yeboah *et al.,* 2016). Another study conducted in Navorongo of Northern Ghana, reported that higher SP doses were not able to protect pregnant women against episodes of malaria (Anto *et al.,* 2019).

This brings to the fore important issues for consideration in the light of the new IPTp-SP upgrade since no document in Ghana is associating the reviewed protocol to complete parasite clearance and absolute chemo-prophylactic protection as in Thailand (Desai *et al.*, 2016).

The lack of data to support the observations in Ghana brings to bear debatable issues. The notable ones are whether the effectiveness of a single dose SP was by chance or because many early pregnancy malarias are mild infections, and that the impact of multiple dosing on birth outcomes remain undetectable before studies fold up. It was observed that most of the study reports obtained from Ghana are mostly cross-sectional and that investigators capture the effects of only single dosing. Additionally, available documents inconclusively adduce that since in practice, women take SP along with folic acid, the practice magnifies SP resistance (Asundep *et al.*, 2014), so that efficacy remains similar irrespective of the dosing frequency. What was missing, pertains to the differential dosing threshold for such resistance or whether the folic acid compromises the effectiveness of the SP or the SP was substandard and rather facilitating the lack of effective treatment. The inconsistencies in the findings of the various published studies necessitated this study to evaluate the effectiveness of the IPTp-SP policy on maternal and neonatal health by using prospective cohort study design. The current study contributed to the ongoing debate by, assessing the adequacy of the SP obtained from the ANCs within the four health facilities studied and determined the current dosing regimen under the new IPTp-SP protocol that effectively protected women against adverse birth outcomes (stillbirth and LBW). Again, the study findings would serve as the current evidence that would provide the needed scientific data required to help shape policy with regards to the pregnancy intervention programmes in Ghana.

1.3 Rational of the Study

The three core strategies needed to help address challenges involved in malaria intervention programmes require a holistic and coordinated approach involving; the SP product, the pregnant woman and the unborn baby. At the center of all these parameters is the SP drug used in the prevention of malaria and or used to offer some level of protection for both mother and the foetus.

SP product and mother

Good quality SP product provided to pregnant women who attend ANC within the Tamale metropolis is expected to decrease parasitaemia and prevent anaemia during the time of their pregnancy. The level of dosing is expected to correspond with the level of protection. It is hypothesized that pregnant women who received with three or more doses would have a better protection than those without or with less doses.

Mother and unborn baby

The effective protection of pregnant women who are offered with three of more doses of SP as well as good quality SP products should have some level of association on birth outcomes with respect to stillbirth and LBW.

SP and unborn baby

It is hypothesized that, pregnant women who are offered three or more doses of SP of good quality should have some level of protection (though indirectly), when the pregnant women adhere to the completion of the required doses.

This provides the background and rationale of the study.

1.4 Conceptual Framework

Maternal malaria and anaemia during pregnancy affect the health of pregnant women and the foetus leading to adverse birth outcomes such as low birth weight and stillbirth. Since, the life of the foetus is supported by the mother, health conditions that negatively affect maternal health directly threatens the status of the foetus. Typically, maternal malaria infections induce placental malaria as maternal Plasmodium-infected RBCs clog the placental intervillous spaces. Subsequently, the clog impedes the movement of nutrients (iron) from the maternal end of the placenta to the foetus (Kaur, Bhatia, Midha, & Debnath, 2017).

The obstruction of placental function, activates compensatory reactions (placental autophagy) to restore oxygen and nutrient flow to the foetus. However, placental autophagy is associated with the accumulation of lysosomes and autophagosomes which dysregulate the autophagic process and further interfere with the transport of amino acid through the placenta. The dysregulated autophagy, increases the vulnerability of the foetus to anaemia, which induce growth retardation and low birth weight at delivery (Dimasuay *et al.*, 2017).

Furthermore, the placental blockage obstructs the passage of maternal antibodies (IgG) to the foetus, leaving it prone to malaria and other infections (Kaur *et al.*, 2017). Eventually, the nutrient deficiency and the reduced immunity facilitates poor foetal growth or death and the resultant pregnancy outcome is either low birth weight or stillbirth (Moormann, 2009; Shulman *et al.*, 2002).

Hence, to improve maternal and neonatal health, health planners formulate policies and programmes targeted at preventing malaria and anaemia in pregnancy. IPTp-SP is one of such programmes implemented to protect pregnant women against malaria infections and malaria-related anaemia. Conventionally, the commencement of pregnancy increases the vulnerability of women to anaemia but after they have been provided with IPTp-SP, hemoglobin concentration improves progressively until the time of delivery (Ouédraogo *et al.*, 2012). Although, other studies have reported some level of ineffectiveness in the use of SP in malaria prevention, it is still used to provide malaria prophylaxis during pregnancy because of its continuous efficacy even in areas of reported parasite resistance to the drug (Nkoka *et al.*, 2018). Nonetheless, the ceaseless reports of parasite detection in the peripheral blood of pregnant women who take SP is generating discussions on the effectiveness of IPTp with SP, in protecting women against malaria in pregnancy (Yeboah *et al.*, 2016).

Accordingly, measures such as early ANC attendance, focused antenatal care, ensuring good adherence to DOTs and securing universal IPTp-SP coverage have been identified as what needs to be done in order to harness the full potential of the IPTp-SP programme (Hill *et al.*, 2014). Yet, it remains prudent to dispense the right quality of SP to be taken under the appropriate dosage regimen in order to obtain desirable pregnancy outcomes (Muanda *et al.*, 2015; Arinaitwe *et al.*, 2013). Taking less than three doses of SP has been identified to provide weaker protection against malaria infection among pregnant women in Central region of Ghana (Yeboah *et al.*, 2016). The above evidence highlights the effect dosage regimen has on the effectiveness of the IPTp-SP programme and have necessitated the Ghana health service to upgrade SP dosage to more than three doses. It must be emphasized that to achieve optimal results, drugs of good quality must be provided under the appropriate regimens. Irrespective of the regimen adapted (less than three or more than three), compromising drug quality through poor manufacturing practices, storage and the use of incorrect excipients render it ineffective.

Consequently, in the context of IPTp, preventing maternal malaria infection will control the occurrence of placental infections and enhance materno-foetal exchanges at the placenta, improving foetal growth and neonatal health (Huynh *et al.*, 2011).The obvious strategy then is to respond to the rising cases of malaria in pregnancy by assessing the existing IPTp with SP to ensure that the health of pregnant women and neonates are protected. The study also assessed the dose of active ingredients in the SP given to pregnant women at ANC. Therefore, samples of the programme SP were analysed. The study drug (SP) was tested against the adapted regimen considered under three stratifications, which were (i) no SP group, (ii) below three and (iii) three and above.

This allowed the current study to evaluate the effectiveness of the IPTp policy on maternal and neonatal health outcomes.

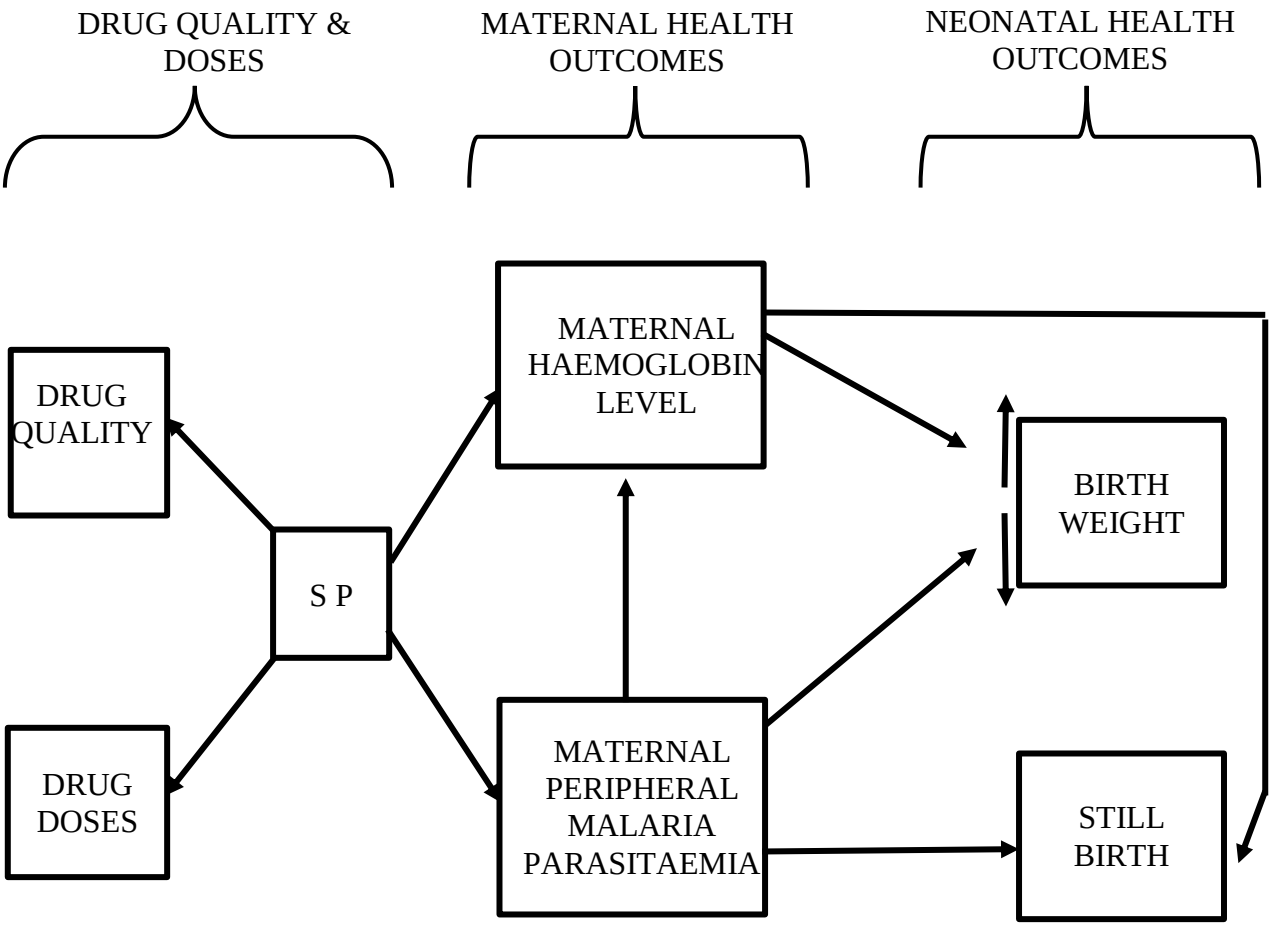


Figure 1.1: Conceptual Framework
Author's Construct, 2017

1.5 Research Questions

The main questions to be addressed by this study were:

1. Is IPTp-SP effective in preventing malaria and improving the haemoglobin level among pregnant women in the Tamale metropolis?
2. Does giving of Sulphadoxine pyrimethamine to pregnant women improve birth weight and prevent stillbirth?
3. Does the number of doses pregnant women take, protect them from the negative effect of malaria on maternal and neonatal health outcomes?

4. What is the adequacy of the SP dispensed to the pregnant women during the antenatal clinic?

1.6 General Objective

To evaluate the effectiveness of the reviewed IPTp policy on maternal and neonatal health in the Tamale Metropolis of Northern Ghana.

1.7 Specific Objectives

1. To assess the effectiveness of IPTp-SP on maternal health by assessing the prevalence of malaria and anaemia (maternal haemoglobin level less than 11g/dl) in third trimester among pregnant women who took IPTp-SP at 36 weeks in the Tamale metropolis
2. To assess the effectiveness of IPTp-SP on birth outcomes by estimating the prevalence of birth weight of mothers with live-singleton babies (less to 2500g) and stillbirths in the Tamale metropolis
3. To establish the association between different doses of IPTp-SP and maternal (e.g., Malaria infection, anaemia) and neonatal health outcomes (e.g., birth weights and stillbirths).
4. To determine the adequacy of the Sulphadoxine Pyrimethamine given to pregnant women

1.8 Scope of the Study

The study was limited to pregnant women in Tamale who attended ANC at the four selected hospitals namely, Tamale Teaching Hospital, Seventh Day Adventist, Central and West hospitals. Even though the use of IPTp-SP was assessed independently, other factors like sleeping in ITN and use of antihelminthics were considered.

1.9 Organization of Report

The project has been organized into six chapters. Chapter one entailed the background to the study, statement of the problem, rational of the study, the logic framework, research questions, general and specific objective and organization of the report.

Chapter two examined the literature related to the topic under research. It has an introductory paragraph that gave an overview of what was contained in this chapter. It also had sections that cover the important aspects of the review such as the overview of the global picture of the disease, Epidemiology, malaria in pregnancy, Intermittent Preventive Treatment of malaria in Pregnancy (IPTp), IPTp-SP and maternal and neonatal outcomes.

Chapter three talked about the profile of the study area, the scope, the methodology employed for this study which included the research methods and design, data collection techniques and tools, the study population, the study variables, sampling procedure employed for the study, pretesting of the instruments, data handling and analysis, ethical consideration and assumptions of the study.

Chapter four contained the primary data from the result of the study, briefly presented. It had the background information in one table and the results have been presented based on the key variables.

Chapter five contained the discussion of the study. A comparison of the findings of the study were made with that in literature in this same chapter.

A summary of the key findings of the study and the relevant conclusions have been presented in chapter six with the necessary recommendations directed for focused pursuance by relevant stakeholders.

CHAPTER TWO

2.0 LITERATURE REVIEW

In this chapter, the literature on the research topic was reviewed. It showed the overview of malaria in pregnancy, the effects of malaria in pregnancy on maternal and neonatal outcomes, intermittent preventive treatment of malaria in pregnancy using Sulphadoxine pyrimethamine, relationship between the SP doses and maternal and neonatal outcomes and implications of SP dose quality on therapeutic and chemoprophylaxis efficacy.

2.1 Malaria in Pregnancy

2.1.1 The Epidemiology of Malaria in Pregnancy

In Africa, the epidemiology of malaria during pregnancy is related to the stability of parasite transmission. Malaria disease is epidemic-prone in areas of unstable transmission and in non-epidemic years, peripheral and placental malaria are very uncommon among pregnant women. Nonetheless, in stable but low transmission areas, peripheral and placental malaria are moderately common in pregnant women (Newman *et al.*, 2003). Factors that determine the prevalence rates of MiP ranges from rejection of chemo-prophylactic drugs in Afghanistan to sample type used for prevalence analysis, area-specific immunity, the presence of parallel control programmes in Sudan. In the Blue Nile region of Sudan, prevalence is high whether peripheral blood films (37.8%) or placental films (59.3%) are used for analysis and active parallel control programmes are lacking. In Sub-Saharan Africa, the prevalence of MiP can be as low as 9% and as high as 60% (Omer *et al.*, 2017). Younger women account for the largest group of pregnant women. For West Africa, almost half of the pregnant women are primigravidae except in Burkina Faso, where secundigravidae dominate.

The risk of infection in the region is highest in younger, primigravidae with low socio-economic status (Berry *et al.*, 2018).

In Ghana, malaria prevalence varies with geographical locations, economic conditions and seasonal changes. In the Kumasi metropolis, malaria prevalence is 19% towards the southern parts of the Ashanti region in the Bekwai area (Asamoah *et al.*, 2018). Malaria prevalence (19.7%) remains markedly similar around the coastal areas of the Dangme-West district in the Greater Accra region but relatively lower (5%) in the Madina Municipality of the Greater Accra region (Stephens, Ofori, Quakyi, Wilson, & Akanmori, 2014). Also, in most parts of Northern Ghana, malaria prevalence is high (47%) including the Kassena-Nankana District of the Upper East region (Clerk, Bruce, Greenwood, & Chandramohan, 2009a). The prevalence of MiP is highest in primigravidae and primiparous women but infections in primigravidae are associated with severe parasitaemia detectable by RDTs or microcopy (Asamoah *et al.*, 2018; Asundep *et al.*, 2014).

2.1.2 Risk factors for malaria in pregnancy

Plasmodium falciparum malaria parasites express a set of six genes (var genes) which play important role in placental malaria. Var genes are comparably transcribed at much higher level in falciparum parasites following infection of pregnant women and are involved in the synthesis of proteins that act as distinct receptors for parasite-binding in the placenta (Francis *et al.*, 2007). Malaria in Pregnancy (MiP) is of two sources, (1) infected women becoming pregnant and (2) pregnant women becoming infected. Clinically, malaria infection may be symptomatic, diagnosed and treated with readily available effective antimalarials. Alternative to this, are asymptomatic, not readily diagnosed and untreated infections which can last for several months and catalyze the development of immunity. Notwithstanding, women with these infections (Asymptomatic infections), become pregnant already harbouring malaria

parasites. Thus, these long-duration preconception infections are passed on into pregnancy to facilitate the onset of MiP in the first or second trimester (Accrombessi *et al.*, 2018; Berry *et al.*, 2018; Newman *et al.*, 2003).

Invariably, seasonal variations in rainfall pattern affect malaria transmission intensity and higher infections are recorded during the time pregnancy encounters the rainy season. Women with a greater number of their pregnancy months occurring in the rainy season are at the highest risk of malaria infection (Jäckle *et al.*, 2013; Bardají *et al.*, 2008). Substantial levels of infections are recorded in women whose entire pregnancy before the first ANC visit, is spent in the dry season. Therefore, Malaria transmission among pregnant women is rather lower but does not entirely stop in the dry season as earlier reported (Cisse *et al.*, 2014; Sonko *et al.*, 2014; Clerk *et al.*, 2009b). Further, transmission rates are particularly highest in the late rainy and early dry months, and risk levels are similar for primigravidae and secundigravidae (Berry *et al.*, 2018; Saute *et al.*, 2002).

As reported in the Hazaribagh area of India, multiple factors influence malaria vulnerability in regions of perennial malaria transmission. The age of pregnant women, lack of education, limited access to control interventions and poverty, promote health and environmental elements suitable for infection establishment. Indoor residual spraying (IRS) is higher in rural Hazaribagh but increasing vector resistance to IRS-chemicals has raised concerns to improve IRS and ITN distribution to reduce MiP burden (Sohail *et al.*, 2015).

Malaria transmission is also affected by geographic variations in vector survival conditions. Therefore, the nature of maternal residence is an important factor that predisposes pregnant women to MiP. There is lower risk of MiP among women in urban contexts because urban-related activities destroy parasite larval breeding sites (Cot *et al.*, 1993). At times, reports of

MiP in rural and peri-urban areas are not readily available to support such comparisons, as observed in Lagos, Nigeria. In such modernized tropical African cities, young maternal age but not gravidity correlates with MiP burden or parasite density. Here, women experience several episodes of malaria prior to their first ANC visit and obtain similar levels of immunity across all gravidities. The knowledge of malaria prevention is balanced across the educational strata because of the extensive educational talks on radio, television and at the child welfare clinics. Hence, educational status is not a predictor of MiP among pregnant women living in Lagos, Nigeria. Also, the high (67%) use of insecticide sprays among pregnant women, at least once a week, lowers their risk to MiP. Nevertheless, poor compliance to ITN use and the complicated biting behavior of mosquitoes expose pregnant women to the dangers of malaria. Although, bed net use translates into modest protection against MiP, poor adherence aided by the use of insecticide sprays have eliminated the significance of ITN use in the Enugu areas of Nigeria (Agomo & Oyibo, 2013).

Generally, most pregnant women rely on free ITN distribution programmes at the ANCs to own or use bed nets. When they miss the opportunity, lack of finances denies them access to acquire one. Adolescents and young adult pregnant women are usually unable to acquire ITNs after missing the opportunity at the ANCs because they have weaker or no employment and are financially incapacitated. Moreover, poor adherence to bed net use is common in adolescents and young adults thereby magnifying their risk to MiP. Thus, younger pregnant women of lower socio-economic status are at the greatest risk of developing malaria later in pregnancy (Berry *et al.*, 2018; Manu *et al.*, 2017; Agomo and Oyibo, 2013).

In addition, factors such as parity, local malaria endemicity, educational status, duration between doses and gestational age contribute to MiP vulnerability. Particularly for Yaoundé pregnant women in Cameroon who sleep in ITNs, primigravidae and women aged between

15 and 19 years are most susceptible to MiP. Here, educational status has little significance on the risk of MiP because of the high poverty rate (40%) which causes people of various educational levels to live together in many disadvantageous neighbourhoods. Again, IPTp-SP doses are served at lengthy intervals so drug effect is lost before the next dose is given, leaving women at high risk of malaria infection. Furthermore, the frequency of malaria infection is related to gestational age. Higher infection rates are recorded in the first and second trimesters than in the third trimester and at the time of delivery (Mbu *et al.,* 2014a).

The effects of malaria on pregnancy is based on factors such as the woman's level of immunity, her gravidity (usually with 1st and 2nd pregnancies) and the trimester of pregnancy (Takem & D'Alessandro, 2013).

Primigravidae and secundigravidae have higher density parasitemia than multigravidae and multigravidae are more likely to have placental parasitemia. This has been attributed to infection-specific immunological and endocrinological factors and also younger maternal age carries a higher risk of infection and adverse effects (Takem & D'Alessandro, 2013). Primigravid women and their offspring have poor outcome (Hartman *et al.*, 2010).

Regardless, according to a qualitative document on the perception and attitudes of pregnant women towards MiP prevention, the awareness of malaria and its management methods influence the commitment of preventing infection. Such that, the actual use of a particular malaria intervention (ITN and/or IPTp-SP) is not a function of its availability but a woman's awareness of MiP and associated dangers. For instance, Onyeneho *et al.,* 2015, found in Enugu (Nigeria) pregnant women that symptoms of malaria such as fever and general weakness are perceived as normal signs of pregnancy. Hence, affirming their decision of not applying any sort of malaria related intervention and remained vulnerable to MiP. Additionally, weak health-provider-pregnant-women interactions at point of care posts

discourage women from using the health system, where malaria preventive interventions are provided to mitigate the risk of MiP. Accordingly, malaria interventions should be made available in the right quantity and quality with antenatal classes designed to raise access in a friendly environment to enhance usage by pregnant women (Onyeneho, Idemili-aronu, Igwe, & Iremeka, 2015).

Similarly, a pregnant woman in rural Mozambique deems malaria harmful but does not consider it dangerous to pregnancy and the foetus. As a result, women are occupied by thoughts of not feeling at risk to the predicaments of MiP in the midst of a potentially efficient system that is already delivering high ANC coverage and appreciable ITN and IPTp-SP services. Also, inconveniences and perceptions of ineffectiveness have promoted low acceptability and adherence to malaria interventions, especially IRS. Thereby, urging pregnant women to choose ITNs over IPTp-SP and other available malaria interventions. Meanwhile, the national ITN coverage is below 30% and many pregnant women are limited in the knowledge of instructions that guarantee maximum benefit of ITN use. So, the factors promoting the preference for ITN over IPTp-SP have to be properly resolved and coverage scaled up in order to witness protection against MiP (Vala, Rupe, Boene, Gonza, & Mene, 2014).

Invariably, maternal immunity is critical in mounting resistance to P. falciparum malaria infections during pregnancy. Acquiring antibodies to VAR2CSA, the focal protein which mediates of infected-erythrocyte adhesion to chondroitin sulfate A (CSA) in the placenta, is key in building defenses against MiP. Antibodies acquired by natural immunity to malaria infections are gender and parity-specific in activity against infecting parasites. The serum of pregnant women especially multigravidae react higher against transcribed proteins from PFL0030c, PFD1140w and PFB0115w (three var genes that encode parasite proteins that

bind to red cells) (Francis *et al.*, 2007). Further, acquiring higher maternal antibody levels to VAR2CSA is gravidity-specific and accumulates over successive pregnancies to effectively improve the risk to MiP. Multigravidae have better immunity against malaria parasites due to durable VAR2CSA antibody responses. On the other hand, secundigravidae require at least one infection during the second pregnancy to stay clinically resistant as multigravidae. Primigravidae are naive with antibody levels that sharply decline after infection, even at delivery. Nonetheless, primigravidae and secundigravidae are at similar risk of higher parasitaemia following infection (Fried *et al.*, 2018; Newman *et al.*, 2003). Yet, adherence to ITN use is better during second pregnancies so secundigravidae have enhanced protection against MiP than primigravidae (Berry *et al.*, 2018).

Therefore, in tropical Africa, the greatest density of infection has always been reported in primigravidae. Age and parity are closely related and predispose women to MiP but analysis of Burkinabe pregnant women highlight parity as the important factor that defines risk to MiP. Again, MiP susceptibility is influenced by genetic factors such as red blood cell disorders and HLA genes. Nevertheless, sickle cell trait in adults unlike children confers no advantage in building immunity against MiP (Cot *et al.*, 1993). Likewise, factors such as haemoglobinopathies (sickle cell, thalassemia, and G6PD deficiency), blood aflatoxin B1 levels and environmental factors predispose pregnant women to pregnancy anaemia and adverse birth outcomes. Topically, since the Ghana Health Service implemented the mandatory intake of malaria and helminth chemoprophylaxis in 2005, the prevalence of adverse birth outcomes has reduced from 45% to 22%. The success has been attributed to high records of IPTp-SP intake after 2006 and the reductions in MiP. However, helminth chemoprophylaxis coverage in pregnant women is fast dropping in the Ashanti Region

(<24%) and the majority of adverse birth outcomes have been linked with the interplay of helminth and malaria infections (Asundep *et al.,* 2014).

2.1.3 The mechanism of malaria infection and the dynamics of immunity

The mechanism of malaria infection begins with the unfolding of a complex immune tolerance phenomenon involving the tolerogenic molecule, Human leukocyte antigen G (HLA-G). The soluble isoform of the molecule, sHLA-G, is a major player in maintaining materno-foetal immune tolerance to enhance efficient host immune responses. P. falciparum evade host immunity by elevating sHLA-G levels to induce immune tolerance and stimulate cytokines to inhibit cell-mediated immune responses (D'Almeida *et al.,* 2017).

During the ring stage of the parasite life cycle, the transcription of var genes increases and the synthesized proteins coordinate the adhesion of sequestered parasite infected-RBCs to the placenta. Infecting parasites bind to placental Chondroitin Sulphate A (CSA) within 10-13 hours after invading peripheral red cells. At about 31 hours, the transcription of PFD1140w, PFB0115w, PFI1785w, PFL0050c, MAL13P1.320 and PFL0030c/ var2csa (var genes) multiplies by two-four-fold. Apart from MAL13P1.320 and PFL0030c/ var2csa, the remaining five var genes code for proteins capable of exiting parasite cells. PFD1140w, PFL0050c and PFI1785w code for proteins that cross parasite cells to aid binding to host erythrocytes through PEXEL or VTS export pathways. Although, studies in East African pregnant women reveal that actual binding to the placental CSA is by a subset of VAR2CSA variants but not VAR2CSA per se. However, PFB0115w and MAL13P1.320 lack the PEXEL or VTS sequences but use an uncharacterized alternative route to colonize the Maurer's clefts of host erythrocyte cytoplasm. Another set of genes comprising two subsets of the HISTa gene family and PF10_0013 have PEXEL sequences and populate the Maurer's cleft but their

role in P. falciparum pathogenesis is unknown. Therefore, the pathogenic processes of falciparum malaria are complex and involve a conglomerate of linked var and non var genes (Francis *et al.*, 2007).

Notwithstanding, host immunological responses to Plasmodium parasites are mainly by humoral (antibody) activity than cell-mediated. Cell-mediated immunity generally suppresses during pregnancy but activates to allow for the infiltration of CD8 T cells and mononuclear cells into placental inflammation sites and to control liver stage infections. Humoral responses are responsible for the acquisition of protective immunity to reduce parasitaemia and the burden of placental infections. There are reports of Plasmodium cross-species immunity but the mechanism in humans and their role in pregnancy lack reliable data. It is unclear whether changes in immunology during pregnancy alter the magnitude of antibody-mediated functions against falciparum antigens. The acquisition and maintenance of species-specific immunity require regular exposure and high parasitaemia densities to boost the efficiency of memory antibody responses. In the absence of continuous exposure, gravidity maintains immunity by preserving pregnancy-specific antibodies (PfVAR2CSA antibodies) and immune memory in-between pregnancies. The half-life of PfVAR2CSA antibodies post-partum (after delivery) ranges from 1-7 years in endemic regions. The longevity of acquired malarial immunity is age dependent and is shorter in younger individuals. Acquired PfVAR2CSA antibodies from earlier pregnancies serve as the main source of defense against P. falciparum infections in subsequent pregnancies (McLean *et al.*, 2015).

Accordingly, malaria infection early in pregnancy but not later (third trimester or delivery) generate high levels of antibodies (anti-VAR2CSA antibodies) to VAR2CSAs adhesion proteins of the parasite. The anti-VAR2CSA antibodies prevent VAR2CSA parasite proteins

from adhering to placental cells. The anti-adhesion function of the anti-VAR2CSA protects women from malaria-related anaemia and bad pregnancy outcomes. As women become pregnant for the first time, any malaria infection during the pregnancy generates anti-VAR2CSA antibodies. The antibodies remain in the women post-delivery, acting as memory-VAR2CSA antibodies and also serving as markers (history) of having had malaria infection during a time of pregnancy. Therefore, women with a history of malaria infection have higher levels of VAR2CSA antibodies. Nonetheless, the levels of antibodies during and after malaria infection are gravidity-dependent. Hence, the ability to retain antibodies at higher levels (after an earlier detectable-infection), beyond post-delivery, is more prominent in paucigravidae than in primigravidae, secundigravidae and multigravidae. Generally, the specificity of memory-VAR2CSA antibodies is substantially weak towards new-VAR2CSA parasite proteins of fresh infections. Therefore, pregnant women remain unprotected against malarial-anaemia and their babies also from adverse pregnancy outcomes (Fried *et al.,* 2018; Gavina *et al.,* 2018).

Naturally, malaria infections trigger higher levels of maternal IgGs and IgMs which protect the foetus against a broad scope of parasite antigens. However, the development of placental infections impairs the materno-foetal transfer efficiency of antibodies. The mechanism leading to this event has remained a debate until recent years. Contrary to evidence from previous studies, McLean and colleagues, 2017, show in Papua New Guinean pregnant women that gestational age and elevations in maternal total serum IgG levels contribute only in small proportions to reduce materno-foetal antibody transfer efficiency. According to them, the direct effects of placental infections are responsible for the greater proportions of inefficient materno-foetal antibody transfer. By their model, placental infections affect placental architecture and the inflammatory responses impact negatively on receptor

expression and materno-foetal transfer. The inflammation disrupts and reduce the expression of placental-immunoglobulin transport receptors, leading to reductions in antibody transfer efficiency (McLean *et al.,* 2017). Largely, IgGs serve as immune markers of protection against bad pregnancy outcomes and IgMs are indicators of parasite exposure. However, the absence of methods that control for heterogeneous exposure to malaria parasites are frustrating efforts to single out the immune responses with specific role of protection during infection. The contention borders on how to disentangle exposure antibodies from protection antibodies and their contributory role against the effects of malaria infection (Mayor *et al.,* 2018).

2.1.4 Symptomatic, Asymptomatic and Submicroscopic malaria infections

Pregnant women with symptomatic malaria infections manifest clinical signs and symptoms together with peripheral parasitaemia levels detectable by microscopes to activate treatment. However, peripheral malaria parasite densities can remain below levels beyond the detection of microscopes (submicroscopic infections), although, parasites inhabit the placenta (placental malaria) or do not inhabit the placenta. Contrastingly, submicroscopic infections do not manifest clinical signs and symptoms for active detection (asymptomatic infections), and subsequent treatment. These untreated malaria infections (submicroscopic, asymptomatic and placental infections) cause severe malaria illness with adverse birth outcomes like spontaneous abortions, stillbirths and low birth weights (Kapisi *et al.*, 2017; Omer *et al.*, 2017). Thus, infected women develop chronic malaria. Therefore, the ability to detect and treat these chronic infections has critical implications on malaria preventative and control programmes. Yet, asymptomatic infections are also submicroscopic and cannot be detected, thereby contributing to the underestimation of malaria disease burden. Since, the majority of sub-microscopic malaria infection is asymptomatic, infected adults carry parasite gametocytes and serves as a source for the local transmission of infection. So, these chronic

infections circulate persistent blood-stage forms of the parasite in the population and pose a threat to vulnerable groups such as pregnant women. The ability to increase the detection of asymptomatic infections for subsequent curative treatment is important as a sustainable measure to eliminate and eradicate malaria. In a public health perspective, treating asymptomatic infections eliminate both individual and population level onward transmissions to improve malaria control (Chen *et al.,* 2016; Idris *et al.,* 2016).

Hence, Chen *et al.,* 2016, argue for the abolishing of classifying malaria infections as being either symptomatic or asymptomatic in order to raise more comprehensive strategies to confront the total burden of the disease. According to them, asymptomatic infections are chronic rather than benign since they create a reservoir of transmissible malaria, and that control tools should inclusively tackle this back-log. However, this comes with operational challenges because detecting and treating chronic malaria infections are scientifically burdensome, costly and politically not feasible (Chen *et al.*, 2016). Consequently, most malaria infections during pregnancy remain asymptomatic and undetected, and increase the risk of maternal anaemia, intrauterine growth retardation, and LBW babies (Darko *et al.*, 2018; Parekh *et al.*, 2007). To a large extent, submicroscopic malaria infection (SMIs) is indicative of frequent malaria exposure and account for 25% MiPs of which greater than 60% develop anti-VAR2CSA antibodies. Consistently, IPTp-SP moderately clears SMIs and provides negligible prophylactic protection to women with SMIs (Gavina *et al.*, 2018; Cohee *et al.*, 2014) . Although, SMIs boost the levels of existing antibodies in multigravidae, no such new antibodies are added in primigravidae (Fried *et al.,* 2018).

2.1.5 Placental malaria infection

Following conception, cell-mediated immune activity is lowered to increase placenta sustenance. However, the immunological shift, makes the placenta a desirable site for P.

falciparum parasites to hide away from host antibody immune responses (Sharma & Shukla, 2017). Hence, parasite infected-red blood cells with the aid of the protein, VAR2CSA, adhere to CSA on the Chondroitin Sulphate Proteoglycans (CSPGs), in the placental syncytium. Thereupon, infecting the placenta and establishing placental malaria (Pereira, Clausen, Pehrson, & Mao, 2016). Placental malaria is classified as acute, chronic or past infection and has varying impact on pregnancy outcomes. Acute infections cause LBW whereas chronic infections are associated with maternal anaemia and preterm delivery (Lufele *et al.*, 2017; Odongo *et al.*, 2016). However, in settings of low malaria transmission outside Africa like Central India, acute PM is related to severe forms of maternal anaemia (1.4g/dl), LBW and shorter gestation. Acute PM with mild placental inflammations shortens gestational age by 4 days and women with moderate or severe inflammations have their gestation being shortened by 8 days. Pathologically, chronic and past PM increases syncytial knots, focal fibrinoid necrosis and calcification of the placenta (Ahmed *et al.*, 2014).

According to the clinical, parasitological, and histological data of pregnant women, placental malaria usually develops from pre-conception infections, rather than new infections acquired after conception (Ofori, Lamptey, Dickson, Kyei-baafour, & Hviid, 2018). Notwithstanding, women are more susceptible to placental malaria infection in the first trimester as general immunity suppresses to accommodate the pregnancy (Sharma & Shukla, 2017). Furthermore, the risk of developing PM remains high throughout pregnancy because the time when peripheral infections generate placental malaria is not known. Again, antibody studies in PM infected Beninese primigravidae showed that 40-70% of the antibodies against placental infected-erythrocytes are produced at the beginning of the second trimester. In addition, the intake of IPTp-SP briefly reduces parasitaemia from 16% to 4% during the pregnancy periods of IPTp service but increases to 12% at delivery (Ndam *et al.*, 2015). However, it has been

hypothesized that not every peripheral infection leads to placental malaria. Some peripheral parasites are deficient of the variant surface antigens (VAR2CSA) that facilitate placental sequestration and antimalarial drugs like IPTp-SP further clears much of these peripheral infections. Yet, some antimalarial drugs like Artemether Lumefantrine are not completely therapeutic in the placenta so parasites that sequester in the placenta are preserved and later enter into the peripheral blood. The prolonged exposure of sequestered parasites to artemisinin derivatives increases the development of parasite resistance to artemisinin drugs (Cohee *et al.*, 2016).

2.1.6 Factors contributing to placental malaria

The trend of PM has reduced over the past ten (10) years but prevalence differs in areas of high, moderate and low malaria transmissions. There remains high prevalence of placental malaria in high malaria transmission settings of Africa. Yet, prevalence is related to country-specific malaria transmission intensity, acquired immunity and the successful implementation of two or more preventive interventions. Consistently, health planners are challenged with the successful implementation and sustenance of two malaria control programmes (IPTp-SP and ITN) in Sudan. Therefore, there is high prevalence of PM (59.3%), in all gravidities among delivering women compared to many African countries (Omer *et al.,* 2017), however, the prevalence of PM was lower than what was recorded in the Southern part of Ghana (Hommerich *et al.,* 2007). It is also common to observe low level of peripheral parasitaemia without placental parasitaemia (Rogerson *et al.*, 2003). Notably, factors such young age and primipara increase the risk of PM (Omer *et al.*, 2017; Bouyou-akotet *et al.,* 2010; Tako *et al.*, 2005). In this region, immunity to PM is acquired over subsequent pregnancies putting primipara and secundiparae Sudanese women at higher risk of PM. Further, health education lectures are not targeted at poor women living in rural settings who are less informed about the dangers of malaria infection during pregnancy and inclined to delivering at home. Hence,

affected women lack the awareness of the need to attend antenatal clinics to benefit from malaria control interventions. The impact of PM is not similar throughout the country. In the Eastern parts of Sudan, PM is not related to LBW but in the north coast, observations of association between PM, maternal anaemia and LBW have been documented (Omer *et al.*, 2017).

According to a clinical trial report in Kampala, Uganda, non IPTp-SP users have higher prevalence of PM (12.5-50%), compared to users. Yet, the effectiveness of SP prophylaxis is dependent on the context-specific prevalence of SP resistance mutations and acquired immunity. Practically, frequent dosing of SP is required to complement established immunity to overcome increasing degrees of resistance. The disease profile of PM (active, chronic and past infections) has remained unchanged over the years and there are no real differences in the birth weights of babies born to SP and non-SP users. Apparently, the majority of PM are acquired in the later stages of pregnancy and inflammation processes in the placenta are short lived to impact foetal nutrition, growth and birth weight (Odongo *et al.,* 2016).

In the Madang province of Papua New Guinea in the Western Pacific region, risk factors include living in rural areas, being primigravid and having symptomatic malaria infection during pregnancy. However, the contribution of foetal sex to the development of PM is inconclusive but a study cites a relationship between female sex and PM in Eastern Sudanese women. Malaria is endemic and the prevalence of PMs recorded among them was18.5%. Preventatively, a combination of SP and azithromycin protects against acute PM but does not translate into reductions in past PM (Lufele *et al.,* 2017).

On the contrary, for the Zanzibar region of Tanzania, the population malaria prevalence is related to that of PM. The overall prevalence of malaria is 1.2% and PM is not common (0.7%) in pregnant non-SP women. In spite of this, occasional localized increases are recorded in periods after the rainy months of May and July. Yet, serving SP to pregnant women throughout the year has no positive impact on the risk of PM during the short periods of increased malaria transmission intensity. PM control strategies have been concentrated on MiP surveillance, high ITN use and access to prompt diagnosis and effective treatment (Plotkin *et al.*, 2014). In Rufiji district within South-Eastern Tanzania, malaria transmission is high (20.8%) and PM prevalence is 8% though parasite resistance to SP has significantly increased across the country. The use of two (2) doses of SP does not protect against PM, LBW and maternal anaemia although reports associate reductions in pre-term births to two SP dose regimens. The association between PM and LBW is not clearly defined in the region (Ndeserua, Juma, Mosha, & Chilongola, 2015).

Generally, studies that have described PM and the concomitant outcomes on maternal and infant health outside Sub-Saharan Africa are meagre. In Central India just as the rest of the country, the prevalence of PM is very low (4.5%) although disease impact is considerable and independent of fever occurrence. Pregnant women (38.0%) experience high rates of active PM compared to pregnant women in areas of high malaria transmission, and are often detectable by conventional microscopy methods of diagnosis. Typically, active PM induce premature delivery so that infections do not linger and progress into chronicity. Again, the appearance of disease symptoms prompts women to access early treatment and forestall the development of chronic PM. The characteristic low malaria exposure in the region catalyzes immunological, physiological and pathological processes that endanger maternal and infant health. First, the creation of low immunity in the population which activate inflammatory processes that results in adverse pregnancy outcomes such as maternal anaemia, LBW, low

gestational age and pre term delivery. Further, a net low parasitaemia in infected placenta causes mild placental inflammations contrary to the much pronounced forms of placental inflammations typical of high parasitaemia in highly endemic malarious areas (Ahmed *et al.*, 2014).

2.1.7 Pathophysiology of placental malaria

The CSA proteins on the maternal side of the placenta bears syndecan-1, receptors to which parasite VAR2CSA ligands adheres, on the apical region of the syncytiotrophoblast and in the villous stroma. Parasites that have sequestered in the placenta express VAR2CSA binding ligands. The VAR2CSA expressing parasites initially cover the apical membrane of the syncytiotrophoblast, penetrate the intervillous space, connect to a matrix-like structure and adhere to syndecan-1 on the placental CSA protein. Syndecan-1 appears very early in pregnancy and are available for binding by the first trimester. Parasite adhesion to syndecan-1 early in pregnancy disrupts the normal development of the placenta and prevents full organ functioning.

The disruption of placental function activates intervillositis (a local innate inflammatory response), and increase the risk of foetal growth restriction and LBW. Parasitized RBCs accumulate in the placental intervillous spaces causing the infiltration of immune cells. Over time, malarial pigments deposit in the placenta and the basement membrane thickens, causing the accumulation of perivillous fibrinoid deposits and the formation of syncytial knots. Eventually, the placenta blackens and the materno-foetal exchange system alters, resulting in insufficient nutrient supply to the foetus (Manirakiza *et al.*, 2017; Pereira *et al.*, 2016).

Accordingly, the placenta responds to the nutrient deprivation invoked by intervillositis and initiate processes such as autophagy to conserve nutrients. However, the inflammatory

response impedes the autophagic process by inhibiting mTOR signaling in the placenta. The autophagic dysfunction, increase the quantities of autophagosomes and lysosomes in the syncytiotrophoblast to activate the formation of the autophago-lysosome complex. The complex formation requires Rab7 protein but its lower level in placental malaria blocks the fusion process. The short fall dysregulate the fusion of autophagosome and lysosome and creates an autophagic flux which impair nutrient transport especially, amino acids to the foetus. Thus, the dysregulated autophagic flux retards foetal growth by enhancing inflammation and increasing placental pathology for foetal nutrient transport to decrease (Dimasuay *et al.,* 2017). Ultimately, the establishment of placental P. falciparum infection induces placental cell damage through the accumulative effect of a worse form of inflammation, oxidative stress, apoptosis, and low levels of Heat Shock Proteins (HSPs) in the placenta. As infection progresses, CMI responses resume for the massive engagement of macrophages and the elevation of interferon (TNF-α and IFN-γ) levels into the intervillous spaces against parasite infected-RBCs. Again, the malaria-infected placenta induces lower concentrations of HSPs, which maintains the normal morphology and physiology of the placenta. However, the immune response damages the placenta through oxidative stress and apoptotic cell deaths and increase the risk of still birth, IUGR, and LBW. Furthermore, the lower HSP levels weakly control the cell damage arising from the malarial infection and contribute indirectly to the placental pathology (Sharma & Shukla, 2017).

Altogether, the pathophysiological mechanisms have direct effect on materno-foetal transfer efficiency of antibodies and are independent of the age or parity of pregnant women. Meaning, pregnant women at various ages and parities are susceptible to malaria infection (Alim *et al.,* 2015). Yet, placental parasite-specific immunity develops over subsequent pregnancies to provide partial immunity for secundigravidae and multigravidae against

malaria infection complications (Manirakiza *et al.,* 2017). Therefore, primigravidae are more susceptible to placental malaria hence experience higher impairment of materno-foetal IgG-antibody transfer efficiency relative to multigravidae (McLean *et al.,* 2017). Likewise, newborn babies living in places with regular exposure to malaria parasites do not develop full immunity until after 9 months of age (Alim *et al.,* 2015). Thereupon, further understanding into the molecular pathways that regulate immune responses against placental malaria and the resulting placental pathogenesis are essential to design therapies to gearshift the immune response to benefit the host (Sharma & Shukla, 2017).

2.1.8 Diagnostic methods for detecting malaria in pregnancy

Health intervention programmes after implementation are to be investigated to demonstrate their effect on the target populations. The IPTp-SP programme protects pregnant women from developing adverse birth outcomes (LBW and stillbirths). Therefore, investigators would require large sample sizes (which may impede study feasibility) to demonstrate an effect. Hence, placental infection analysis becomes the logical choice because it measures malaria infections that occurred throughout pregnancy. Again, this method can detect the majority of past infections and reveal whether an infection occurred before receiving the first dose of SP or during the intervals between doses. However, practical inconsistencies associated with the method makes it not ideal for assessing IPTp-SP effectiveness. In that, the method in one breath measures clear reductions in placental malaria parasitaemia following the receipt of SP and in another, fails to show the significant effects of the SP on neonatal outcomes (LBW and stillbirths). Moreover, the exact effect SP intake brings to improve both maternal and infant outcomes cannot be measured at the same instance. So, the lack of SP effectiveness is explained as a reflection of infections that happened either before the first

intake of SP or between dose intervals (Mosha, Chilongola, Ndeserua, Mwingira, & Genton, 2014).

Alternatively, Polymerase Chain Reaction (PCR) testing correctly identifies Plasmodium infections and greatly reduces the proportion of undetectable infections. Additionally, PCR testing is valuable for confirming the results of microscopy, mixed infections, parasite species and detecting drug resistant strains (World Malaria Report, 2017). Even though PCR are capable of detecting very low parasite densities (10 parasites per µL), in Ghana, PCR sensitivities on peripheral blood are slightly lower than that of RDTs (Williams *et al.*, 2016). RDTs allows for quick point-of-care malaria testing in the absence of PCR or microscopy capable laboratories. In addition, the sensitivity of available RDTs, to detect malaria in West African primigravidae and secundigravidae is generally high except in The Gambia, where transmission is lowest. Sensitivities at ANC enrollment vary among countries, 91% in Burkina Faso, 59% in The Gambia and 89% in Ghana. In Ghana, RDT sensitivity vary with subsequent ANC visitations, it is 83% at second visit, 77% at third visit and a substantial drop of 49% at delivery. Considerably, RDT testing at enrollment identifies 56% of total infections detectable throughout pregnancy. Moreover, the RDTs at Ghanaian point-of-cares are equally good in detecting active placental infections with general sensitivities of 73% and 82% in primigravidae. Diagnostically, although RDT sensitivity are not exactly the same as microscopy or PCR, all the same, in Ghana, RDT negative malaria infections are usually not missed infections and without adverse birth outcomes (Williams *et al.*, 2016).

Further, RDTs are of similar performance to standard clinical microscopes. Yet, compared to PCR, significant proportions of low-density infections characteristic of infected pregnant women are missed. So, the use of RDTs for routine malaria tests at the ANCs and labour

wards contribute to the underestimation of malaria infections in pregnant women. Malarious pregnant women are often asymptomatic with submicroscopic parasitaemia and RDTs are poor in detecting asymptomatic malaria. Additionally, RDTs come with several limitations: poor in detecting parasites with pfhrp2/pfhrp3 deletions, high false positivity and cross-reactivity rates. However, obtaining placental tissue or blood during pregnancy for routine malaria testing is practically impossible (Medina *et al.,* 2018). Moreover, RDTs are limited in detecting certain species of Plasmodium parasites and distinguishing uncomplicated malaria from severe cases to initiate appropriate treatment (World Malaria Report, 2017). Additionally, in semi-immune women as multigravidae, parasitaemia are often low in the peripheral blood and hinder diagnosis by RDTs (Fried & Duffy, 2017).

Although, placental samples are preferred for many MiP investigations, malaria parasites can still be detected in the peripheral blood of most pregnant women who have placental malaria infections of different parasite intensities (Idris *et al.,* 2016). Therefore, diagnostic tests capable of detecting placental infections in peripheral blood are important tools to advance the control of MiP. Across the world, RDTs are of lower performance in detecting placental malaria using peripheral blood (Medina *et al.,* 2018). However, the sensitivity of microscopes to detect malaria parasites in the peripheral blood of pregnant women infected with placental malaria is 36%. In terms of parasite grading, sensitivity is 62%, 33% and 5% for mild, moderate and hyper parasitaemia respectively. Also, with placental blood, parasite detection sensitivities of 59% is attained and for grading placental infections as mild, moderate and hyper parasitaemia, sensitivities of 35%, 38% and 27% are obtained respectively (Omer *et al.,* 2017). Hence, the use of thick blood films under microscopy has the advantage of concentrating greater volume of blood to maximize sensitivity of detecting malaria parasites

in a blood sample. Classically, microscopy remains the best method to diagnose malaria infections in resource deficient settings like Ghana (World Malaria Report, 2017).

2.1.9 Treating malaria in pregnancy

The dangers of not treating malaria in the first trimester meaningfully outweigh the adverse effects disease on-set produce. All the same, the outcomes of treating malaria in the first trimester of pregnancy are still of concern. Generally, treatment outcomes depend on the safety and efficacy of the antimalarial drug. Antimalarials like chloroquine, quinine and artemisinin are of minimal adverse effects for treating malaria in the first trimester of pregnancy (McGready *et al.*, 2012). Currently, recommendations support 7-day oral quinine regimen in early pregnancy and a 3-day regimen of Artemisinin Combination Therapy (ACT) in the second and third trimesters. Yet, recent meta-analysis of African documents shows that quinine incompletely treats malaria due to poor adherence, leading to higher records of ACT use in the first-trimester. Clinically, ACTs are consistently very effective, have lower rates of foetal resorption, with less excesses of malformations, relatively tolerable and widely available. The observable safety and preference for ACTs are fueling advocacies to expand ACT treatment to include the first trimester (Dellicour *et al.*, 2017).

All the same, several reasons are not supporting the recommendation for first-trimester artemisinin treatment. Available data on first-trimester artemisinin treatments are not enough to draw definite conclusions regarding its effect on congenital malformations. Furthermore, in practice, the routine surface examination and heart auscultation only detect congenital malformations present at birth. Therefore, there is high tendency to underestimate the prevalence of major congenital malformations since those relating to cardiovascular, often appear later in life. On the other hand, quinine is no more radically curative and recurrent first-trimester malaria is detrimental to both pregnant women and feotuses. Hence, women are increasingly receiving artemisinin once quinine treatment fails. In this light, Moore and

colleagues, 2016, recommend the inception of robust pharmacovigilance to monitor artemisinin treatment in pregnancy. At length, treating initial and recurrent first-trimester malaria with artemisinin, requires considerable assessment of the risks non-treatment of falciparum malaria has on birth outcomes against those of artemisinin treatment (Moore *et al.*, 2016).

Two MiP-related vaccines (PRIMALVAC and PAMVAC) are currently under development and are facing inter-study comparison complications. Notable controversies focus on, variation in allelic forms, domain boundaries, timing of antibody measurement, assay and other unspecified variables. Fried and colleagues, 2018, propose that harmonizing variables from alternate studies represent a potential break-through to allow direct comparisons between studies. Again they conclude that recombinant VAR2CSA domains and fragments (potential vaccine candidates) do not re-create native epitopes for protective antibodies to initiate humoral responses (Fried *et al.,* 2018). Thus, the variation in allelic forms of VAR2CSA locus is creating population-based antigenic diversity and impeding the progress in the development of VAR2CSA-based vaccines. Therefore, scientists are shifting attention towards addressing this growing evolution in genetic diversity. Hypothetically, Verity and colleagues, 2018, advocate for the synthesis of broad multivalent VAR2CSA vaccine for stable malaria transmission regions and areas with common population genetic variation (Verity *et al.*, 2018).

Importantly, understanding malaria immunity is instrumental in vaccine studies because such knowledge defines the parameters of interest. Recent information indicates that considerable portions of the MBC pool, which constitute host immune defenses against P. falciparum infections, are non-IgG MBC. Wherefore, indicating that apart from the usual memory B cells (IgG+ MBCs), other memory B cells (Pf+ non-IgG+ MBCs), play pivotal role in host

defense mechanisms against malaria (Lugaajju, Reddy, Wahlgren, Kironde, & Persson, 2017).

2.1.10 Intervention programmes

Malaria in pregnancy intervention programmes include the use of insecticide-treated nets (ITNs), intermittent preventive therapy with antimalarials like SP (IPTp-SP) and active or passive case detection for effective management (S. M. Taylor & Kuile, 2017). According to meta-analysis report, the use of IPTp-SP or ITN during pregnancy reduced the rate of stillbirths especially in endemic countries (Ishaque *et al.,* 2011). However, poor adherence to IPTp-SP increases the risk of maternal and neonatal malaria in the third trimester with higher stillbirth delivery outcomes (Iyoke, Lawani, Onoh, Okeke, & Onyebuchi, 2014).

Pregnant women in Cameroon poorly utilise available interventions that protect women against malaria in pregnancy. Contributory factors are individual, provider, system and/or community related. At the individual level, one in three pregnant women own ITNs and ownership is related with maternal educational status, the population of young children in a house, and antenatal care. Bed net distribution is prioritized among young children and pregnant women. Education on the importance of ITNs by health providers has reached wider target groups such as younger women, poorer and women in rural communities. However, bed net usage like the rest of Sub-Saharan African is still low (16.9%) and common among educated women. Additionally, most (60%) pregnant women enroll on IPTp at the ANCs but the number that take two (2) or more doses of SP is low (27.2%). All the same, available systems that control access to essential drugs also make antimalarials equally affordable to all class of people (Odom *et al.,* 2017).

The main MiP interventions in Malawi since 1997 are IPTp-SP administration and the use of ITNs. Enhanced coverage of ITNs and IPTp-SP since 2001 has resulted in decreased prevalence of maternal malaria parasitaemia, maternal anaemia and LBW until 2010. However, recent coverage rates of IPTp-SP are dropping due to reduced work rate of ANC staff, resource constraints related to the training of health staff and procurement and delivery challenges of SP drugs. The association between IPTp-SP and maternal parasitaemia, maternal anaemia and LBW changes over time. In Blantyre, Malawi, SP under IPTp was associated with reduced placental malaria, maternal anaemia and LBW between 1997 and 2001 but such observation was lost between 2002 and 2006. The interaction of two main factors contributed to the loss; the elevated rates of SP resistant parasites and increased coverage of ITNs over SP and growing parasite resistance, induced treatment failure and compromised the efficacy of SP. Fundamentally, the protective effect of ITNs and SP are not the same. The effect of SP is at the individual level but with ITNs because mosquitoes are also killed, its protective effect is extended to the community level. However, increased ITN coverage (from 14.4-60.5%) provided meager protection and significantly masked the effect of SP and rendered it less effective. Outside of this, the loss of SP efficacy also related with other environmental modifications that positively affected malaria transmission intensity and malaria-related morbidity. Correspondingly, the combined use of ITN and IPTp-SP gave additional protection against peripheral malaria, placental malaria infection and LBW. IPTp-SP administration is synergistic with ITN use in Malawi but the influence of education and poverty to such observation remains undetermined. ITN use alone did not protect pregnant Malawian women against malarial anaemia (Feng, Simpson, Chaluluka, Molyneux, & Rogerson, 2010).

According to Boudová *et al.*, (2015), the community level protection associated with universal ITN distribution and usage is dependent on several factors. They showed that one in every five ITN beneficiaries recorded malaria (individual level) at the time of first ANC visit even in the months of lower malaria prevalence (13%) in the Blantyre city of Malawi (community level) (Boudová *et al.*, 2015). Heavy rains might have destroyed vector larvae and allow for lower malaria prevalence in the rainy season but the reverse in the dry season (Berry *et al.,* 2018). Notwithstanding, ITN use in pregnancy has a strong relationship with the prevalence of malaria (Boudová *et al.*, 2015; van Eijk *et al.*, 2015; Rogerson, Mwapasa and Meshnick, 2007). Using the ITN in an appropriate manner has shown to decrease malaria transmission by 90% and has also helped to reduce miscarriage and stillbirths by 33% in Ghana (Ghana Statistical Service, 2011). Decline in ITN use among pregnant women in Malawi in 2014, correspondingly resulted in increased MiP prevalence. Consistently, intervention fatigue (drops in ITN use) after a massive bed net campaign and the loss of ITN chemical potency are linked with increases in MiP prevalence. Therefore, ITNs provide inadequate individual protection but significantly affects the community MiP prevalence for women to experience some degree of protection before their first ANC visit to access IPTp-SP (Boudová 2015).

The usage of Insecticide Treated Net (ITN) is greatly influenced by the knowledge of the people in using ITN as a means to prevent infection (Diema, Dodam, Aarah-Bapuah, & Asibi, 2017; Ankomah *et al.,* 2012). Several studies have assessed the utilisation of ITN usage and barriers in Ghana (Aberese-Ako *et al.*, 2019; Diema *et al.*, 2017; Axame *et al.*, 2016; Teye and Awetoriyaro, 2013). A study and in Nigeria (Ankomah *et al.,* 2012) and in Sub-Saharan Africa (Anna Maria Van Eijk *et al.,* 2013). A study assessed the utilisation of ITNs in the Middle Belt of Ghana showed that Ghanaian pregnant women in the Kintampo

area know that ITNs are used to prevent malaria during pregnancy (Manu *et al.,* 2017). Some studies have reported higher percentage in ownership and utilisation of ITN. A study by Axame *et al.,* (2016) conducted a study in the Volta region of Ghana and reported in their findings that, ownership (81.4%) and usage (42.5%) of the ITN were high (Axame *et al.,* 2016). However, some studies have reported low usage and ownership if ITN. In Nigeria it was reported that ITN ownership (28.8%) and usage (7.5%) were low (Ankomah *et al.,* 2012) which is consistent with what was found in Kassena-Nankana (usage 24.0%) (Teye & Awetoriyaro, 2013), Kintampo (usage 47.0%) (Manu *et al.,* 2017)and in Sub-Saharan Africa (Van Eijk *et al.,* 2011). Knowledge of practices that promote the good handling and maintenance of ITNs prolong durability and sustain supply. Manu and colleagues, 2017, advocate that health providers and retailers should educate prospective ITN users on methods that mitigate repulsive factors in order to boost usage. For instance, mass ITN distribution programmes should come with education such as hanging nets in airy places for 24 hours before use to minimize chemical scent. Again, materials that permit more circulation of air should replace the polyester used to manufacture ITNs to allow for better ventilation. Moreover, cream repellents should be encouraged as an alternative to ITNs especially during the dry months when women are unlikely to sleep in bed nets due to heat (Manu *et al*., 2017). Some people and households do not use ITN because of poverty, inconvenience (Axame *et al.*, 2016; Teye and Awetoriyaro, 2013), weather changes in the Northern region and belief that this intervention was not an effective in controlling malaria (Teye & Awetoriyaro, 2013). In a study done by Feng *et al.,* in Malawi, they found out that, ITN utilisation protected the pregnant women from malaria, LBW but not maternal anaemia (Feng *et al.,* 2010).

2.1.11 Alternative intervention approaches

Preventing malaria infection of the placenta is vital in controlling materno-foetal anaemia and LBW. The efficacy of SP is dropping and there are no available drugs for replacement.

Intermittent screening and treatment in pregnancy (ISTp), presents as an alternative approach. ISTp encourages testing and increases infection detection in-between routine ANC visits for treatment. This intervention proves valuable in SP-resistant regions and serves as a future option to replace IPTp-SP so long as SP-resistance rises. Also, ISTp is implementable in the first trimester therefore; women are at a better chance of experiencing protection early in pregnancy. Notwithstanding, the programme is expensive to sustain, very complex for routine practice and its impact on placental malaria is inclusive. (Tagbor *et al.,* 2015).

According to meta-analysis reports from Africa and Asia, quinine is inadequately clearing early pregnancy infections and is increasing the risk of miscarriages. Besides, artemisinin derivatives such as artesunate-amodiaquine, mefloquine-artesunate, artesunate-clindamycin, artesunate monotherapy and dihydroartemisinin-piperaquine, are serving as better prescriptions. Therefore, advocacy for Artemisinin derivatives to replace quinine are far advanced because of several positive observations. ACT treatments in the first-trimester and during embryo sensitive periods are of comparable major congenital anomalies consistent with quinine treatments and have no evidence of embryotoxicity in human pregnancies. However, making appropriate risk-benefit assessment of the toxicity of ACTs in early pregnancy requires large volume of data sources from different studies (Randomized Control Trials and Observational). Moreover, persisting ethical issues are dragging the implementation of experimental studies to compare the safety of ACTs against quinine in treating first trimester malaria infection. Thereupon, scientists are relying on available data across nations as the only feasible method to gain a fair picture in order to assess congenital anomalies originating from ACT toxicity. This obviously requires many years of such data collection and cannot desirably respond to the immediate need to protect pregnant women from early malaria infections (Dellicour *et al.,* 2017).

2.2 Effect of Malaria in Pregnancy on Maternal Health and Birth Outcomes.

Maternal anaemia, intrauterine death, preterm delivery and low birth weight are the negative effect associated with malaria in Pregnancy (Boudová *et al.*, 2015; McClure *et al.*, 2013; Desai and Dellicour, 2012; Desai *et al.*, 2007).

2.2.1 Malaria and Maternal Anaemia

According to the WHO, haemoglobin concentration below 11.0g/dl defines anaemia during pregnancy (WHO, 2016). The benefits of high haemoglobin concentration during pregnancy for both the woman and the foetus cannot be exaggerated. Haemoglobin transports oxygen to body tissues and reductions below acceptable levels has devastating effects on both mother and foetus. Studies show that, 56.0% of pregnant women in low and middle income countries have anaemia (Black *et al.,* 2013). In Nigeria, the prevalence of anaemia in pregnancy is almost 60% and more than 7.0% of the pregnant women are severely anaemic (Agan *et al.,* 2010). In a study done among Eastern Sudanese pregnant women attending ANC at Halfa Teaching Hospital, 62.6% of them had anaemia (Adam *et al.,* 2005). The degree of hemolysis of RBCs depends on the density of parasites (Kotepui *et al.,* 2015).

The underlying relationship between malaria and anaemia is well defined. The expression of clinical symptoms and signs are related to parasite density, parasite species and the form the disease takes, either being acute or chronic. Peripheral malaria with higher parasite density increases the tendency of exceeding the febrile threshold to manifest fever in infected persons. However, the process is dependent on acquired immunity and is shorter in individuals without immunity than those of partial immunity and much quicker in P. falciparum infections than P. vivax infections. Disease symptoms appear quicker in non-immunity and much later, if at all, in partial immunity and trigger early treatment in non-immunity, and causing the habouring of low-density parasitaemia (asymptomatic malaria) in

partially immune individuals. Asymptomatic malaria is chronic, with minimal haemolysis and periodic reappearance of higher intensity symptomatic infections. The more frequent the resurgence, more non parasitized red cells are destroyed, red cell and haemoglobin levels drop drastically, as this lasts longer, red cell production is impaired and the bigger the anaemia burden becomes. Asymptomatic malaria and malnutrition are common in pregnant women of resource-constrained countries like Ghana, therefore, quantifying malaria-attributed anaemia can be daunting (Chen *et al.,* 2016). Nonetheless, the implementation of new and the reinforcement of existing interventions that prevent intra-uterine growth restriction (IUGR) and anaemia in an environment of innovative ability to manage preterm newborns, can reduce the burden of malarial stillbirths and neonatal deaths worldwide as well as supplement available preventive interventions for MiP (Moore *et al.,* 2017).

In malaria endemic areas, malaria-related anaemia is higher in primigravidae than in secundigravidae and multigravidae (Ouédraogo *et al.,* 2012; Bam, 2009), however, a study done in Eastern Sudan found multigravidae to be at higher risk of anaemia (Adam *et al.,* 2005). Typically, pregnant women in Ghana are anaemic regardless of malaria infection (Yeboah *et al.,* 2016), although anaemia is an important consequence of malaria infection during pregnancy (Yeboah *et al.,* 2016; Clerk *et al.,* 2009b). Anaemia in pregnancy causes LBW and low haemoglobin in the newborn (Yeboah *et al.,* 2016). Although the direct causes of anaemia in African pregnant women are multi-factorial and include malnutrition and poverty, in malarious regions, placental malaria is responsible for greater proportions of maternal anaemia during pregnancy (Omer *et al.,* 2017). In places outside Sub-Saharan Africa, like India where malaria transmission is low, sub-patent malaria infections are associated with lower maternal haemoglobin. Acute but not chronic placental malaria infections are responsible for severe forms of maternal anaemia with haemoglobin levels

dropping as low as 1.4g/dl (Ahmed *et al.,* 2014). Maternal anaemia is not correlated with neonatal or post-neonatal deaths as is the case in malaria endemic Sub-Saharan Africa. Most women are moderately anaemic unlike endemic areas where maternal anaemia is severe and the supply of routine iron and folic acid supplements have little impact. Meanwhile, malaria-related maternal anaemia affects thiamine levels and results in late Infant deaths (Luxemburger *et al.,* 2018).

Plasmodium falciparum parasite resistance to IPTp-SP affects the protective effect of the drug against maternal malarial anaemia. The administration of IPTp-SP in Tanzania (a place known for high parasite resistance), correlated with reductions in placental malaria but did not reflect corresponding decrease in maternal anaemia. The observation affirms reports that associate maternal anaemia in malaria endemic settings with multifactorial factors (malnutrition, other infections and socio-economic factors) other than malaria alone (Mosha *et al.,* 2014). Elsewhere outside Africa, malaria infections of P. vivax origin in pregnancy are accompanied by pronounced severe maternal anaemia among pregnant Hazaribagh residents of Jharkhand district in India. Malaria transmission is low and women of reproductive age acquire partial immunity so gravidity has no effect on malaria infection. All the same, the effect of parasite sequestration on placental pathology is related with gravidity hence the severity of anaemia is not the same for all pregnant women. The clinical significance of haemoglobin reduction depends on levels before parasite infection. Importantly, the developmental, public health and socioeconomic implications of malaria in pregnancy has received little attention and not properly quantified (Sohail *et al.,* 2015).

It is commonly believed that anaemia in pregnancy increases with increasing parity due to repeated drain on iron stores (Acheampong *et al.,* 2018; Nwizu *et al.,* 2011; Olubukola *et al.,* 2011; Adinma, 2002), however, the study done by Olatunbosun and colleagues, revealed an

inverse relationship between parity and anaemia, as the percentage of anaemic pregnant women decreased as parity increased (Elzahaf and Omar, 2016; Olatunbosun *et al.*, 2014) found no relationship between anaemia and parity.

Bam in 2009 conducted a study on Control of Pregnancy-Associated Malaria through Community Involvement in Rural Ghana, specifically Afigya Sekyere. The study identified age, parity, parasitaemia and gestational age as risk factors for anaemia in pregnancy. Adolescents were at a higher risk of anaemia and the study found 78% of them to be anaemic. However, Adam *et al.*, found in Eastern Sudan that age and parity were not significantly associated with anaemia (Adam *et al.*, 2005).

2.2.2 Maternal Malaria Infection and Infant Birth Weight

Low birth weight (LBW) is the absolute weight (<2500g) of a new born regardless of gestational age and is a valuable public health measure of the quality of healthcare (Cutland *et al.*, 2017). Procurable literature that relates malaria in pregnancy with LBW are well elaborate. The debate about using LBW as the primary outcome measure is inconclusive but it remains the most preferred variable in many MiP studies. Malaria in pregnancy contributes to Preterm birth (PTB), small-for-gestational-age (SGA) and LBW. Estimating the impact of MiP depends on determining the proportions of PTB, SGA or LBW. The challenge however, is accurately quantifying birth outcome proportions as PTB, SGA or LBW. SGA is the ideal outcome measure because it varies with GA and the majority of infants born from 39-41 weeks of gestation suffer SGA. Nevertheless, LBW which is only a substitute for SGA remains the favorite outcome measure in most MiP studies because it offers several advantages over SGA and PTB. LBW is independent on the availability of well dated pregnancy data, convenient and easy to measure. Also, the problem of misrepresenting the

impact of MiP through over-estimating for PTB and under-estimating for term birth is corrected by adjusting for GA (Rijken *et al.,* 2014).

Reviewed documents indicate that nearly one in four pregnant women experience at least one microscope-detectable malaria infection during the first trimester. However, effective and safe prophylaxes that prevent MiP in early gestation (within the first trimester) are rare. Moreover, current MiP preventive strategies do not include the first trimester. Wherefore, most early MiP infections are confined to the first weeks of gestation before the sixth week. Meanwhile, successful treatment of early gestation malaria infections in the absence of later infections improves birth weight (Fitri *et al*., 2014; McGready *et al.*, 2012). However, diagnostic methods for identifying parasitaemic women earlier for treatment are unreliable (Newman *et al.*, 2003). Therefore, the opportunity to prevent the incidence of MiP in early gestation, to reduce and eliminate the risk of malaria (symptomatic or asymptomatic) is missed. Ultimately, infected women develop peripheral malaria and the placenta becomes infected (placental malaria) (McGready *et al.,* 2012). Wherefore, by way of parasitic cellular adhesion, cytokine production and monocular cell infiltration, the transfer of oxygen and nutrients from the mother to the unborn baby is altered. The foetus to a large extent, suffers Intrauterine Growth Retardation (IUGR) which hampers foetal weight gain, causing low birth weight (Hartman and Rogerson 2010).

Often, peripheral parasites hide in the placenta and compromise the development of placental barriers (Accrombessi *et al.,* 2018). The presence of parasites in the placenta creates a (mother-foetal) parasite density gradient which facilitates the transmission of maternal parasites to the foetus (Mayor *et al.*, 2018). The parasites induce high levels of HLA-G in the foetus and increase its susceptibility to congenital malaria (D'Almeida *et al.,* 2017). As

placenta barriers become properly established, the addition of maternal parasites to foetal parasites is blocked. Accordingly, the foetal parasite densities directly affect haematological parametres such as hemoglobin level, erythrocyte amount, and hematocrit level to effectuate foetal anaemia (Fitri *et al.,* 2014). Malaria-anaemia affect foetal growth and increase the risk of IUGR and low birth weight (Saba *et al.*, 2008).

2.2.2.1 The risk factors of Low birth Weight

Published documents reveal that the risk of LBW varies with gestational age and gravidity. However, LBW is also influenced by the number of malaria episodes (Berry *et al.,* 2018; Kalilani *et. al,* 2010; Newman *et al.,* 2003). Consistently, babies of P. falciparum infected women are 3-fold susceptible to under development in the first trimester. Again, the odds of foetal damage is estimated at a rate of 50% per each 10-fold increase in maternal malaria parasitaemia (McGready *et al.,* 2012). Nonetheless, higher parasite densities in first time pregnancies correspond to higher boost of IgMs in primigravidae. Yet, the higher magnitude of IgM increase is associated with magnified risk of LBW (Mayor *et al.,* 2018). Thus, primigravidae remain vulnerable to malaria infection until first ANC visit when ITNs and IPTp-SP are given. Moreover, the full benefit of chemo-prevention under the IPTp-SP programme is not realized because infection takes place before first ANC visit (Berry *et al.*, 2018; Souza, Gonc, & Silva, 2018). Meanwhile, early gestation infections in primigravidae increase the risk of maternal anaemia, touching foetal growth to induce LBW (Huynh *et al.*, 2011).

On the other hand, having had more than one pregnancy shields the unborn baby against growth restrictions associated with maternal malaria infection (McGready *et al.*, 2012). Still, multiparous and multigravidae women in the second trimester of gestation are at higher risk

of developing malaria (Saba *et al.,* 2008). Likewise, P. falciparum infections acquired around 32-37 weeks (third trimester) of gestation increase the risk of LBW in all gravidities (Souza *et al.,* 2018). Outside of this, primigravidae are highly predisposed to hyper-parasitaemia upon infection, which further raises the risk of IUGR and LBW. Regardless, first-trimester infections have minimal effect on foetal growth seeing infected women show efficient recovery as gestation progresses (McGready *et al.,* 2012). Besides, the detrimental effect of placental infections reduces with increasing parity and the differential use of preventive methods contributes to parity risk differences of malaria infection. Notably, multigravidae adhere better to ITN use and obtain significant protection against malaria-related LBW than primigravidae (Mayor *et al.,* 2018).

Over the years, the age of a pregnant woman has become an important determinant of LBW deliveries (Igboeli, Adibe, Ukwe and Aguwa, 2018). Teenage pregnant women (<20 years old), are most susceptible to malaria infection within the first trimester of pregnancy. However, especially in primigravidae, high proportions of such ages are required in a population to significantly express effects that increase estimated risks of LBW (Igboeli *et al.,* 2018). Old maternal age (>30 years old), independently contributes to bad pregnancy outcomes in pregnant women (McGready *et al.,* 2012). Also, seasonal variations in rainfall pattern affect malaria transmission intensity to influence birth weight. The heaviest birth weights are obtained during the dry season and the lowest birth weights are recorded during the rainy months (Bam, 2009). Factors like peripheral malaria infection, placental malaria, maternal anaemia and no ANC visit are contributing to high prevalence (56%) of LBW in the Blue Nile areas of Sudan. Strikingly, peripheral and placental malaria at delivery contribute to maternal anaemia which induce LBW in young aged and primipara mothers (Omer *et al.,* 2017). A Tanzanian study revealed that, pregnant women with anaemia were 11 times more

at risk of LBW (aOR 1.11; 95%CI 1.07-132.2; p=0.04) compared to those who were not anaemic (Mikomangwa, Oms, Aklillu, & Kamuhabwa, 2019).

In another breath, anaemia and preeclampsia are other risk factors of LBW aside malaria that show parity-specific effect and predominantly predispose primigravidae to LBW deliveries. However, maternal anaemia is a common consequence of malaria infection in endemic areas; therefore, it does not magnify the association of malaria and LBW at the population level. Again, the rates of preeclampsia in Sub-Saharan Africa are so low (1.2-3.3%) to affect the sensitivity of an analysis that measures the relationship of malaria and LBW. Other factors like smoking, nutritional deprivation, and sex of the baby which also increase the risk of LBW do not express the parity-specific effect that malaria have on foetal growth. So, their contribution on the risk of LBW deliveries among primigravidae is insignificant in any analysis that links malaria and LBW (Igboeli *et al.*, 2018).

Precisely, the quality of infant health during pregnancy is determined by IUGR, which is maternal, placental and foetal in origin. IUGR can be symmetrical, being the cause of genetic, placental insult (structural and functional impairment) because of malaria infections occurring earlier in pregnancy. Or, asymmetrical, being the result of utero-placental nutrient insufficiency during late pregnancy *(Cutland et al.*, 2017). According to histological data, placental infections that occur late in pregnancy are active infections and pathological damage to the placenta is short-lived to significantly affect foetal growth and induce low birth weight. Therefore, in contexts where placental malaria is rampant especially in late pregnancy, SP intake has no effect on birth weight as observed in the Kampala area of Uganda (Odongo *et al.*, 2016). According to epidemiological data, higher malaria parasitaemia in Ghanaian pregnant women accounts for the difference in the prevalence of

LBW in Ghana (14%) and Southeast Nigeria (3%). Regionally, gravidity is positively correlated with birth weight and in the Bekwai area of the Ashanti region, multigravidae are at highest risk of delivering babies with LBW (Asamoah *et al.*, 2018).

2.2. 3 Malaria and stillbirth

Every New-born Action Plan was launched in mid-2014 with a World Health Assembly Resolution and includes clear targets to end preventable neonatal deaths and stillbirth in every country by 2030 (WHO, 2015; WHO, 2015; Lawn *et al.*, 2016). The launch of Every New-born Action Plan (ENAP) has helped to reposition the prevention of stillbirth back on the global health agenda after suffering neglect for a while. Malaria infection from three sources during pregnancy increases the risk of stillbirth and includes antenatal infections, placental infections and maternal infections at delivery (S. M. Taylor & Kuile, 2017). Generally, stillbirth is of two classifications, antepartum (death in utero) or intrapartum (death during labour). In low malaria transmission areas, MiP contributes to total population stillbirth by adding on antepartum stillbirths. Antepartum stillbirth has strong association with symptomatic falciparum malaria infection in the third-trimester. The strength of the association is because of the differential expressivity of cytokines and fever that characterize symptomatic and asymptomatic infections. Though asymptomatic infections weakly relate with antepartum stillbirths, yet, pose grave threats to the developing foetus. Early trimester, chronic and sub-patent infections (asymptomatic) can become patent and often detectable by the third trimester and like new infections in the third trimester, are particularly harmful, irrespective of treatment and strongly enlarge the hazard of antepartum stillbirth (Moore *et al.*, 2017).

Commonly, most low-income countries report on stillbirths occurring at the health facility level. The definition of stillbirth varies among countries; upper middle-income countries classify stillbirths as foetal loss between 20 and 22 weeks of gestation and at ≥28 weeks of gestation for low-income countries and lower middle-income settings including Ghana (Aminu *et al.*, 2014). Stillbirth is not a preferable primary outcome in many MiP studies because of its rarity. The scarcity of such studies is contributing to the under-estimation of Population Attributable Fractions (PAFs) in low falciparum endemic settings, where population stillbirth prevalence is lower. Again, the absence of standard definition for stillbirth and gestational age threshold (to differentiate foetal deaths as miscarriages or stillbirths), is badly affecting data synthesis for systematic reviews and meta-analysis. Further, many studies are not reporting the association between MiP and stillbirth, after collecting the necessary data and is increasing the risk of publication bias. Likewise, most moderately sizeable studies are not reporting stillbirth data in the methods or results sections, creating evidence of small-study effect. In as much as, stillbirth is a perceptive determinant of maternal health and the quality of care, its reportage is becoming essential in MiP studies. The use of RDTs empower MiP studies to operationally detect malaria infections and illustrate its interaction with stillbirth (Moore *et al.*, 2017).

A notable association exist between infection and gestational age. A study reported that, the earlier the foetal death during gestation, the more likely it was caused by an infections caused by various organisms such as bacteria, viruses, protozoa, helminths and fungi (Goldenberg and Thompson, 2003). *Plasmodium falciparum* malaria has been associated with stillbirths especially among the primigravids due to high prevalence and extensive placental damage. A study conducted in Nigeria by Iyoke *et al.*, found an association between women who had malaria infection in the third trimester and those who delivered stillborn babies. Again,

neonatal malaria contributed to 18% of neonatal care admissions among those who did not adhere to the prescribed IPTp-SP (Iyoke *et al.,* 2014).

2.3 Intermittent Preventive Treatment During Pregnancy (IPTp) using Sulphadoxine Pyrimethamine

2.3.1 Introduction of IPTp-SP Revised Policy

In 2003, the Global Fund round two (2) malaria grant ensured intensification of malaria control interventions in 20 districts across Ghana. This resulted in improved health indicators across the country. However, the emergence of Chloroquine resistance made Ghana to adopt Artemisinin-based combination therapies (ACTs) as first-line treatment for uncomplicated malaria in 2004. In that same year, IPTp with the drug, Sulphadoxine-Pyrimethamine, (SP), was adopted as the national policy to control malaria in pregnancy. The policy was implemented in all public health facilities, faith-based facilities, and private maternity homes by the Reproductive Health Division of the Ghana health service in collaboration with the National Malaria Control Programme (NMCP). Under the programme, a maximum of two (2) SP doses were dispensed to pregnant women primarily at the antenatal clinics of health facilities (NMCP, 2013).

The purpose of dispensing the IPTp-SP was to prevent adverse maternal, foetal and birth outcomes associated with malaria in pregnancy. Since its implementation in areas of low, stable and high malaria transmission, IPTp-SP has been beneficial to pregnant women of all gravidities (primigravidae, secundigravidae and multigravidae) who enroll on the programme. Nonetheless, the programme has encountered challenges in scaling up coverage to one hundred percent (100%). Yet, efforts that aimed to maximize SP uptake has witness some gains. There are reports of significant reductions in the prevalence of placental

infections, decrease incidence of Low Birth Weights (LBWs) and frequencies of composite birth outcomes (still birth and neonatal anaemia) (Mosha *et al.,* 2014) . However, these feats were short lived because the 2 doses of IPTp-SP lost efficacy in the field due to the emergence of SP-resistant parasites. Malaria parasites resistant to SP are now spreading and taking dominance because of changing malaria epidemiology (Baraka *et al.,* 2015).

Chronologically, reports of parasite resistance first emerged in East Africa few years after the implementation of the 2 doses of IPTp-SP. The development negatively affected the effectiveness of the required 2 doses to prevent placental malaria in pregnant women. Over time, there were growing reports across the world of the inefficiency of 2 SP doses in protecting pregnant women against malaria parasitaemia, placental malaria, maternal anaemia and LBW. Ultimately, the 2 SP doses could no longer treat and provide malaria prophylaxis to pregnant women enrolled on the IPTp programme (Arinaitwe *et al.,* 2013). Meanwhile, existing protocols ensured active detection of malaria cases for treatment and strict adherence (through Directly Observed Therapy) to taking the maximum (2) doses of IPTp-SP. The loss of effectiveness resulted in the rise of submicroscopic malaria infections among pregnant women reporting for their first ANC visit. These low-density parasitaemia cause placental infection, reduce maternal haemoglobin concentrations and are only diagnosed by the rather expensive PCR method (Cohee *et al.*, 2014).

In lieu of this, the WHO evidence review group met in Geneva in July 2012 and reviewed evidence from both published literature and unpublished studies on the current efficacy and effectiveness of IPTp with SP in order to make recommendations related to the timing and number of doses of SP. In all they reviewed seven (7) clinical trials conducted in Africa in areas of stable transmission with different levels of SP resistance. Based on this, they recommended that, 3 or more doses of IPTp-SP provided a better maternal and neonatal

outcomes than the standard two doses of IPTp-SP in all gravidae and HIV groups (WHO, 2012).

Consequentially, 840 million pregnancies would be at risk of malaria infection in endemic countries of the world. In response, the WHO now recommends that 35 million pregnant women should be enrolled unto a new IPTp-SP programme each year. The new policy has been implemented in WHO member countries since 2014. The new programme delivers at least 3 and a maximum of 5 doses of SP at first ANC visit (second trimester) until delivery. However, in many African countries, efforts to maximize the uptake of the new IPT policy have been generally poor (WHO, 2017). Again, there is low compliance to the new IPTp-SP programme and is negatively affecting uptake in Ghana. Late enrolment of pregnant women for first ANC clinic which is about 56% in the Central Region has been reported by investigators as one of the main factors of low compliance (Yeboah *et al.*, 2016). According to Iyoke et.*al*., poor adherence to the IPTp-SP regimen is responsible for the MiP increase in Nigeria (Iyoke *et al.*, 2014) .

2.3.2 The therapeutic and chemoprophylactic effect of Sulphadoxine-Pyrimethamine doses

The physio-pathological mechanism of the efficacy of SP doses taken intermittently during pregnancy to improve birth outcomes have not been fully understood. An earlier opinion explained that taking two doses of SP increased birth weight and sustained neonatal life throughout the ages of gestation. This school of thought could not be applied to situations where reduced adverse neonatal outcomes (low birth weight and stillbirth) are also seen among non-IPTp-SP induced pregnant women. In this light, a recent explanation that cites parasite presence in the placenta or in cord blood to have negative effect on neonatal survival

is more acceptable. Here, the action of IPTp-SP reduces infant death by protecting against placental malaria, low birth weight, cord blood parasitaemia and pre-term birth, which are stronger risk factors of infant death. The effect of SP will be due to reductions in placental and cord blood infections since they are in the causal pathway between the intervention and death (Bardajı *et al.,* 2010). The debate now concerns the determination of acceptable SP doses capable of providing effective treatment of existing malarial infections and longevity of prophylaxis against new infections.

In the past, systematic review of clinical trials had advocated for the intake of two SP doses in the first and second pregnancies to effectively reduce the likelihood of severe maternal anaemia, low birth weight and perinatal mortality (stillbirth)(Hamer *et al.*, 2007; Garner and Gülmezoglu, 2006). Later evidence indicated that uptake of two SP doses had limited prophylaxis potency, so new infections were not averted (Igboeli *et al.*, 2018; Kayentao *et al.*, 2013; Hommerich *et al.*, 2007). Besides, protection against placental infections and low birth weight was confined to only paucigravidae while multigravidae were just protected from premature births (Mace *et al.*, 2015).

In Uganda, pregnant women still suffered malaria and negative pregnancy outcomes (low birth weight and stillbirth) after being dosed with two SP doses (Arinaitwe *et al.*, 2013). Again, in Tanzania and Malawi, the acceptable two SP doses lost efficacy against placental malaria, maternal anaemia and low birth weight (Gutman *et al.*, 2013a; Harrington *et al.*, 2011). Also, the prophylaxis duration of two SP doses was constricted to 4-6 weeks, so pregnant women remained highly vulnerable to malaria infections during most of their 40 weeks of pregnancy (Mosha *et al.*, 2014).

Therefore, increased dosing with at least three SP doses was advocated for in order to ensure maximum protection against malaria in pregnancy. For instance, meta-analysis and mathematical models showed that taken at least three SP doses provided additional protection against malaria and accompanying low birth weight and stillbirth (Mosha *et al.*, 2014). Therefore, Cates *et al.*, 2018, proposed that pregnant women should be given higher SP doses of three or more to improve birth weight and increase foetal survival (Cates *et al.*, 2018). Nevertheless, the shift to higher SP doses (at least three doses) encountered inherent challenges like spreading drug (SP) resistant parasite strains across malaria endemic countries like Ghana. Hence, the minimum inhibitory concentration required for longer prophylactic duration could not be sustained (Desai *et al.*, 2016; Mosha *et al.*, 2014; Gutman *et al.*, 2013). Furthermore, the time of pregnancy at which women taken the recommended doses (either two or more doses) affected drug (SP) efficacy. Principally, the maternal placenta responsible for materno-foetal nutrient exchanges forms around the 14th week of gestation (Kalilani *et al.*, 2010; Cottrell *et al.*, 2007; Taha *et al.*, 1993). Meaning, earlier infections that preceded placentation interfered with placenta establishment and impaired foetal growth (Rogerson and Boeuf, 2007; Brabin and Johnson, 2005).

Meanwhile, IPTp-SP is teratogenic in the first trimester and can safely be applied (even under the higher SP dosing system) only in the second trimester. Implying that pregnant women remained unprotected against malaria infections at the beginning of pregnancy and were not fully secured against the consequences of malaria throughout pregnancy (Huynh *et al.*, 2011). Notwithstanding, the taken first SP dose effectively cleared pre-IPTp-SP infections. Additionally, pregnant women were privileged to receive at least four extra doses (under the higher SP dosing system) and prevent new infections until delivery (Huynh *et al.*, 2011; Kalilani *et al.*, 2010). Yet, higher dosing of SP still showed limited potency to control the

damaging effects associated with late gestational malaria and maternal anaemia before delivery (Huynh *et al.,* 2011). Importantly, late gestational malaria increases the risk of maternal anaemia and worsens the physiological demand for iron and folic acid (necessary for the regeneration of RBCs) before delivery (Fleming, 1989). Unfortunately, pregnant women poorly adhere to nutrient supplements which further impede optimal foetal growth around the last months of pregnancy (week 20-30) (WHO, 2009; WHO, 2004). Hence, taking extra SP doses to protect against late infections and improve maternal hematological status (Huynh *et al.,* 2011), does not necessarily prevent low birth weight and stillbirth deliveries.

The concept of pregnancy specific malarial immunity is greatly influenced by the number of SP doses taken. The intake of IPTp-SP during the initial phase of pregnancy interferes with antibodies activities in the placenta. Yet, the short fall activates cell-mediated immune responses and protect the pregnancy against the deleterious effects of malaria. Besides, optimal doses of SP are required to complement antibody functions against placental parasites (Odongo et al., 2016). Taken SP doses clears blood-stage parasites and decrease the risk of peripheral malaria infection. The antimalarial action modifies acquired host malaria immunity during the pregnancy periods of IPTp-SP treatment. Subsequently, pregnant women can still experience at least one episode of malaria infection during pregnancy. This increases the binding inhibitory capacity of the plasma (a resistive force that acts against parasite attachment to host erythrocytes). Hence, post IPTp infections decrease host IgG activity against parasite variants of VAR2CSA antigens. However, increased plasma binding inhibitory capacity eliminates the likelihood of placental malaria and low birth weight outcomes at delivery. Consequently, IgG levels may either remain unchanged or increase at the time of delivery (Ndam *et al.,* 2015)

2.4 Relationship between SP doses and Maternal and Neonatal Health Outcomes.

2.4.1 IPTP-SP and Maternal Malaria (Parasitaemia) during Pregnancy

Multiple factors such as, increased parasite resistance to SP drug, differences in SP dosage completion and malaria parasite re-infections among pregnant women are contributing to high prevalence of malaria during pregnancy (Desai *et al.*, 2017; Desai *et al.*, 2016; Orish *et al.*, 2015). According to the WHO regulations of IPTp-SP, at least two doses of SP should have been taken by the third trimester. Nevertheless, inadequate coverage of SP administration has always been a great challenge to the IPTp policy in malaria endemic Africa. For example, in Tanzania, particularly around the Rufiji region, very few pregnant women (6.9%) never take SP at all yet the coverage of high doses (more than two doses) is sub-optimal (40.6-52.6%) (Ndeserua *et al.,* 2015). Similarly, in Uganda, IPTp-SP coverage has been lower for two doses (20.5-36.9%) and above two doses (7.0-8.0%) since 2011 (Abeku *et al.,* 2015).

Consequently, malaria prevalence in SP-induced women though lower (8.0%) in Tanzania, the burden has remained largely unchanged across the country in the past 7 years. A recent document showed that two doses of SP had lost effectiveness in preventing malaria during pregnancy. Additional factors like increased drug resistance and co-morbidities of malaria and HIV infections in pregnancy had mediated the process. Therefore, researchers propose that HIV infections should be properly managed during pregnancy to enhance the efficiency of IPTp with SP (Ndeserua *et al.,* 2015). In North-Western Tanzania, SP coverage is below the national target (60.0%) and most women took one dose (31.1%) than two (24.1%) or more doses (6.0%). Though pregnant women are faithful with their ANC appointments, they still miss the opportunity of being served with SP because of perennial shortages in health facilities. Ultimately, more than a quarter (38.7%) of pregnant women do not take SP at all.

Apparently, malaria prevalence remains high (29.7%) and even among women that take two doses of SP (25.3-36.8%). Meanwhile, malaria is transmitted under high intensity with seasonal variability. Pathologically, parasitaemia levels less than 100-168 parasites/µl in the peripheral blood and placenta induce placental malaria. Fortunately, consuming three doses of SP reduce placental malaria prevalence (15.4%) compared to non-users (43.1%). Although, IPTp-SP provides four weeks prophylaxis and higher doses (three or more doses) reduce the odds of placental malaria, the risk of prematurity remains high. Nevertheless, taking the last SP dose four weeks before delivery can reduce the likelihood of preterm birth by 62.0%. (Mpogoro *et al.*, 2014).

In the Eastern and North-Eastern parts of Tanzania, IPTp-SP utilisation is high (91.0%) and slightly differ under varying malaria transmission intensities. SP coverage is marginally higher (93.1%) in high parasite transmission areas compared to low transmission areas (89.0%). Notwithstanding, the risk of placental malaria is nine times increased in high malaria transmission areas compared to lower transmission regions. Accordingly, uptake of at least one dose of SP is associated with increased malaria prevalence under high transmission intensity (14.7%) than lower intensities (2.0%). Also, placental malaria prevalence is higher (41.70%) among non-SP living in high transmission areas (41.7%) than in lower transmission areas (5.3%). Though, SP show no dose-dependent protective efficacy under varying disease transmission intensities, taking at least one dose of SP confers 60-80% protection against gestational malaria. Importantly, preventing the incidence of a single case of placental malaria under intense parasite transmission requires the treatment of four pregnant women with at least one dose of SP. Under low parasite transmission intensity however, thirty-three (33) pregnant women are required to be treated with at least one dose of SP to avert a single case of placental malaria. In terms of gravidity, four primigravidae and three multigravidae

need to be treated with at least on dose of SP to prevent a single case of placental malaria under circumstances of high parasite transmission intensity. On the other hand, twenty-five multigravidae are required to be treated with at least one dose of SP in lower parasite transmission intensities to prevent a single case of placental malaria (Mosha *et al.*, 2014).

Implementation challenges of IPTp-SP is not peculiar to Tanzania and East Africa, in Cameroon, SP administration by health care professionals show unsteady patterns. The second SP dose is usually served either within 26-28 weeks or 28-30 weeks of gestation. This pattern of IPTp-SP service delays the intake of the second SP dose by most pregnant women until more than ten weeks after the first dose. Therapeutically, the prophylactic efficacy of the first dose disappears before the second doses is taken. Hence, pregnant women are unduly exposed to malaria infections within 20-30 weeks of gestation especially in the Yaoundé area. Meanwhile, symptomatic and asymptomatic infections are associated with high White Blood Cell counts (1,600-16,000 cells/µl) and parasite densities (7,834.7-13,234.5 ring trophozoites/µL). Increased parasitaemia occlude blood vessels and interfere with blood flow to major organs just like thrombotic crisis in sickle-cell disease (Mbu *et al.*, 2014a).

In West Africa, uptake of IPTp-SP is related with the prevalence of malaria in pregnancy. High dosing (three or more doses) is common in settings with high prevalence of malaria in pregnancy. For example, in Burkina Faso, prevalence is 27.9% and almost half of pregnant women (49.2%) ingest three or more doses of IPTp-SP. On the contrary, in Gambia where prevalence is lower (5.3%), coverage of high SP dosing (three or more doses) is also lower (3.7%) and most women consume two doses instead. Regardless, the lower doses still show 36% and 15.0% reduced odds of peripheral and placental malaria infections respectively. Higher doses (three or more doses) can though provide 63-72% and 63-90% reduced odds of peripheral and placental malaria respectively. All the same, among populations that take three

or more doses prevalence of peripheral and placental malaria can range from 9.4-15.4% and 30.0-44.0% respectively. Contrary, prevalence is reduced with lower SP doses (less than three doses) and can range from 0-12.26% for peripheral malaria and 11-30% for placental malaria (Scott *et al.*, 2019). In Benin, optimal dose of IPTp-SP is two doses which still demonstrate effective parasite clearance and reduces pre-IPTp malaria prevalence from 16.00-4.00%. However, current lapses in preventative methods, pregnancy induced plasma expansion and limited parasite exposure during the periods of IPTp-SP services negatively impact on host malarial immunity and balloons malaria prevalence to 12% at delivery. The period of IPTp-SP services is characterized by sub-optimal levels of antibodies that target parasite adhesive proteins in the peripheral blood and placenta. This creates conditions for increased malaria prevalence (up to 46.0%) after IPTp administration (Ndam *et al.*, 2015).

According to clinical trial reports in the Calabar area of Cross River State in South-East Nigeria, IPTp-SP is still effective in reducing the risk of third trimester anaemia and gestational malaria. Yet, SP remains weak in clearing parasite gametocytes and pregnant women treated with SP serve as reservoirs for infection transmission. Also, the prophylactic effect of SP in pregnant women that test negative for malaria after being dosed with SP is doubtful because of increased new infections in-between ANC schedules (Esu *et al.*, 2018). In the Western region of Ghana, SP uptake in the third trimester is high (83.2%). Almost half of the pregnant women (47.7%) in the sub-region take at least two doses of SP, 35.50% take only one dose while 16.8% do not consume any doses of SP at all. Nevertheless, malaria prevalence of SP-induced women is still high with one dose (20.70%) and at least two doses (13.7%). Health workers lament of irregular patronage of antenatal service which facilitates differential distribution of SP to pregnant women. So, women obtain insufficient doses of SP and remain vulnerable to malaria infections before delivery. Further, taking at least one dose

of SP remain protective against malaria with stronger reduced odds achieved under higher doses (two or more doses). Yet, third trimester malaria prevalence is still high (15.70%) especially among pregnant women in the Takoradi area (Orish *et al.*, 2015).

2.4.2 IPTP-SP and Maternal Anaemia during Pregnancy

Consistently, pregnant women in Sub-Saharan Africa are unable to complete the required more than three doses of SP as per the revised WHO IPTp protocol. Incomplete subscription of three or more doses of IPTp-SP shrinks drug efficacy and prophylactic potency. Consequentially, placental parasite densities are reduced but the parasite levels in the peripheral blood remains elevated (Mpogoro *et al.*, 2014). Despite, the IPTp method has empowered SP to retain its antimalarial activity even in the dominance of antagonistic factors like inadequate dosage completion, poor drug quality, increased drug resistance and weakened immunity. Yet, active placental infections do occur in the later parts of pregnancy among SP users (Odongo *et al.*, 2016).

The science of the IPTp-SP policy is to protect against maternal peripheral and placental malaria parasitaemia to reduce the risk of malaria-related maternal anaemia so that negative birth outcomes like low birth weight and stillbirth are prevented. However, the relationship could be altered because of differences in geographical malaria transmission intensity, malaria prevalence and low birth weight prevalence. For instance, in Tanzania, where the local transmission intensity varies regionally and the country prevalence of low birth weight is low; IPTp with SP is very effective against placental malaria but the efficacy does not positively impact on maternal anaemia. Here, pregnant women living in high malaria transmission areas are at greatest risk of maternal anaemia and protection depends on the effectiveness of IPTp-SP. However, taking at least one dose of SP under IPTp does not protect against maternal anaemia during pregnancy. The prevalence of anaemia in SP-users is

similar (46.2-61.0%) as non-SP users (27.3-56.0%). Hence, pregnant women who do not use IPTp-SP are not disadvantaged in any way in terms of protecting their haemoglobin concentration during pregnancy. On the other hand, receipt of antihelminthics, iron and folate supplementation does not improve maternal anaemia in pregnancy (Mosha *et al.,* 2014).

Likewise, Orish *et.al.,* showed in Ghanaian pregnant women that IPTp-SP in-take was not protective against anaemia during pregnancy. Their results also indicated similar prevalence of anaemia among IPTp-SP induced (36.2%) and non-induced (31.8%) pregnant women. They further asserted that increasing the SP dose to three or more possesses no potential efficacy to provide meaningful protection against maternal anaemia in pregnancy. All the same, the authors agreed that more robust study designs could help address the debate about the significance of ingesting high SP doses to control anaemia in pregnancy (Orish *et al.,* 2015).

Nevertheless, a multi-center study (The Gambia, Benin and Burkina Faso) found increased SP doses (≥3 doses) to remarkably reduce the likelihood of maternal anaemia at delivery though not statistically significant. The published results showed that anaemia prevalence among women that took lower SP doses (less than three) was higher (48-54%) compared to their counterparts (24-29%) that took higher doses (greater than two) (Scott *et al.,* 2019). This observation was similar in Hohoe municipality of Ghana, where most pregnant women (42.4%) were never dosed with IPTp-SP throughout the period of pregnancy. However, the number of SP doses taken during pregnancy showed protective potency against maternal anaemia. For instance, any extra dose of SP taken corresponded to a significant reduction of malaria parasite density. Consistently, uptake of three or more doses of SP provided 57.0% less likelihood of developing any malaria-related anaemia in pregnancy. This dose-dependent effect was however, much prominent in older women compared to their younger counterparts (Kweku *et al.,* 2017). On the contrary, in Tanzania, anaemia prevalence is high (59.3%)

among pregnant women and the odds is three times higher among women with placental malaria infections. Yet, the intake of optimal SP doses during pregnancy showed no significant reduction of maternal anaemia (Ndeserua *et al.,* 2015).

2.4.3 IPTP-SP and Low Birth Weight

The major determinants of low birth weight are malnutrition, malaria, anaemia, other infections and socio-economic factors. However, malaria infection during pregnancy is the primary contributing factor of maternal anaemia and low birth weight especially in middle-and-low income African countries (Mikomangwa *et al.*, 2019; Feresu *et al.*, 2015; Liu *et al.*, 2008). Therefore, modifications in malaria transmission intensity has important implications on the pathology of maternal malaria and the processes that bring forth low birth weight.

However, in Tanzania, changes in malaria transmission intensity and subsequent intake of IPTp-SP does not show any dose-dependent risk reduction of maternal anaemia and low birth weight. Relatedly, other factors like placental malaria, previous gestational malaria infection, receipt of antihelminthics and the ingestion of iron and folate supplements not less than one month in pregnancy have no impact on the risk of low birth weight. Essentially, anaemia prevalence among women that took at least one dose of SP (3.8-5.5%) remained similar as those who had never taken SP (5.3-16.7%). Likewise, the prevalence of low birth weight among SP-users (89.3%) and non-users (85.7%) were not significantly different *(Mosha et al.*, 2014).

Later reports in Tanzania indicated that the lower prevalence of low birth weight (6.3%) in the country had positively affected the risk of malarial low birth weight. Currently, placental infections are significantly related with premature births rather than low birth weight. Therefore, taking optimal doses of IPTp-SP did not significantly reduce rates of low birth

weight. However, increased SP dosage (≥3 doses) is related with ten-fold decreased risk of prematurity (Ndeserua *et al.,* 2015) and 83.0% (aOR 0.17; 95%CI 0.03-0.88; p=0.05) decrease in the risk of LBW compared to pregnant women who did not take IPTp-SP (Mikomangwa *et al.*, 2019).

Regionally, the prevalence of low birth weight is much lower in North Western Tanzania (2.32%) and the infants are usually of high birth weight (3187.9g), especially in the Geita and Katoro regions. Here, high prematurity rates (9.43-19.88%) are closely associated with placental malaria and low birth weight. Typically, placental parasitaemia less than 100 parasites/μL induces prematurity within 34-36 weeks of gestation and taking the last IPTp-SP dose earlier than four weeks to delivery increases the risk. Unfortunately, IPTp-SP are usually of limited supply so access to higher doses (≥3 doses) is limited. Therefore, the effect of high (≥3) SP doses and the odds of low birth weight has no relationship. Rather, birth weight is more related with ANC attendance during pregnancy than IPTp-SP intake. Higher (≥4) visitations to the ANC creates the opportunity for increased contacts of lectures such as education on good dieting and the uptake of dietary supplements that improve nutrition. In a public health perspective, all prenatal care factors including ANC attendance, the utilisation of ITNs and increased (≥3) dosage of IPTp-SP require further analysis to properly establish their relationship with the odds of peripheral malaria parasitaemia and low birth weight (Mpogoro *et al.*, 2014). Notwithstanding, Ugandan pregnant women that use SP under IPTp still suffer significant risks of low birth weight though the antimalarial activity of the drug remains effective against placental malaria. Currently, SP beneficiaries are unprotected against placental parasitaemia and the risk of active placental infections is high especially during the later weeks of pregnancy (Odongo *et al.*, 2016).

In recent times, West African countries resolved to change the IPTp drug policy from chloroquine to SP in order to improve birth outcomes. For instance, Nigeria changed the IPTp policy from chloroquine to SP, expecting to offset excess risk of low birth weight in primigravidae. However, after the policy change in 2010, the risk of LBW has rather increased in all gravidities and primigravidae still carried higher excess risk compared to their multigravidae counterparts. In the South-Eastern parts around Nsukka and Calabar area, the policy failure has been ascribed to improper implementation, low (13.2%) coverage of optimal SP doses (≥2 doses) and poor documentation of IPTp services (Igboeli *et al*., 2018). All the same, the risk of low birth weight decreased significantly with the intake of high IPTp-SP doses (≥3). Moreover, both lower (≤2) and higher (≥3) doses of SP were associated with respective 46.0% and 56-67% reduced likelihood of anaemia (which is strongly associated with low birth weight). Correspondingly, low birth weight prevalence was lower (0-10%) in women that took higher (≥3) SP doses than lower (≤2) doses (10-15%) (Scott *et al.*, 2019). Immunologically, high levels of anti-parasite VAR2CSA antibodies secreted early in pregnancy (before IPTp) and the ability to effect antibody responses against limited targets of parasite VAR2CSA variants post-IPTp, prevent new infections and adverse birth outcomes (low birth weight). Ndam *et al.,* 2015, demonstrated this relationship in Beninese pregnant women where they showed that IPTp-SP and immunity interact to confer 67% reduced likelihood of low birth weight (Ndam *et al.*, 2015).

2.4.4 IPTp-SP and stillbirths

Reviewed documents revealed that malarial scientists have not researched much on the relationship between IPTp-SP utilisation during pregnancy and stillbirths (Goldenberg and Thompson, 2003). Though, a number of documents have related malaria infectivity and treatment with stillbirth, investigations of the impact of IPTp-SP treatment during pregnancy

on stillbirth are rare. For instance, recent reports indicate that IPTp-SP treatment in pregnancy does not adequately reduce the risk of maternal anaemia and low birth weight (which are strongly associated with stillbirth outcomes) (Darko *et al.*, 2018).

Moreover, malaria during pregnancy is associated with 1.69 increased odds and high stillbirth prevalence (13.1/1000 live births) in low transmission settings outside Africa. Specifically, around the Thai-Myanmar border area, malarial stillbirths account for 4.5% of all stillbirths and symptomatic rather than asymptomatic malaria in the third trimester is more devastating (2.99 odds versus 1.35 odds respectively). Accordingly, antenatal care which includes IPTp-SP administration has been made mandatory and more participatory to involve all pregnant women but submicroscopic malaria still persists in pregnancy. For instance, effective ANC practices has eliminated the relationship between malaria and intrapartum stillbirth but missed falciparum malaria alone causes 6.7% antepartum stillbirths. Apparently, only one episode but not recurrent infections is required during the entire course of pregnancy to induce antepartum stillbirth. However, recurrent malaria episodes after treatment (either by IPTp-SP or Artemisinin-based under any dosage) in any trimester (first, second, or third) induces miscarriage and stillbirth. Pathologically, maternal anaemia and small for gestational age (SGA) mediate almost half (42%) of the antepartum stillbirths recorded in this low malaria transmission intensity area (Moore *et al.*, 2017).

According to Christou *et al.*, 2017, the relationship between IPTp-SP and stillbirth is affected by differences in the content and quality of ANC services rendered as well as the timing and number of antenatal contacts made during pregnancy. Also, effective ANC service thrives on efficient emergency maternity care systems to decrease stillbirth rates (Christou *et al.*, 2017). Therefore, reductions of stillbirth risk depend on the activities at antenatal clinics and the efficiency of other obstetric support systems. All the same, the relationship of IPTp-SP and stillbirth show a dose-dependent effect such that higher doses are associated with reduced

odds of stillbirth. Agbozo *et al.*, demonstrated this effect in Ghanaian pregnant women who lived in the Hohoe municipality. Their results showed moderate uptake of SP doses (50.90%) in general but lower uptake of two and three doses (5.60-12.5%) in the pregnant women than those who never took any SP (30.9%). Yet, the intake of one dose or an absence of SP exposure increased the risk of low birth weight which stimulated high stillbirth prevalence in the pregnant women (57%). Moreover, these lower SP doses (one dose or no SP at all) were associated with 5.6 times increased likelihood of macerated and fresh stillbirths (Agbozo *et al.*, 2016).

Mosha *et al.*, 2014, have proposed that methods used to assess the dose-dependent relationship of SP and malaria parasitaemia be revised. The norm is that the total number of SP doses taken during pregnancy is analysed against the status of malaria parasitaemia at any point of gestation. For example, if a woman had taken three doses by the third trimester and a malaria screen was done at this point, the protective efficacy would have been determined by equating the cumulative number of SP doses taken (three doses) with the malaria status. However, they hypothesize that women should be screened for malaria within the intervals between the last and ensuing doses of SP. Per this model, dose-dependent prophylaxis could be properly ascribed especially, under high transmission intensities where women are more likely exposed to multiple potentially infectious mosquito bites (Mosha *et al.*, 2014).

2.5 Implications of SP dose of active ingredient on Therapeutic and Chemoprophylaxis Efficacy

Malaria and its related public health issues continue to cause significant losses in the health economy of most developing and low-middle income countries such as Ghana. Recent WHO estimates, indicate that there were over 200 million cases of malaria in 2015 and over 400,000 deaths. The tropical regions of the world including Africa is the most hit and

affected (WHO, 2017). Various methods and techniques needed to help curb this deadly menace have resulted in achieving significant levels of prevention. However, the use of antimalarial medicines in the management and treatment of malarial cases remain key in the prevention of malaria especially amongst the vulnerable population (children under 5 years and pregnant women). The medicines used in the prevention and treatment of malaria must conform to quality standards by having the right amount of the drug needed to completely eliminate the parasites in the bloodstream. Thus, the quality of such medicines must be guaranteed to the utmost level. Otherwise, any compromise on the required quality standards may lead to serious public health concerns such as increase of morbidity and mortality, failure in the prevention of parasitaemia in pregnant women, failure in disease treatment, development of drug resistance, etc. sub-optimal medicines continue to pose a harmful threat to the public health worldwide, particularly in under-resourced countries (Newton *et al.*, 2016; Dégardin *et al.*, 2014; Tabernero *et al.*, 2014).

On the other hand, Yeboah *et al.*, attribute the loss of IPTp-SP efficacy in Ghana to the low quality of SP served to Ghanaian women at the ANCs (Yeboah *et al.*, 2016). In a study conducted in Kenya on the quality of SP, they reported that out of the 27 tablets sampled and analysed, 13(35.1%) of the SPs failed to meet the accepted criteria (Amin, Snow, Kokwaro, & Amin, 2005). There was another study by Taylor *et al.*, in Nigeria and they analysed the active content of different drugs including Chloroquine and Sulphadoxine Pyrimethamine. They found that, the drugs contained 50% or less of the stated amount of active ingredient. They concluded the use of sub-optimal doses of antibiotics and antimalarials may be a factor in the selection pressure for drug-resistant organisms reported from developing countries. Sub-standard drugs decrease the therapeutic effect and this results in the risk of treatment failure. the reason being that, most of these drugs that fail the accepted criteria is comparable to an individual taking low doses of drugs (Taylor *et al.*, 2001).

In spite of this, SP still has a short-duration of temporary benefit in reducing malaria parasitaemia. Moreover, the majority of the studies (cross-sectional) in high SP resistant settings are vulnerable to type II errors due to the lack of statistical power to detect the protection that SP provides against individual birth outcomes. Again, authors are not endorsing the abandoning of IPTp-SP but to evaluate its operations in order to maximize the gains towards reducing the risk of placental malaria (Arinaitwe *et al.*, 2013). There is therefore the need to assess the quality of antimalarial medicines with standard methods as an assurance of effective prevention and treatment of malaria especially in Ghana.

Expectedly, the uncertainties raised by malaria investigators have activated investigations (like the current study) to assess the effectiveness of the new policy upgrade in pregnant women who are given SP under the recently modified regimen.

CHAPTER THREE

3.0 RESEARCH METHODOLOGY

This chapter discusses the methodology adopted for the study and included an explanation of the research setting, research approach, instrument design, sampling, and the data analysis techniques that were employed in the study. The selection of approaches and techniques was guided by the objectives of the research.

3.1 Profile of Study area

The Northern Region, specifically Tamale, was chosen to be the study setting. The Northern region has a poor resource setting in Ghana and considering the climatic conditions, Tamale has both a hot and dry climatic condition and this makes malaria severe in people living there as compared to other regions because of dehydration. The temperature is also high that favours the development and breeding of the mosquitoes. The Tamale Teaching hospital (TTH), Central Hospital, West Hospital and Seventh Day Adventist Hospital in the metropolis serve ethnically and socioeconomic diverse population and TTH is the referral center for the region as well. This study was conducted in the selected health facilities within the catchment area of the Tamale Metropolis situated in the Northern Region of Ghana.

3.1.1 Location, Size and Physical Features

The Tamale Metropolis, which serves as the administrative capital of the Northern Region of Ghana, is centrally located among twenty-five other districts in the region. It is bounded on the north and west by the Sagnarigu district; on the east by Mion; south by East Gonja and south-west by Central Gonja. It has as estimated land size of 646.90180sqkm (GSS, 2010). Geographically, the Metropolis is sandwiched between latitude 9º16 and 9º 34 North and then, longitudes 0º 36 and 0º 57 West.

By its unique location as a nodal town or settlement, Tamale has, over the years, grown into a viable market or commercial centre easily accessible by commuters and business-oriented people from not only the regions in Ghana, but also the entire West African sub-region.

As a strategic market centre, it takes in varied local goods from the agricultural, commercial and industrial sectors from the adjoining districts in the region and the country as a whole. Besides its comparative site value, the Metropolis derives inestimable benefits from the neighbouring countries such as Burkina Faso, Niger, Mali and the northern part of Togo, who traverse the Metropolis enroute to the middle belt and southern parts of Ghana.

Historically and demographically, the Northern region of Ghana has vast land cover with very sparse population distribution. However, the area began seeing considerably high population growth following the intrusion of migrants (especially migrant farmers) from other communities or parts of the country such as the Mamprusi, Komkobas and other ethnic groups. The 2010 Population and Housing Census put the population of Tamale Metropolis at 233, 252, representing 9.4% of the entire Northern Region. The demographics or the main features revealed by the 2010 Population Census indicated the following gender disparity in the Metropolis: 49% males and 50.3% females. Another very important demographic feature was that, the population was more urbanised as 80.8% lived in the urban areas with the rest 19.1% living in the suburban and rural localities. Ghana is generally a high fertility country. Consequently, the age structure is basically shaped by the effect of mortality. The metropolis thus has a youthful population of almost 36.4% made up of youth below 15 years, depicting a broad-based population pyramid, which tapers off to a small number of elderly persons aged 60 years and above, also representing 5.1% as a result of mortality. The youthful population connotes a high potential for human resource development to enhance social, economic and political development. The total age dependency ratio for the entire Metropolis is 69.4%. The

ratio for the rural localities is higher (86.5) than that of the urban localities (65.7) (GSS, 2010/ /Population and Housing, 2010).

There is a total of 116 communities in the Metropolis. The urban communities are 41 representing 35%; the peri-urban 15, making up 13%; while the rural dominates with 60 communities also representing 52%. Land for agricultural activities is available, to a large extent, in the rural parts of Tamale, which serve as the food basket for the Metropolis. Nonetheless, these agricultural communities still lack basic social and economic infrastructure such as good road network, school blocks, hospitals, market and recreational amenities.

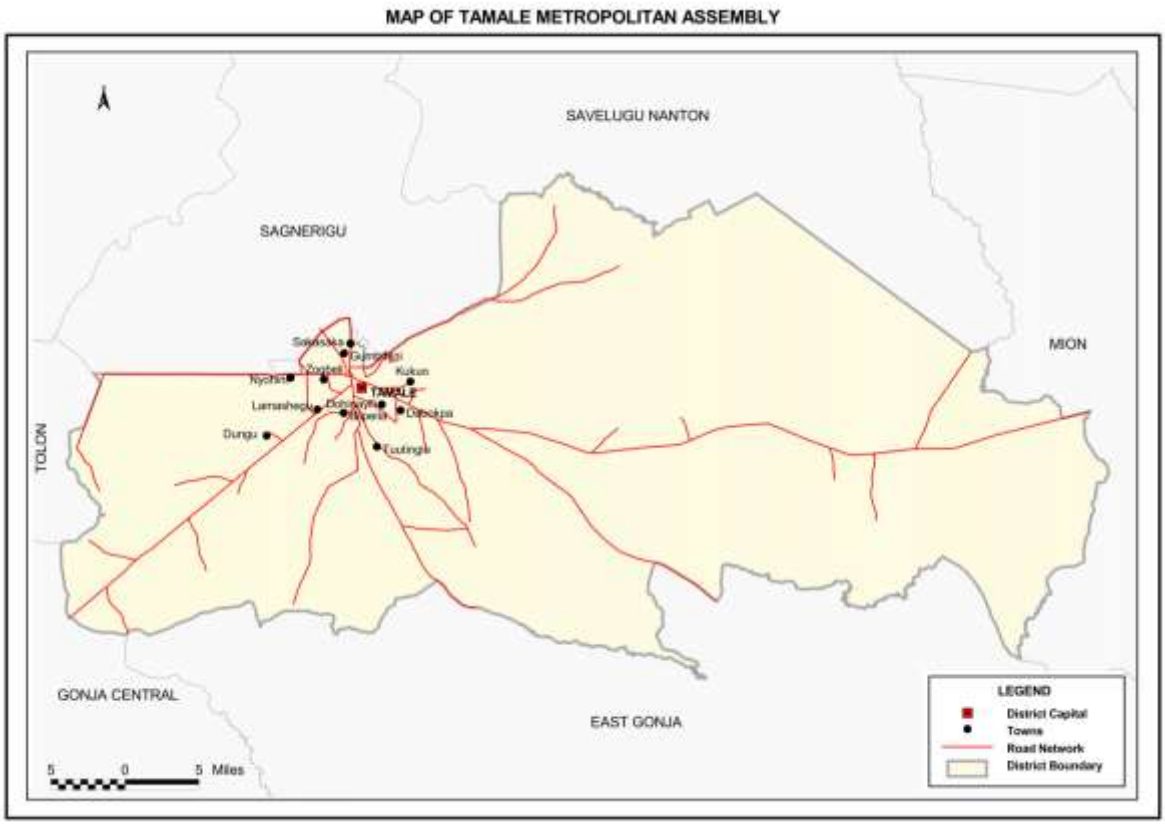


Figure 3.1 Map of the Tamale Metropolis
Source: Ghana Statistical Service, 2010 Population and Housing Census

3.1.2 Geophysical features

The Geophysical features of the Metropolis comprise the topographic, relief, climate, drainage patterns, soil and vegetation of the area under review.

3.1.2.1 Relief and Climate

Generally, the Metropolis has an elevation of 180 meters above the sea level. It is largely a low-lying land with isolated hills. This unique relief and landscape make it ideal for road construction, laying of cables to link the national grid for electricity expansion to and across the Metropolis to other districts and regions, and housing projects in the area. The Metropolis and the rest of Northern Ghana receive a single rainfall only in the year. This is a big challenge making the region dependent on rain-fed agriculture lasting only one season. This inevitably calls for large-scale irrigational facilities to enhance year-round farming activities to replace the traditional shifting cultivation by small holder peasant farmers. Daily weather conditions (especially temperature) vary from season to season. There is high humidity, slight sunshine with heavy thunderstorms in the rainy season, which spans June through October.

Conversely, the dry season is characterized by hazy conditions and dry harmattan winds from November through February and high sunshine from March-May. The harmattan season enables farmers in the area to harvest and preserve their crops/produce mainly cereals thus limiting post-harvest losses. The Metropolis also has another latent potential in the availability of several artificial parks and gardens which still largely remain untapped. The local authorities and other private developers could take advantage of the high sunshine in the area to build swimming pools, recreational parks for both children and adults for relaxation during this unfriendly excessive harmattan and high sunshine period. Indirectly, most farmers and residents would be able to enjoy good family re-union and have a well-deserved rest and relaxation during this lean season. It would also help the Metropolitan Assembly to rake in more internally generated revenue for the development of the Metropolis.

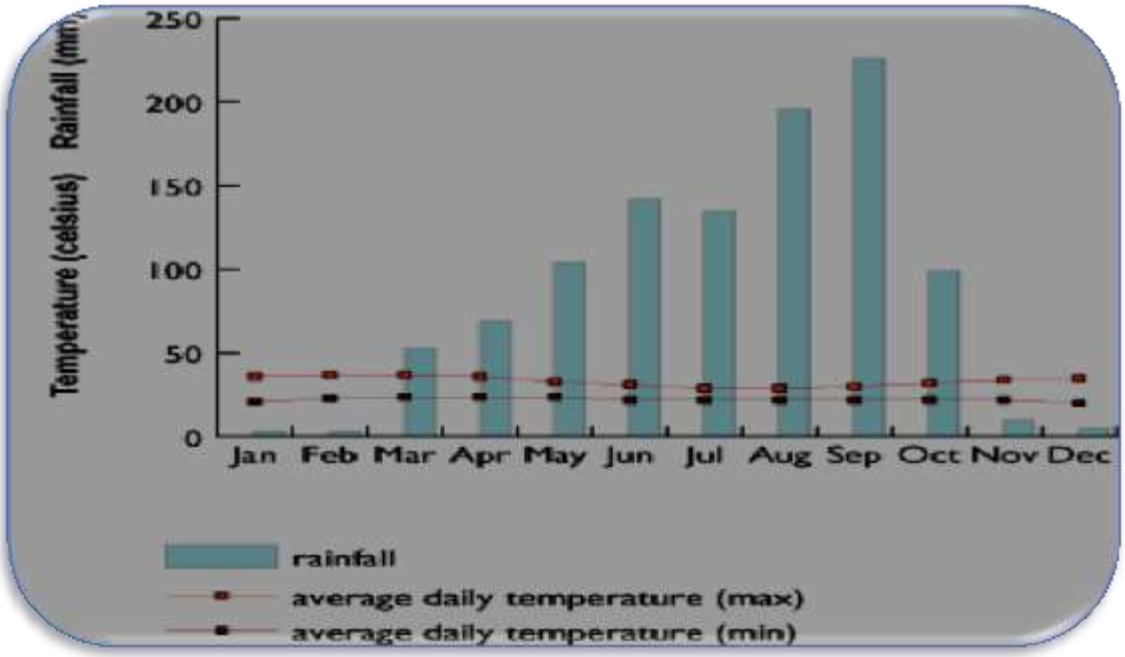


Figure 3.2 Rainfall and Temperature Ranges

3.1.2.2 Drainage

The Metropolis, being a generally low-lying land with isolated hills, is largely well-drained. However, it is largely bereft of perennial streams and rivers. It can only boast of a few seasonal streams, which come to life only during the single rainy season. This is attributed to the low water table sitting on impervious underlying bed rocks. The few seasonal streams derive their headwater from around Tamale, which is situated on a higher ground. Regular water supply for the Metropolis is assumed by several artificial dams, dug-outs and boreholes that have been constructed by individual community members and Non-Governmental Organisations (NGO's). Two of such facilities worthy of mention are the Buipela and Lamashegu dams. These and other dug-outs provide regular water supply for domestic purposes and also for farm animals. Despite the poor drainage challenges, the Metropolis still has favourable conditions for irrigation schemes. For instance, the Pagazaa stream is ideal for agricultural production if it could be dammed for irrigation farming.

3.1.2.3 Soil and Vegetation

The vegetation cover of the Metropolis is predominantly savannah woodland with characteristic flora made up of short and scattered trees including Acacia, "Dawadawa", Shea, Nim, Mahogany and Giant Boabab, among others. There are also naturally grown tall grasses during the rainy season that are used to make the local "Zanamat" in the metropolis. The "Zanamat" which is made by many farmers during the dry season, helps to reduce rural-urban migration among the youth.

The Shea and "Dawadawa" tress are the major economic trees, which have gained international recognition. Thousands of households in the metropolis and the entire Northern region are engaged in the picking, processing and marketing of Shea nuts and "Dawadawa" for their livelihood.

Cashew is also emerging as one of the major cash crops grown in the Metropolis. These agricultural activities have offered employment especially to the youthful population thereby increasing household incomes thus reducing poverty levels.

Each vegetation belt in the country is usually characterized by different soil types. In the savannah bely across the Tamale metropolis, the major soil types include sandstone, gravel, mudstone and shale. Seasonal erosion and weathering process have conspired to break-down these solid mass of rocks into different soil grades including sand, clay and laterite ochrosols. The availability of these economically viable stones or soil types has led to the emergence of rapid real estate development in the area, as these soil types provide ready raw materials for real estate developers in the construction industry.

Tamale can boast of two forest reserves located in the central part of the metropolis, namely the Nyohini and Agric Forest Reserves. These facilities are being managed by the Forestry Services Department to help achieve the vision and mission for creating the reserves.

However, the Department is saddled with serious challenges including personnel deficit and financial resources to manage these facilities well. Another constraint is encroachment and poaching by unauthorized persons who use it for illegal economic activities. Other environmentally unfriendly persons use them for open defecation and dumping of refuse, thus increasing sanitation hazards in the city. To address or pre-empt these phenomena, the local government authorities or appropriate state institutions should search for strategic investors to acquire and manage them for viable economic activities such as picnics and holiday inns.

3.1.3 Migration, Fertility and Mortality

3.1.3.1 Migration

Migration may broadly be defined as the process of animals and humans moving from one geographical location to another for security, shelter or job opportunities. It may involve moving from one country to another or even internally from one district community to another to seek greener pastures or even to establish a new home, permanent or temporary. Thus, it can be established that, migration is generally caused by social and economic factors and many other considerations.

Ashanti region has the highest number of migrants in the Tamale with a total of 3,271. It is followed serially by the Upper East and Brong Ahafo regions with migrant population of 3,114 and 1,848 respectively. The Western and Central regions have the lowest numbers of migrants in the Metropolis with population of 505 and 650 respectively.

3.1.3.2 Fertility

The term fertility generally refers to a woman's ability to have children of her own. Medically, it refers to the number of live births a woman has in her life time. The analysis was based on the birth histories of women aged 15-49. The Tamale Metropolis has a fertility

rate of 2.8 children per woman aged 15-49 years. This was lower than the regional average of 3.5, implying that a woman in the age bracket 15-49 years residing in the Metropolis could have, on the average 2.8 children by the end of her reproductive age period.

3.1.3.3 Mortality

Statistics on mortality are used as benchmarks to ascertain the health status and growth potential of the population. Information on the potential growth of the population in the future and prevailing patterns of various causes of death can also be derived from data on mortality. Female population 12 years and older by age, children ever born, children surviving and sex of children in the Metropolis are detailed in Table 3.1. The table also shows that, the total number of children ever born to the female population 12 years and older in the Tamale Metropolis is 176,800 out of which 84.2% are children surviving. The proportion of males surviving is 83.4% while that of females surviving is 85.1%, which means that, the survival rate for females is more than that of the males in the Metropolis.

Table 3.1 Female population 12 years and older by age, children ever born, children surviving and sex of child

	Number of Females	Children Ever Born			Children Surviving					
Age		Both sexes	Male	Female	Both sexes	Survival rate	Male	Survival rate	Female	Survival rate
All ages	78,442	176,800	90,025	86,775	148,900	84.2	75,041	83.4	73,859	85.1
12 14	6,436	25	10	15	19	76.0	6	60.0	13	86.7
15 -19	11,946	830	422	408	689	83.0	343	81.3	346	84.8
20 24	12,233	6,334	3,254	3,080	5,632	88.9	2,814	86.5	2,818	91.5
25 29	11,129	15,311	7,871	7,440	13,712	89.6	6,942	88.2	6,770	91.0
30 34	8,514	21,802	11,020	10,782	19,545	89.6	9,811	89.0	9,734	90.3
35 39	6,756	23,637	11,938	11,699	20,822	88.1	10,467	87.7	10,355	88.5
40 44	5,095	21,864	11,091	10,773	18,914	86.5	9,492	85.6	9,422	87.5
45 49	3,668	18,002	8,992	9,010	15,182	84.3	7,527	83.7	7,655	85.0
50 54	3,196	16,490	8,522	7,968	13,625	82.6	7,005	82.2	6,620	83.1
55 59	1,734	9,593	4,864	4,729	7,817	81.5	3,941	81.0	3,876	82.0
60 +	7,735	42,912	22,041	20,871	32,943	76.8	16,693	75.7	16,250	77.9

Source: Ghana Statistical Service, 2010 Population and Housing Census

3.1.3.4 Crude Death Rate

Crude death rate is defined as the number of deaths per 1,000 populations in a given year. The crude death rate for the Tamale Metropolis is 5.6 percent and this means that 5.6 percent of every thousand population in the Metropolis die annually, that is1, 257 deaths out of the total.

3.1.3.4.1 Age specific death rates

Age specific death rates are calculated for specific age groups in order to compare mortality at different ages or at the same age over time. The age specific death rate is computed as a ratio of deaths of people in a specified age group, for example, deaths among the (20-24) year-group to the population in the age-group (20-24) multiplied by 1,000. Figure 3.3 shows the death rate of the population by sex in the Metropolis. It can be seen from the figure that infant mortality in the Metropolis is almost 0.0 percent. The figure shows that from ages 0-14 years, deaths for both males and females fall sharply and starts rising thereafter. The death for males is lower from ages 15 years to 54 years while that of the females rises for the same age groups. The high deaths of females within these ages could be as a result of maternal mortality and other issues related to women and birth since this occurs within the reproductive ages of females. Within the late ages of 55 years onwards, death rates for both sexes' increases but with the male death rate higher than that of the females.

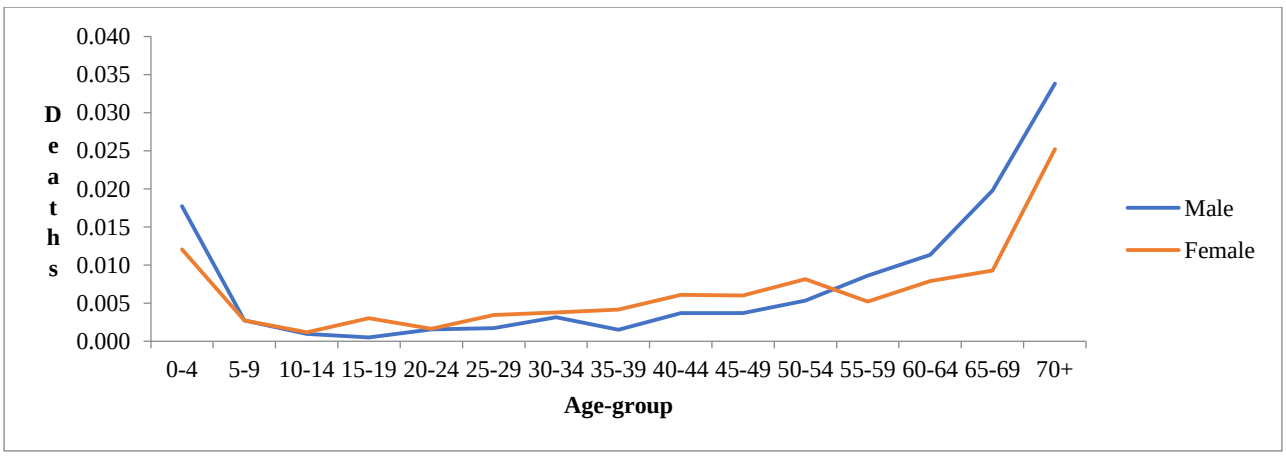


Figure 3.3 Reported age specific death rates by sex
Source: Ghana Statistical Service, 2010 Population and Housing Census

3.1.3.4.2 Causes of deaths in households

Table 3.2 below shows the causes of death in the Metropolis. The causes of death include accident/violence/homicide/suicide and pregnancy related. The table reveals that 9.5% of deaths in the metropolis are due to accidents/suicide while more than half (90.5%) are due to other causes. This is higher than both the regional and national figures (90.3% and 88.4%) respectively in comparative terms.

With regards to pregnancy related deaths for females' age 15-54 years, 2.0% of the population within this category die in the Metropolis as compare to 2.2% and 1.9% for both the Northern Region and Ghana respectively. Deaths not due to pregnancy related is 98.0% for the Metropolis while that of the region are 97.8% and that of the country are 98.1%.

Table 3.2 Causes of death in households

Country/ Region/ District	Accident/ violence/ homicide /suicide n (%)	All other causes n (%)	Total deaths	Pregnancy related death (female 15-54 years) n (%)	Not pregnancy related n (%)
Ghana	18,938(11.6)	144,596(88.4)	163,534	3,026(1.9)	160,508(98.1)
Northern	1,434(9.7)	13,281(90.3)	14,715	322(2.2)	14,393(97.8)
Tamale Metropolis	119(9.5)	1,138(90.5)	1,257	25(2.0)	1,232(98.0)

Source: Ghana Statistical Service, 2010 Population and Housing Census

3.1.4 Size, Household Composition and Headship

3.1.4.1 Household Size, Composition and structure

The 2010 Population and Housing Census defined a household as "a person or a group of persons, who lived together in the same house or compound and shared the same house-keeping arrangements" (PHC Report, 2010). In general, a household consists of a man, his wife, children and some other relatives or a house-help who may be living with them. It is, however, important to state that membership of a household does not necessarily depend on blood ties. The number of persons who belong to a household constitutes the household size.

Table 3.3 shows the household size, composition and headship in the Tamale Metropolis. The composition of the household is made up of the head, spouse, child, parent/parent in-law, grandchild, brother/sister, step child, adopted/foster child, other relatives and non-relatives. The table shows a total number of 219,971 households in the Metropolis comprising 109,506 males and 110,465 females. Out of this, the total headship is 16.1% of the total population in the metropolis. The total male heads are 24.2% of the total headship and the female headship of 8.1% of the total headship in the metropolis. As can be seen, there are more male heads than female heads in the metropolis. For spousal distribution, the table shows that the total spousal population is 9.4% of the total household composition. The proportion of males is 1.2% of the total spousal population. The number of females in the spousal population is 17.5% of the total indicating that there are more female spouses (wives) than males. This could be as a result of the practice of polygamy in the Metropolis.

The proportion of children in the households is 40.4% of the total household composition in the Metropolis. Out of this, 44.1% are males and 36.7% are females, which mean that there are more male children than females in this category of the household composition. It can be seen that there are more children than any other groups in the household composition.

Parent/parent in-law has a population of less than 1% (0.9%) of the total household composition. From this, it is obvious that, the total numbers of males are less than 1% (0.2%) and the total numbers of females are a little over 1% (1.5%). Here, it can be seen that the number of female parents is more than the number of male parents. The population of sons/daughters' in-law is also a little over 1% (1.6%) of the population. From this, it can be seen that, there is a total of 0.3% sons in-law and a little closer to 3% (2.9%) of daughters' in-law.

From Table 3.3, other relative population is 12.9% and the males constitute 9.8% while female constitute 16.0% of females. As can be seen, the number of females in this category of the household composition is more than the number of males. The table also shows that the number of non-relatives is less than 2% (1.1%) of the total household composition.

Table 3.3 Household populations by composition and sex

	Total		Male		Female	
Household composition	Number	%	Number	%	Number	%
Total	219,971	100.0	109,506	100.0	110,465	100.0
Head	35,408	16.1	26,454	24.2	8,954	8.1
Spouse (wife/husband)	20,613	9.4	1,282	1.2	19,331	17.5
Child (son/daughter)	88,795	40.4	48,251	44.1	40,544	36.7
Parent/Parent in-law	1,967	0.9	270	0.2	1,697	1.5
Son/Daughter in-law	3,510	1.6	286	0.3	3,224	2.9
Grandchild	21,105	9.6	10,606	9.7	10,499	9.5
Brother/Sister	13,141	6.0	8,158	7.4	4,983	4.5
Step child	2,817	1.3	1,476	1.3	1,341	1.2
Adopted/Foster child	1,809	0.8	752	0.7	1,057	1.0
Other relative	28,368	12.9	10,714	9.8	17,654	16.0
Non-relative	2,438	1.1	1,257	1.1	1,181	1.1

Source: Ghana Statistical Service, 2010 Population and Housing Census

3.1.4.2. Household population by structure and sex

Household structure is defined as classification of ties of affiliation of persons who constitute households. In table 3.4, the household structure in the Metropolis. The table shows that with regards to "head only", the total population is a little over 2% (2.2%) of the total. Out of the total heads only, 3.3% are males while 1.0% are females, an indication that there are more male heads than females in the metropolis.

For "head and spouse only", the total number is 2,640 (1.2%) with (1.2%) being males and (1.2%) being females. For the nuclear family (head, spouse and children), the proportion is 19.5% of the total household structure. Within this category, the number of males is 20.2% and female's 18.8%. In the extended structure (head, spouse, children and head's relatives) the proportion is (46.1%) of the total household structure. Here, males are 46.2% and females

are 46.1%. The proportion of single parent nuclear is (4.8%) comprising (4.1%) males and (5.6%) females. In the table, it can be seen that single parent Extended plus non relative has the lowest population of 2,965 (1.3%).

Table 3.4 Household population by structure and sex

	Total		Male		Female	
Household structure	Number	%	Number	%	Number	%
Total	219,971	100.0	109,506	100.0	110,465	100.0
Head only	4,755	2.2	3,615	3.3	1,140	1.0
Head and a spouse only	2,640	1.2	1,339	1.2	1,301	1.2
Nuclear (Head spouse(s) children)	42,817	19.5	22,093	20.2	20,724	18.8
Extended (Head spouse(s) children Head's relatives)	101,495	46.1	50,625	46.2	50,870	46.1
Extended + non relatives	8,477	3.9	4,266	3.9	4,211	3.8
Head spouse(s) and other composition	5,091	2.3	2,551	2.3	2,540	2.3
Single parent Nuclear	10,654	4.8	4,512	4.1	6,142	5.6
Single parent Extended	28,150	12.8	12,357	11.3	15,793	14.3
Single parent Extended + non relative	2,965	1.3	1,314	1.2	1,651	1.5
Head and other composition but no spouse	12,927	5.9	6,834	6.2	6,093	5.5

Source: Ghana Statistical Service, 2010 Population and Housing Census

3.1.5 Marital Status

Marriage is a formal union of a man and woman legally recognized by customary law or the ordinance by which they become husband and wife. It is a very important social institution in the Ghanaian society and much revered by the predominantly Muslim community in the Tamale Metropolis. Marriage is one of the factors that influence demography (population increase) in the society. Any of the following types of marriage is recognized and practiced in the Metropolis and in the Ghanaian society as a whole: civil, traditional and common law/consensual.

However, the situation whereby two individuals (a man and a woman) are locked up officially in a relationship without the performance of any marital rites is no uncommon in

Tamale, which is gradually assuming a cosmopolitan status. There are norms governing marriage in every human society, which make the union socially and legally acceptable.

The minimum age for marriage differs from one society to another. In Ghana, 18 years is the minimum legal age for marriage. However, cultural practices in some ethnic and religious (especially Muslim community) within the Metropolis allow much younger girls to be given out in marriage.

To capture empirical data on girls who marry below age 18, the 2010 Population Census solicited information from persons/girls aged 12 years and above. Figure 3.4 below shows that, 48.6% are married while the "never-married" constitute 44.2%.

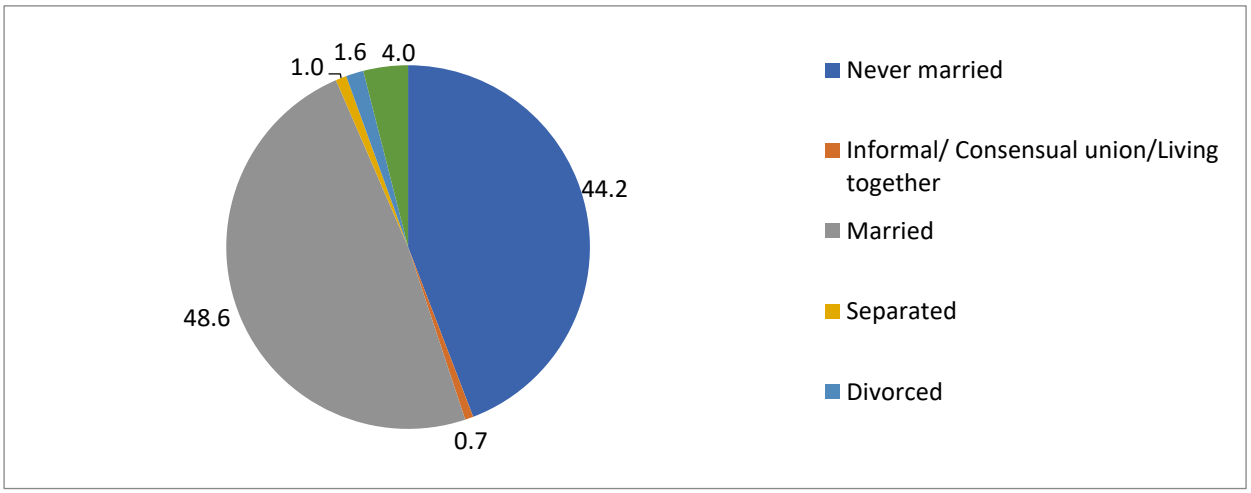


Figure 3.4 Marital status in the Metropolis
Source: Ghana Statistical Service, 2010 Population and Housing Census

3.1.5.1. Marital status by sex and age-group

Table 3.5 below shows the percentage distribution of marital status by sex and age-group. The table shows that a high proportion of females married were within age cohort of 35-39 years representing 85.4% while that of male is within 50-54 years representing 88.9%. In terms of age distribution, both sexes (over 80%) between the ages of 12-19 years are never married. The percentage of females married between the ages 15-39 years is a little higher than males within the same age category.

Table 3.5 Persons 12 years and older by sex, age group and marital status

Sex/Age-group	Number	Total	Never married	Informal/ Consensual union/Living together	Married	Separated	Divorced	Widowed
Both Sexes								
Total	155,046	100.0	44.2	0.7	48.6	1.0	1.6	4.0
12 - 14	12,950	100.0	93.4	0.2	6.4	0.0	0.0	0.0
15 - 19	24,198	100.0	91.4	0.4	8.0	0.1	0.1	0.1
20 - 24	23,837	100.0	72.0	1.1	25.9	0.4	0.3	0.3
25 - 29	20,966	100.0	46.3	1.4	50.5	0.6	0.7	0.5
30 - 34	16,531	100.0	22.4	1.1	72.8	1.3	1.5	0.9
35 - 39	13,431	100.0	11.9	0.8	81.6	1.6	2.6	1.5
40 - 44	10,502	100.0	6.1	0.5	85.5	1.8	3.0	3.1
45 - 49	7,756	100.0	4.5	0.5	84.5	2.1	3.9	4.5
50 - 54	6,585	100.0	2.9	0.6	81.1	2.2	4.2	9.0
55 - 59	3,712	100.0	3.4	0.4	77.8	2.2	4.2	12.0
60 - 64	4,308	100.0	3.4	0.5	70.2	2.3	4.2	19.4
65+	10,270	100.0	6.2	0.3	58.8	1.5	3.4	29.9
Male								
Total	76,604	100.0	52.2	0.7	44.6	0.7	1.1	0.7
12 - 14	6,514	100.0	93.8	0.2	6.0	0.0	0.0	0.0
15 - 19	12,252	100.0	94.3	0.2	5.4	0.1	0.0	0.0
20 - 24	11,604	100.0	88.4	0.5	10.8	0.1	0.1	0.1
25 - 29	9,837	100.0	67.4	1.3	30.2	0.4	0.5	0.2
30 - 34	8,017	100.0	35.1	1.4	61.5	0.8	0.8	0.3
35 - 39	6,675	100.0	18.0	0.9	77.8	1.2	1.6	0.5
40 - 44	5,407	100.0	8.5	0.5	87.2	1.5	1.7	0.6
45 - 49	4,088	100.0	6.5	0.5	88.0	1.3	2.8	0.9
50 - 54	3,389	100.0	4.3	0.7	88.9	1.5	3.1	1.5
55 - 59	1,978	100.0	4.6	0.5	87.8	1.9	3.6	1.7
60 - 64	2,029	100.0	4.7	0.5	86.2	1.7	3.6	3.2
65+	4,814	100.0	7.6	0.4	81.8	1.5	3.2	5.5
Female								
Total	78,442	100.0	36.3	0.8	52.5	1.2	2.0	7.1
12 – 14	6,436	100.0	93.0	0.2	6.8	0.0	0.0	0.0
15 - 19	11,946	100.0	88.4	0.6	10.7	0.1	0.1	0.1
20 - 24	12,233	100.0	56.5	1.7	40.2	0.6	0.6	0.5
25 - 29	11,129	100.0	27.7	1.5	68.4	0.7	0.9	0.7
30 - 34	8,514	100.0	10.5	0.8	83.5	1.8	2.1	1.4
35 - 39	6,756	100.0	6.0	0.6	85.4	2.0	3.6	2.5
40 - 44	5,095	100.0	3.4	0.5	83.8	2.0	4.4	5.8
45 - 49	3,668	100.0	2.4	0.4	80.5	3.0	5.2	8.5
50 - 54	3,196	100.0	1.4	0.4	72.9	3.0	5.4	16.9
55 - 59	1,734	100.0	2.1	0.2	66.4	2.6	4.9	23.8
60 - 64	2,279	100.0	2.2	0.6	56.0	2.7	4.7	33.8
65+	5,456	100.0	4.9	0.1	38.5	1.4	3.5	51.5

Source: Ghana Statistical Service, 2010 Population and Housing Census

3.1.5.2 Marital status and level of Education

Table 3.6 shows the marital status and level of education; married persons with higher education are lower for all the categories than those with no education. From the table it can be seen that the percentage of married persons with no education (57.5%) is higher than those with education (42.5%). The figure is also higher in the female categories (65.5%) than the male (48.0%). Those with basic education who have never married are 50.0% of which (48.8%) are males and (51.7%) are females. Also, those with secondary education who have never married is higher in males (23.2%) than females (20.1%). Widows with no education records (84.9%) and the proportion of males within this category is (68.3%) while that of females is (86.6%).

Table 3.6 Persons 12 years and older by sex, marital status and level of education

Sex/Marital status	Number	All levels	No Education	Basic	Secondary	Vocational/Technical/ Commercial	Post middle/ secondary certificate/ diploma	Tertiary
Both Sexes								
Total	155,046	100.0	40.6	34.7	14.4	1.6	6.7	2.0
Never married	68,482	100.0	17.0	50.0	21.9	1.6	7.5	2.0
Informal/Consensual union/Living together	1,154	100.0	34.2	34.7	16.6	2.4	10.3	1.7
Married	75,343	100.0	57.5	23.3	9.1	1.6	6.2	2.2
Separated	1,492	100.0	59.0	24.5	6.4	2.0	7.2	0.8
Divorced	2,420	100.0	62.4	23.9	5.8	1.7	4.7	1.5
Widowed	6,155	100.0	84.9	10.6	1.5	0.6	2.1	0.4
Male								
Total	76,604	100.0	31.3	37.8	17.5	1.7	8.6	3.1
Never married	39,988	100.0	15.6	48.8	23.2	1.5	8.4	2.5
Informal/Consensual union/Living together	503	100.0	28.2	34.4	16.7	3.4	13.7	3.6
Married	34,142	100.0	48.0	25.7	11.4	2.0	8.9	4.0
Separated	548	100.0	54.6	27.2	7.5	1.8	8.2	0.7
Divorced	849	100.0	59.2	23.9	7.3	1.6	6.0	1.9
Widowed	574	100.0	68.3	22.0	4.0	1.6	3.8	0.3
Female								
Total	78,442	100.0	49.8	31.7	11.5	1.4	4.8	0.9
Never married	28,494	100.0	18.9	51.7	20.1	1.7	6.3	1.2
Informal/Consensual union/Living together	651	100.0	38.9	35.0	16.4	1.7	7.7	0.3
Married	41,201	100.0	65.5	21.3	7.2	1.3	4.0	0.7
Separated	944	100.0	61.5	23.0	5.8	2.1	6.7	0.8
Divorced	1,571	100.0	64.1	23.9	5.0	1.7	4.0	1.3
Widowed	5,581	100.0	86.6	9.5	1.2	0.5	2.0	0.4

Source: Ghana Statistical Service, 2010 Population and Housing Census

3.1.6 Metropolitan Health Department

The Health services in the Metropolis are managed at three (3) levels namely: Metro. Health Administration level, Sub-district level and the Community level.

3.1.6.1 Metro. Health Administration

At the administration level, the Metropolitan Health Management Team (MHMT) is responsible for overall planning, monitoring, supervision, evaluation, training and co-coordination of all health programmes in the Metropolis. It is having the mandate to conduct operational research and link up with other agencies and NGOs in the provision and promotion of health.

Under the Health division, the Metropolis is sub-demarcated into six (6) sub-districts, each with a management team known as the Sub-district Health Management Team (SDHMT). The six sub-districts are:

1. Bilpela Sub-district
2. Choggu Sub-district
3. Sagnerigu Sub-district
4. Taha/Kamina Sub-district
5. Tamale Central Sub-district
6. Vittin Sub-district

The SDHMTs are responsible for programme planning and implementation of health activities in their respective sub-districts, including organizing and conducting integrated static and outreach activities such as immunization, reproductive health, disease control, growth monitoring, health education/promotion and clinical care

Training and supervision of community-based health workers such as traditional birth attendants (TBAs), Community Based Surveillance (CBS) volunteers and village Health Committees.

Health services are provided at the community level by sub-district staff supported by TBAs, and CBS volunteers.

The Metropolis has thirty-four (34) health facilities including the Teaching Hospital. The breakdown is as follows:

1. Teaching hospital 1
2. Government facilities 20
   - Hospitals 2
   - Health center or clinics 9
   - Rehabilitation / nutrition centers 3
   - CHPS compounds 6 (2 functional)
3. Community initiated clinics 1
4. Private facilities 10
5. Quasi-Government facilities 2

3.1.7 Top diseases

Malaria was persistent and had been recorded as the top most disease in all OPD reported and recorded cases.

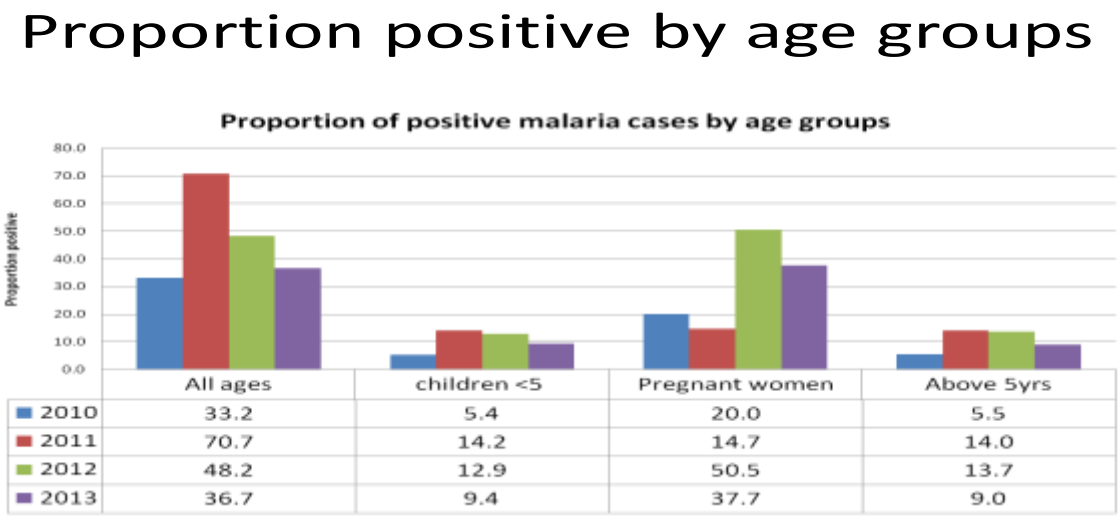


Figure 3.5 Proportion of positive malaria cases by age groups
Source: Ghana Statistical Service, 2010 Population and Housing Census

3.2 Study design

The study was a prospective cohort of pregnant women who attended Antenatal clinic in four health facilities (Tamale Teaching Hospital, Tamale West Hospital, Tamale Central Hospital and Tamale SDA Hospital) within the Tamale metropolis. Pregnant women that met the study inclusion criteria and sought antenatal care in any of the study facilities were recruited. Prospective pregnant women who consented to the study were enrolled as study participants. A structured questionnaire was used to obtain information on the reproductive history, ITN usage and the socio-demographic characteristics of the participants and recorded in the study data base. The participants were stratified into three groups, namely those who did not take IPTp-SP, those who took less than three (<3) doses of IPTp-SP and those who took three or more doses (≥3) doses of IPTp-SP. The participants were followed-up until 36 weeks of gestation. At this same period, blood samples were taken and analysed to detect the presence of peripheral malaria parasites at the Tamale Teaching Hospital Laboratory. Anaemia at 36 weeks of gestation was extracted from the antenatal records of the participants. Babies were

weighed within 6 hours of birth and recorded immediately to prevent errors. Birth outcomes such as stillbirth were immediately recorded and later confirmed from delivery records in the maternity wards. Samples of the IPTp-SP dispensed to the pregnant women who participated in the study were collected and analysed at the KNUST School of Pharmacy laboratory to obtain information on the adequacy of the programme drug. Descriptive statistics including means and standard deviations (SD) were used for continuous variables and frequency distributions were used for categorical variables. Pearson chi-square test was used to find associations between categorical variables and outcome variables. Multivariable logistic regression was used in the analyses of the data to find the odds of the association. The results obtained from the three study groups (No SP, <3 doses of SP and ≥3 doses of SP) were compared to one another. Associations were drawn between the doses of IPTp-SP taken, maternal health (maternal malaria parasitaemia and maternal anaemia) and neonatal health (birth weight and stillbirth).

3.3 Data collection techniques and tools

A pre-validated questionnaire was developed using extracts from the Ghana Multiple Indicator Cluster Survey (MICS) with an enhanced Malaria Module and Biomarker 2011 (Ghana Statistical Service, 2012) on maternal and new born health originally designed by UNICEF and also from published studies (Orish *et al.*, 2015; Mosha *et al.*, 2014; Mpogoro *et al.*, 2014; Arinaitwe *et al.*, 2013; Kayentao *et al.*, 2013; Filler *et al.*, 2006). The study questionnaire was designed to collect the following variables: socio-demographic information (maternal age, marital status, education, residence, ethnicity and occupation), reproductive information (parity, gravidity and gestational age at first ANC). The questionnaire also captured the intervention history (SP and ITN usage), haemoglobin level (at registration and at the end of 36 weeks of gestation). The study data were taken from three main sources: the

maternal health record book, the ANC register and through participant interviews. Data extracted from the maternal health record book were cross checked with the register at the ANC in accordance with the study protocol and the participants were subsequently interviewed directly to corroborate the validity of all obtained information. During the interviews, the questionnaires were administered by the principal investigator and the study research assistants (who could also speak the local dialect) to the pregnant women. The respondents who could not understand and communicate in English language were interviewed by a research assistant in Dagbani, Hausa or Akan. The responses were then transcribed back to English and documented on the questionnaires. Data collection spanned a period of 12 months, from September 2016 to August 2017 to help account for seasonality in malaria.

The haemoglobin level and the malaria parasitaemia status of the study participants at enrolment (extracted from the ANC card and the ANC register) served as the baseline data. The investigators of the current provided the same weighing scale to the four selected facilities and confirmed efficiency of the weighing scales used to measure the weights of babies unlike an earlier study that could not fully ascertain equipment efficiency (Afeke *et al.,* 2017), weight measurement for new born babies in this study followed standard procedure. Again, delivery outcomes such as stillbirth and the birth weight of babies were taken immediately after delivery at the Labour ward. Haemoglobin at 36 weeks of gestation was also extracted from the ANC card and confirmed with the ANC register. For malaria parasitaemia at 36 weeks, blood samples were taken from the participants and processed for microscopic analysis at the Tamale Teaching hospital laboratory.

3.4 Inclusion criteria

The following criteria qualified a pregnant woman to be recruited into the study:

1. Pregnant women of at least 16 weeks gestation.
2. Pregnant women who were HIV negative.
3. Pregnant women who attended antenatal clinic at the study facilities until delivery.
4. Women who delivered in the selected study facilities.

3.5 Exclusion criteria

Pregnant women with the following characteristics were excluded from the study:

1. Women who migrated out of the study area before the end of the study period.
2. Women with co-morbid conditions such as hypertension and diabetes were excluded during the birthweight analysis
3. Women who were not a resident of the study catchment area.
4. Sickle cell positive woman

3.6 Study Population

The study population was sampled from pregnant women in the Northern region of Ghana who attended antenatal clinic at any of the following hospitals, Tamale Teaching Hospital, Tamale West Hospital, Tamale Central Hospital and Tamale SDA Hospital. Pregnant women at 16 weeks of gestation and/or those who have experienced quickening qualified to enter the study. Only pregnant women who consented to the study were recruited into the study. A total of 1,188 pregnant women satisfied the study criteria, consented to the study and were subsequently enrolled into the study as participants.

3.7 Study variables

The variables measured in this study included:

1. **Independent variable**: IPTp-SP intake.
2. **Dependent variables:** are the primary and secondary outcomes (maternal haemoglobin level, maternal peripheral malaria parasitaemia, birthweight and stillbirth).
3. **Primary outcomes variables:** maternal haemoglobin level, maternal peripheral malaria parasitaemia, birthweight
4. **Secondary outcome variables**: Stillbirth.
5. **Active ingredient of SP products analysed**

Table: 3.7 Operational definition and indicator of measuring study variables

Variable	Operational Definition	Indicator of Measurement
SP (drug) intake.	1. Pregnant women who never received IPTp-SP. 2. Pregnant women who received and took the IPTp-SP they were served.	1. Never took IPTp-SP. 2. Took less than three doses of IPTp-SP 3. Took more than three doses of IPTp-SP.
Birth weight (kg).	Live-singleton babies who were weighed at delivery.	1. Weight less than 2.5kg. 2. Weight more than 2.5kg.
Haemoglobin level (g/dl).	Pregnant women whose haemoglobin readings were documented at both registration and 36 weeks of gestation.	1. Haemoglobin values less than 11g/dl. 2. Haemoglobin levels more than 11g/dl.
Miscarriage	Pregnant women who delivered non-viable foetuses.	A non-viable foetus that was delivered before 28 weeks of gestation.
Stillbirth.	Babies who are born dead after 37 complete weeks of gestation.	1. Babies who died in utero before the onset of labour (macerated stillbirth). 2. Babies who died during the process of labour (fresh stillbirth)
Maternal peripheral malaria (parasitaemia)	1. Absence of malaria parasites in the peripheral blood of pregnant women. 2. Presence of malaria parasites in the peripheral blood of pregnant women.	1. Negative thick blood film microscopy. 2. Positive thick blood film microscopy.

3.8 Sampling

3.8.1 Sample size estimation

The ANC attendance in 2015 for West hospital, Tamale Teaching hospital, Central and SDA hospital was 19206, 16293, 22409, and 7000, respectively, with the total being 64908. Using an estimated proportion of 85%, that is, the national target for IPTp coverage among pregnant women for 2011(Ghana Statistical Service, 2011), at 95% confidence level and a precision of 3%, assuming a design effect of 2, the sample size obtained was calculated as 1080. In order to obtain a more precise estimate or statistically significant results, a precision of 3% was assumed, which will increase the sample size as well as the confidence in the results and decrease any uncertainty about the data. This was calculated using the formula below;

$$n = deff \times \frac{\mathrm{N}\hat{p}\hat{q}}{\frac{d^2}{1.96^2}(N-1)+\hat{p}\hat{q}}$$

Where

n= sample size

deff= design effect

N= population proportion

$\hat{p}$ = the estimated proportion

$\hat{q}$= 1- $\hat{p}$

d= desired absolute precision

Thus, substituting the various parameters into the formula where;

Population (N) = 64908

Estimated population $\hat{p}$= 85% that implies $\hat{p} = 0.85$

Therefore $\hat{q}$ =1 - 0.85 = 0.15

Desired absolute precision (d) = 3% = 0.03

Design effect = 2

$$\mathrm{n} = 2 \times \frac{64908(0.85 \times 0.15)}{\frac{0.03^2}{1.96^2}(64908-1)+(0.85 \times 0.15)}$$

$$\mathrm{n} = 2 \times \frac{8275.77}{15.33}$$

n=2x539.8= 1,079.7
n ≈ 1080

We adjusted for a 10% non-response rate (108) and the required sample size was increased to 1188

3.8.2 Sampling techniques

There are four (4) main hospitals which serve as the main referral centers in the Tamale metropolis, namely, Tamale Teaching Hospital (TTH), Tamale Central Hospital (TCH), Tamale West Hospital (TWH) and Tamale SDA Hospital (TSH). The facilities (TTH, TCH, TWH and TSH) have high ANC attendance and most ANC attendees return to the facility to give birth during the time of delivery. Moreover, data on pregnant women throughout the course of their pregnancy is readily available. Therefore, the investigators of the current study settled on choosing these health facilities ((TTH, TCH, TWH and TSH) to facilitate the sampling of 1188 pregnant women (the study sample size) within the study period.

Various cadres of health workers were trained (Nurses, Midwives and Medical Laboratory Scientists) as study research assistants to help in the sampling of prospective study participants. Ten health workers which consisted of five midwives and five general nurses were trained by the investigators in each facility on how to recruit participants at the antenatal clinic. The research assistants were given education on the purpose of the study as well as the details of the study components. Again, the content of the informed consent forms was extensively discussed and research assistants were trained on how to introduce the study to a prospective participant and administer consent forms to interested pregnant women. Pregnant women at 16 weeks of gestation and/or experienced quickening were informed about the study by the consulting midwives at the ANC and interested women were referred to the research assistants. Further insight was given by research assistants to the women and

informed consent administered to those who expressed the desire to participate. Non-consenting pregnant women exited the study. A quota of 298, 410, 352 and 128 pregnant women were allocated to TTH, TCH, TWH and TSH respectively based on the 2015 ANC attendance for Tamale Teaching Hospital, Tamale Central, Tamale West and Seventh Day Adventist Hospitals as shown in Table 3.8.

The register for the various facilities served as the sample frame and respondents were randomly selected from each of the hospital, by using the lottery method, to obtained the predetermined sample size for each of the facility. Those who selected yes from the opaque envelops were given codes to prevent reselection. The principal investigator coordinated the activities in all the four facilities and tallied the number of participants enrolled in the study each day. The process was repeated until all the required 1188 (the study sample) pregnant women were obtained.

Table 3.8 Proportional allocation of study population for the longitudinal study

Health facility	Clients' attendance Ni (2015 data)	Proportion of attendance wi =Ni / N	Sample size ni= wi*n
Tamale West Hospital	19206	0.296	352
Tamale Teaching Hospital	16293	0.251	298
Tamale Central hospital	22409	0.345	410
SDA Hospital	7000	0.108	128
TOTAL	**N= 64908**	**1**	**n=1188**

The number of pregnant women sampled from each study facility was determined by dividing the respective facility antenatal attendance in 2015 with the total attendance of the year (2015) and multiplying the proportion by the study sample size.

The ANC attendance in 2015 for Tamale West hospital, Tamale Teaching hospital, Tamale Central and Tamale SDA hospital was 19206, 16293, 22409 and 7000 respectively, the total attendance was 64908 and a sample size of 1188. Therefore, by applying the calculating

formula, Tamale Central hospital was allocated with 410 respondents, 352 respondents for Tamale West, 298 respondents for TTH and 128 respondents for Tamale SDA hospital. In all, one thousand, one hundred and eighty-eight (1188) pregnant women were enrolled into the study.

3.9 Pilot study

According to Gorard, (2010), the study design and instruments should be piloted among willing respondents to assess the performance of the instruments in capturing the study variables for the necessary analysis. This allows researchers to identify inappropriateness of questions, possible ambiguous questions, misleading and/or offensive questions, grammatical errors and spelling mistakes for correction before data collection in the field (Gorard, 2010). Therefore, the current study was piloted at the Savulugu District Hospital in the Northern Region. Fifty pregnant women consented to the pilot study and were interviewed.

Blood samples were taken at the end of 36 weeks and tested for malaria parasites using malaria Rapid Diagnostic Test (RDT) kits in accordance with the routine practice. The study questionnaire could capture all the necessary variables of interest.

However, the *Plasmodium falciparum* (Pf)-malaria RDT kits failed to detect malaria parasite among the pregnant women even in women with detectable clinical signs and symptoms of malaria infection such as fever, vomiting, headache etc. This finding informed further investigations to assess the sensitivity and specificity of the test kits. Therefore, twenty (20) of the blood samples were tested by microscopy (the gold standard). Ten out of the 20 samples were confirmed positive with high Pf parasitaemia level of >40 parasites/µl by microscopy. However, all the samples had tested negative on the Pf-malaria RDT kits, meaning the Pf-malaria RDTs kits failed to detect *Plasmodium falciparum* malaria infection.

The investigators, therefore, resolved to use the microscopy method as the technique to test for malaria parasitaemia.

3.10 Data handling

Every participant was given a unique study code which was written on their antenatal cards and the study questionnaires. Data collection and processing occurred concurrently. At the end of each interview, data collectors checked and corrected all errors on site to enhance data quality. Information on all the completed questionnaires was later validated by the principal investigator to correct omissions or ambiguities to avoid misunderstanding and misinterpretations. Data entry accompanied data collection and rolled out concurrently for the entire duration spent to collect data in the field. A database was created and the information on the completed questionnaires was entered by two data clerks into the database. Each participant was identified by their corresponding study code in the database.

The data sheets were edited and verified before data entry into the computer to minimize errors before analysis. Two methods were implemented to enhance data reliability. Firstly, consistency and plausibility checks were run on the data to pick up errors for subsequent cleaning. Secondly, completed questionnaires were selected at random by the field supervisor to re-interview the original respondents to assess the consistencies in the responses. The database required a password to open and this was only available to the principal investigator. Daily update of information in the database was also saved on external hard drives and on the internet cloud, all under password entry to enhance data safety.

The completed questionnaires have been kept under lock and key and the soft data pass-worded for safety and privacy. All the study records (database, analysis, completed questionnaires and consent forms) would be stored for five years.

3.11 Data analysis

All data entry and management were conducted using the Statistical Package for the Social Sciences software, SPSS version 20.0 for Windows (SPSS Inc., Chicago) and transported to STATA 12.1 for the analysis (Stata Corporation, College Station, TX, USA). The study data were categorized as follows:

Participants were classified as primigravidae, secundigravidae and multigravidae based on their pregnancy history. The age of gestation was classified as first, second and third trimesters. SP intake was grouped as no IPTp-SP, less than three (<3) IPTp-SP doses and greater than or equal to three (≥3) IPTp-SP doses. Intervention use was graded as no intervention, bed net only, IPTp-SP only and both IPTp-SP and bed net. With respect to bed net use, participants were classified into two groups of either owning a bed net or not and ownership was further grouped into two, use bed net every evening or once a while.

Haemoglobin level was graded as anaemic (< 11g/dl) and non anaemic (≥ 11g/dl); and birth weight as low birth weight (≤ 2.5kg) and normal weight (≥ 2.5kg). Residence was classified as peri-urban, urban and rural. Possible confounding variables such as parity, gravidity, educational level, bed net use and residence were controlled in the multivariate logistic regression.

Descriptive statistics were used for the socio-demographic characteristics and IPTp-SP uptake. Chi-square test was used to measure the statistical significance of calculated proportions. Odd ratios were computed to describe the relationship between the exposure variable (SP ingestion) and the study outcomes (maternal parasitaemia and anaemia at 36 weeks of gestation, stillbirth and birth weight). Confidence intervals were constructed around the odds ratios at a confidence level of 95% and a statistical significance of $p<0.05$ was considered significant.

During the analysis of the effect of IPTp-SP on haemoglobin level and peripheral parasitaemia, women who delivered before 36 weeks of gestation were excluded and in the birth weight analysis, women who delivered premature babies, had stillbirths, multiple births, diabetic and hypertensive women were all excluded from the analysis (restricted to live singleton babies).

Specific objective 1a: Assessing the percentage of IPTp-SP beneficiary and non-beneficiary pregnant women with peripheral parasitaemia at 36 weeks.

The percentage of peripheral parasitaemia at 36 weeks of gestation were calculated for the no IPTp-SP group, <3 IPTp-SP group and the ≥3 IPTp-SP group. A univariate regression was run on the proportions to generate odds ratios, confidence intervals and p-values. The level of protection of IPTp-SP was interpreted from the obtained analysis.

Specific objective 1b: Determining the prevalence of screened pregnant women with anaemia among IPTp-SP beneficiary and non-beneficiary (haemoglobin level <11g/dl) at 36 weeks.

The prevalence of maternal anaemia at 36 weeks of gestation were calculated for the no IPTp-SP group, <3 IPTp-SP group and the ≥3 IPTp-SP group.

A univariate regression was run on the proportions to generate odds ratios, confidence intervals and p-values. The level of protection of IPTp-SP was interpreted from the obtained analysis.

Specific objective 2a: Estimating the proportion of IPTp-SP beneficiary and non-beneficiary pregnant women with low birth weight (<2500g) live-singleton babies at delivery.

The proportions of low birth weight at delivery were calculated for the no IPTp-SP group, <3 IPTp-SP group and the ≥3 IPTp-SP group. A univariate regression was run on the proportions to generate odds ratios, confidence intervals and p-values. The level of protection of IPTp-SP was interpreted from the obtained analysis.

Specific objective 2b: Assessing the percentage of stillbirths among IPTp-SP beneficiary and non-beneficiary pregnant women at delivery.

The proportions of stillbirths were calculated for the no IPTp-SP group, <3 IPTp-SP group and the ≥3 IPTp-SP group. A univariate regression was run on the proportions to generate odds ratios, confidence intervals and p-values. The level of protection of IPTp-SP was interpreted from the obtained analysis.

Specific objective 3: Establishing the association between the different doses of SP served under IPTp, maternal health (malaria parasitaemia and anaemia) and birth outcomes (low birth weight and stillbirth).

Multivariable logistic regression was performed to generate adjusted odds ratios, confidence intervals and p-values. The contractions of the adjusted odds ratios controlled for all confounding variables and the true relationships between IPTp-SP ingestion and the study variables (maternal parasitaemia and anaemia at 36 weeks of gestation, birth weight and stillbirth) were interpreted from the obtained analysis.

Specific objective 4: Determining the adequacy of SP dispensed to pregnant women in the Tamale metropolis.

A standardized analytical protocol from the United States Pharmacopoeia (USP 29) was employed in analysing all samples of SP products obtained. This official method of analysis involved the use of High-performance Liquid Chromatography (HPLC).

3.12 Laboratory testing of malaria parasites

Thick blood smear preparation, staining and microscopy.

Blood lancets were used to make small incisions on the left ring finger after making the site sterile with 70% methylated spirit. A single drop of blood from the finger prick was placed on a clean frosted microscope slide and was spread to a diameter of 2cm to make a thick blood smear. All slides were labelled with the corresponding participant identification number used for the study. The blood smears were allowed to air-dry and fixed with absolute ethanol on the field before transporting to the Tamale Teaching Hospital laboratory for reading. At the laboratory, 5% Giemsa solution was poured to cover the smears and the slides were allowed to stand for 5 minutes. The slides were washed and air-dried before microscopy (WHO, 2010). All slides were observed under oil immersion objective lens and blood smears were classified as negative if no asexual parasites were identified after 1,000 WBC count and positive if malaria parasites were detected at any stage of the WBC count. Microscopy was done by two different senior biomedical scientists. If there were discrepancies in the reading of slides, the slide was read the third time. All the study slides have been stored in slide storage boxes for five years.

3.13 Quality control

Several precautionary measures were undertaken to enhance the quality of the study data. The study questionnaires were designed by using portions of UNICEF documents and extracts of published studies so it reflected universal standards. A pilot study was done to ensure that the best methods were used to collect, process and examine study data and outcomes to avoid exaggerations. Again, three dummy sessions were held for study data collectors to rehearse methods and communication strategies designed to extract the relevant information from interviewees. Data were edited daily on the field for necessary corrections by the principal investigator to minimize errors in the database. Two different data entry clerks were trained to enter the same data into the database to minimize errors and enhance data quality. There were four scheduled data cleanings to ensure that all relevant information had been captured. Two different statisticians were made to analyze the study data to enhance the quality of analysis. All collected study documents and data had restricted access, with access allowed for limited persons when necessary. Laboratory procedures were done in accordance with WHO standards and the malaria microscopy was performed by WHO certified malaria microscopists.

3.14 Ethical Considerations

Ethical clearance was also obtained from the Committee on Human Research, Publication and Ethics of Kwame Nkrumah University of Science and Technology/Komfo Anokye Teaching Hospital and Tamale Teaching Hospital respectively before the commencement of the study (CHRPE/AP/375/16).

Administrative clearance and permission were sought from the Regional Health Administration, the Metropolitan Health Directorate and the Chief Executive Officer of the Tamale Teaching Hospital as well as all the heads of the Health institutions where the study

data were collected. The officers in-charge of the obstetric and gynecological departments of the various hospitals gave their permission before the pregnant women were recruited.

Obtaining consent from participants before carrying out research ensures that participants independently decide to be involved in the study (Robinson, 2011). Prior to participating in the quantitative study, potential respondents selected were asked to give either written or verbal informed consent. The consent form clearly explained the study, the purpose of the study, and any potential risks as well as benefits associated with participation. Prior to asking for written informed consent, the potential respondents were given the opportunity to ask the interviewer questions. They were also made to know that participation is voluntary, there was no form of coercion and they could decline to participate even after giving their consent at any stage. The women were assured of confidentiality were told that their names were not required in order to participate in the study. They were also assured that, the information obtained from them would be used only for the purpose of the study. Pregnant women were also assured that, they will not be denied of routine ANC care and any rights if they decide not to be part of the study, refuse to complete the questionnaire or refused to answer specific questions.

3.15 Dissemination plan

Bound copies of the research findings would be given to the School of Public health, KNUST, Northern Regional Health Administration, the Chief Executive Officer of the Tamale Teaching Hospital and the Regional Malaria Control Coordinator for their review. The consensus arrived at by these persons would determine if National level discussions should be initiated. If their consensus necessitates changes to current practice then National level discussions will be initiated through the Regional Malaria Control Coordinator. On the other hand, if the research findings do not call for changes to current practice then working

through the Regional Health Administration, all Antenatal centers would be encouraged to continue current standard operating procedures. Also, relevant portions of the thesis would be published in appropriate scientific journals to add to current knowledge in malaria control in pregnancy.

3.16 Assumptions

The study was based on the following assumptions

1. The study was based on research findings which have shown that, the IPTp-SP given to pregnant women is able to protect them against malaria in pregnancy and also improve their hemoglobin level.
2. Another assumption was that the pregnant women who took the IPTp-SP would have an improved birth outcome such as improved birth weight and prevention of stillbirth as suggested by literature.
3. The last assumption was that, the IPTp-SP that is given to the pregnant women have the right and adequate active ingredient to protect the mother and the unborn baby against malaria.

CHAPTER FOUR

4.0 RESULTS

This chapter contains the results of the work based on the study objectives. Tables and bar charts were used in presenting the results.

4.1 Baseline characteristics of the participants

4.1.1 Socio-Demographic Characteristics of study participants

A total of 1188 pregnant women were sampled from four antenatal clinics in the Tamale metropolis, however, 7 (0.6%) were lost to follow up. Overall, 1181 (99.4%) were included in the analyses.

As shown in Table 4.1.1, the most represented age group in this study were pregnant women below 24 years old (34.1%) and the least represented age group were women either 35 years or above (12.5%). Majority of the women were married, (92.8%), and few widows (0.2%) were recorded in the study. Most of the participants were Muslims (89.2%) and this may be due to the fact that, Northern region is highly populated with Muslims.

Urban dwellers were more (66.6%), than Peri-urban residents (19.6%), who were also more than those living in Rural areas (13.7%). Almost half of the pregnant women had no formal education (49.5%) and only (14.0%) had attained tertiary education. As far as occupation is concerned, the pregnant women were engaged in various types of economic activities; farmers, artisans, salary workers, business, petty trading, food vendors, domestic activities and students. Most Pregnant women were involved in petty trading (39.4%) with the least involved in domestic activities (0.9%). Unsurprisingly, a greater part of the women was of the Dagomba ethnic group (77.05%) and few were of other ethnic background (23.0%), (Table 4.1.1).

Table 4.1.1 Socio-demographic characteristics

Socio-demographic variables	Frequency(n) 1181	Percent (%) 100
Age group (years)		
<24	403	34.1
25-29	383	32.4
30-34	248	21.0
35+	147	12.5
Marital status		
Married	1096	92.8
Cohabiting	39	3.3
Widow	2	0.2
Single	44	3.7
Religion		
Muslim	1053	89.2
Christian	128	10.8
Residence/locality		
Rural	162	13.7
Peri-urban	232	19.6
Urban	787	66.6
Educational level		
No school	585	49.5
Primary	253	21.4
Secondary	178	15.1
College/tertiary	165	14.0
Occupation		
Farmer	44	3.7
Artisan	235	19.9
Salaried employment	149	12.6
Petty trading	465	39.4
Business owners	23	1.9
Food vendor	26	2.2
Domestic activities	10	0.9
Student	56	4.7
Unemployed	170	14.4
Other	3	0.3
Ethnicity		
Dagomba	910	77.1
Other	271	22.9

Source: field study 2017

4.1.2 Reproductive health history of participants

From table 4.1.2, the mean age of the 1181 pregnant women was 27.1 years (SD ± 5.93) and ranged from 15-48 years. Among the study respondents, eight hundred and twelve (812) pregnancies were recorded with the number of pregnancies ranging from 1-9 and a mean pregnancy of 2.56 (SD±1.45). Seventy-one (8.7%) out of the Eight Hundred and twelve (812) previous pregnancies had experienced an average of 1.37 miscarriages (SD±0.76) in the range of 1-5 miscarriages. An average of 1.23 abortions (SD±0.43) were reported among 47 (5.8%) women. 762 (93.8%) of the women had previous births with an average of 2.41 births (SD±1.38) and within the range of 1-9 births. Among the 1181 pregnant women, the average gestational age at first antenatal visit was 15.3 weeks (SD±5.71), within the range of 2 weeks to as late as 34 weeks.

Regarding obstetric history, 29.6% of the women were primigravidae, 22.8% were secundigravidae and about one-half were multigravidae (47.6%). In terms of parity, 33.1% of the women were nulliparous, 21.8% were primiparous and almost half, (45.1%), being multiparous. Most of the respondents visited the antenatal clinic for the first time during the second trimester of pregnancy, (53.9%), 42.5% during the first trimester and very few, (3.2%), reported to the clinic in the third trimester of pregnancy, (Table 4.1.2).

Concerning ownership of Insecticide Treated Net (ITN), 64.7% of the pregnant women in this study owned ITNs. Out of the 64.7% women who had ITNs, 68.5% had ever use the bed nets before (over the last week). In reference to the frequency of use, less than half, (44.0%) slept in ITN the night before the interview (every evening) and those who used the ITNs once a while, were in the majority, (56.0%) (Table 4.1.2).

During the time of registration at first ANC visit, (4.5%) of the participants carried malaria parasites in their peripheral blood. On the other hand, majority were anaemic (54.1%) (Table 4.1.2).

Table 4.1.2 Reproductive health and obstetric history of participants

Characteristic	N	Mean
Reproductive health history		
Age (years)	1181	27.1
No. of pregnancies	812	2.6
No. of miscarriages	71	1.4
No. of abortions	47	1.2
No. of births	762	2.4
No. of living children	745	2.2
No. of dead children	167	1.2
Gestational age at 1st ANC (weeks)	1181	15.3
Obstetric history	**Frequency(n)**	**Percent (%)**
Gravidae		
Primigravidae	349	29.6
Secundigravidae	269	22.8
Multigravidae	563	47.6
Parity		
Nulliparous	391	33.1
Primiparous	257	21.8
Multiparous	533	45.1
Trimester at 1st ANC		
1st trimester (0-12weeks)	507	42.9
2nd trimester (13-24weeks)	636	53.9
3rd trimester (25-to term)	38	3.2
ITN ownership		
Yes	764	64.7
No	417	35.3
ITN use		
Yes	523	68.5
No	241	31.5
Frequency of use		
Every evening	230	44.0
Once a while	293	56.0
Malaria parasitaemia at registration		
Negative	1127	95.5
Positive	54	4.5
Anaemia status at registration		
Not anaemic	542	45.9
Anaemic	639	54.1

Source: Field work 2017

4.2 Association between baseline characteristics and maternal outcomes

4.2.1 Association between baseline characteristics and malaria prevalence at 36weeks

The results of table 4.2.1 is the cross tabulation done to find the association between the baseline characteristics and malaria prevalence at 36 among the study participants. Statistically, there was no significant relationship between maternal age (X^2=7.2784; p=0.06), marital status (X^2=3.6452; p=0.61), ethnicity (X^2=0.2074; p=0.65), residence (X^2= 3.6452; p=0.16), religion (X^2= 2.5578; p=0.11) and malaria infection among pregnant women at 36 weeks of gestation, however, malaria prevalence was related to educational level (X^2= 23.5835; p<0.001) and occupation (X^2= 22.4134; p<0.001). Although age and malaria prevalence were not statistically significant, pregnant women who were below the age of 25 years had malaria prevalence of 30.6% compared to those between 30 to 34 years (22.1%). Pregnant women who resided in the rural areas within Tamale Metropolis had malaria prevalence of 32.1% as compared to peri-urban (25.8%) and urban (24.7%) dwellers, however, there was no significant difference between peri-urban (25.8%) and urban (24.7%) dwellers.

Concerning educational level and malaria infection, the prevalence of malaria among pregnant women with no formal education was 31.5% compared to 13.5% of pregnant women with college/tertiary educational level (X^2 =23.5835; p = <0.001. It was seen that the prevalence of malaria decreases with increased level of education. With regards to occupational status, pregnant women who were farmers had a significantly higher malaria prevalence (43.9%) at the end of 36 weeks of gestation compared to salaried workers (14.2%) with a Pearson Chi-square (X^2) of 22.413 and a p value of <0.001. However, there was no statistically significant relationship between gravida (X^2 =0.9670; P=0.617), parity (X^2

=0.3147; p=0.854) and trimester (X^2=4.7882; p=0.091) with malaria infection at 36 weeks of gestation.

Primigravidae had a higher prevalence of malaria (27.8%) among all the different gravidity compared to secundigravidae (24.7%). Attending ANC early helps prevent malaria during pregnancy; those who attended ANC in the third trimester had a higher prevalence of malaria (35.1%) as compared to those who attended ANC at the first week of gestation (23.0%) at 36 weeks of gestation. Looking at parity and malaria infection, there was no significant difference between the nulliparous 102/384(26.56%) and multiparous 134/514(26.1%) women. The percentages were quite similar.

Table 4.2.1 Association between baseline characteristics and malaria prevalence at 36weeks

Variable	Malaria prevalence at 36 weeks n (%)		N	Test statistic (Pearson chi2)	P-value
	297(25.9)	849(74.1)	1146	X^2	
Age (years)	**Positive**	**Negative**			
<24	120(30.6)	272(69.4)	392	7.2784	0.06
25-29	91(24.5)	281(75.5)	372		
30-34	53(22.1)	187(77.9)	240		
35+	33(23.2)	109(76.8)	142		
Marital status					
Married	273(25.7)	788(74.3)	1061	3.6452	0.61
Single	24(28.2)	61(71.8)	85		
Religion					
Christian	25(20.0)	100(80.0)	125	2.5578	0.11
Muslim	272(26.6)	749(73.4)	1021		
Residence/locality					
Rural	50(32.1)	106(67.9)	156	3.6452	0.16
Peri-urban	57(25.8)	164(74.2)	221		
Urban	190(24.7)	579(75.3)	769		
Educational level					
No school	176(31.5)	383(68.5)	559	23.5835	**<0.001**
Primary	58(23.5)	189(76.5)	247		
Secondary	41(23.2)	136(76.8)	177		
College/tertiary	22(13.5)	141(86.5)	163		
Occupation					
Farmer	18(43.9)	23(56.1)	41	22.4134	**<0.001**
Artisan	57(25.7)	165(74.3)	222		
Salaried worker	21(14.2)	127(85.8)	148		
Trading	139(27.7)	363(72.3)	502		
Unemployed	50(30.3)	115(69.7)	165		
Others	12(17.6)	56(82.4)	68		
Ethnicity					
Dagomba	226(25.6)	657(74.4)	883	0.2074	0.65
Other ethnicity	71(27.0)	192(73.0)	263		
Gravidity					
Primigravidae	96(27.8)	249(72.2)	345(100)	0.9670	0.62
Secundigravidae	64(24.7)	195(75.3)	259(100)		
Multigravidae	137(25.3)	405(74.7)	542(100)		
Trimester					
First trimester	114(23.0)	381(77.0)	495(100)	4.7882	0.09
Second trimester	170(27.7)	444(72.3)	614(100)		
Third trimester	13(35.1)	24(64.9)	37(100)		
Parity					
Nulliparous	102(26.6)	282(73.4)	384(100)	0.3147	0.85
Primiparous	61(24.6)	187(75.4)	248(100)		
Multiparous	134(26.1)	380(73.9)	514(100)		

4.2.2 Association between baseline characteristics and anaemia at 36 weeks

Table 4.2.2 shows the association between the baseline characteristics and anaemia at 36 weeks of gestation. It was found that, there was an association between anaemia and maternal age, marital status, religion, residence, educational level and occupation but not ethnicity.

The prevalence of anaemia among women less than 24 years (69.4%) was high compared to pregnant women between the ages of 30 to 34 years old (59.2%). The prevalence of anaemia decreases with increasing age except among those who were 35 years and above, however, anaemia prevalence was relatively high among all the age groups. The prevalence of anaemia among rural dwellers was high (75.0%) compared to urban dwellers (59.4%). Further, more than half (68.9%) of women without formal education were anaemic at 36 weeks of gestation as compared to those who had attained college or tertiary education (46.6%). Regarding the occupation of the women, farmers (80.5%) had higher prevalence of maternal anaemia as compared to salaried workers (43.2%).

There was an association between the trimester a woman first attended ANC and anaemia prevalence (X^2=18.0398; p<0.001). Those who attended ANC during the first trimester of pregnancy had anaemia prevalence of 56.6 % at 36 weeks of gestation as compared to those who attended ANC in their third trimester (83.8%). However, there was no statistical association between anaemia and parity (X^2=2.5880; p=0.27) and gravidity (X^2=0.2529; p=0.88). The prevalence of anaemia among primigravidae (61.2%), secundigravidae (63.3%) and multigravidae (61.8%) were similar as well as nulliparous (61.2%), primiparous (66.9%) and multiparous (61.5%) women in this study (see table 4.2.2).

Table 4.2.2 Association between baseline characteristics and anaemia at 36 weeks

Variable	Anaemia at 36 weeks n (%)		N	Test statistic (Pearson chi2)	P-value
	717(62.6)	429(37.4)	1146	X^2	
Age (years)	**Anaemic**	**Non- Anaemic**			
<24	272(69.4)	120(30.6)	392	13.1043	**0.004**
25-29	226(60.8)	146(39.2)	372		
30-34	135(56.2)	105(43.8)	240		
35+	84(59.2)	58(40.8)	142		
Marital status					
Married	655(61.7)	406(38.3)	1061	4.2201	**0.04**
Single	62(72.9)	23(27.1)	85		
Religion					
Christian	63(50.4)	62(49.6)	125	8.8658	**0.003**
Muslim	654(64.1)	367(35.9)	1021		
Residence/locality					
Rural	117(75.0)	39(25.0)	156	13.9633	**0.001**
Peri-urban	143(64.7)	78(35.3)	221		
Urban	457 (59.4)	312(40.6)	769		
Educational level					
No school	385(68.9)	174(31.1)	559	28.1892	**<0.001**
Primary	151(61.1)	96(38.9)	247		
Secondary	105(59.3)	72(40.7)	177		
College/tertiary	76(46.6)	87(53.4)	163		
Occupation					
Farmer	33(80.5)	8(19.5)	41	51.6898	**<0.001**
Artisan	143(64.4)	79(35.6)	222		
Salaried worker	64(43.2)	84(56.8)	148		
Trading	312(62.2)	190(37.8)	502		
Unemployed	130(78.8)	35(21.2)	165		
Other	35(51.5)	33(48.5)	68		
Ethnicity					
Dagomba	556(63.0)	327(37.0)	883	0.2651	0.60
Other ethnicity	161(61.2)	102(38.8)	263		
Gravidity	Positive	Negative			
Primigravidae	218(61.2)	127(36.8)	345	0.2529	0.88
Secundigravidae	164(63.3)	95(36.7)	259		
Multigravidae	335(61.8)	207(38.2)	542		
Trimester at 1st ANC					
First trimester	280(56.6)	215(43.4)	495	18.0398	**<0.001**
Second trimester	406(66.1)	208(33.9)	614		
Third trimester	31(83.8)	6(16.2)	37		
Parity					
Nulliparous	235(61.2)	149(38.8)	384	2.5880	0.27
Primiparous	166(66.9)	82(33.1)	248		
Multiparous	316(61.5)	198(38.5)	514		

4.3 Association between baseline characteristics and neonatal outcomes

4.3.1 Association between baseline characteristics and birthweight

Table 4.3.1 below shows the association between baseline characteristics and birthweight. Chi-square test showed that prevalence of low birth weight was associated with the type of hospital one attended ANC (X^2=13.5630; p=0.004), age (X^2=8.3045; p=0.04), religion (X^2 =4.5303; p=0.03), educational level (X^2=8.6426; p=0.03) and ethnicity (X^2=3.8963; p=0.05) but not marital status (X^2=2.3145; P=0.13), residence and occupation (X^2=8.0371; p=0.15).

The place of ANC attendance was a significant predictor of low birth weight. pregnant women who attended ANC at the SDA hospital had the highest prevalence of low birth deliveries (24.2%) as compared to those who attended ANC at TTH (9.1%). Again, it was seen that Low birth weight was high among those who were below 24 years of age (18.2%) as compared to those who were between 30-34 years (9.9%). Further, women without formal education recorded a higher prevalence (17.2%) of LBW babies and compared to those with college or tertiary level of education (9.0%) in this study.

Pregnant women who resided in the rural areas of the Northern region had 20.3% LBW babies and compared to the urban dwellers (13.3%).

The association between birth weight and gravidity was assessed. It was found that, there was an association between the two (X^2=25.8450; p<0.001). Women with their 1st pregnancy (primigravidae) had higher rate of having low birth weight (22.7%) and compared to secundigravidae (7.8%). The story was not different from parity and birth weight. The nulliparous (21.1%) had a higher percentage of low birth weight as compared to the primiparous (9.2%)

Table 4.3.1 Association between baseline characteristics and low birth weight

Variable	LBW at 36 wks n (%)		N (%)	Test statistic (Pearson chi2)	P-value
	125(14.0)	771(86.0)	896(100)	X^2	
Hospitals	**<2.5kg**	**≥2.5kg**			
TTH	20(9.1)	200(90.9)	220(100)	13.5630	**0.004**
Central	34(12.5)	239(87.5)	273(100)		
West	49(15.7)	263(84.3)	312(100)		
SDA	22(24.2)	69(75.8)	91(100)		
Age (years)					
<24	57(18.2)	257(81.8)	314(100)	8.3045	**0.040**
25-29	34(11.8)	254(88.2)	288(100)		
30-34	19(9.9)	172(90.1)	191(100)		
35+	15(14.6)	88(85.4)	103(100)		
Marital status					
Married	111(13.4)	715(86.6)	826(100)		
Single	14(20.0)	56(80.0)	70(100)		
Religion					
Christian	7(7.0)	93(93.0)	100(100)	4.5303	**0.03**
Muslim	118(14.8)	678(85.2)	796(100)		
Residence/locality					
Rural	24(20.3)	94(79.7)	118(100)	4.8892	0.09
Peri-urban	21(11.80)	157(88.20)	178(100)		
Urban	80(13.33)	520(86.67)	600(100)		
Educational level					
No school	75(17.2)	362(82.8)	437(100)	8.6426	**0.03**
Primary	24(13.1)	159(86.9)	183(100)		
Secondary	14(9.9)	127(90.1)	141(100)		
College/tertiary	12(8.9)	123(91.1)	135(100)		
Occupation					
Farmer	3(12.5)	21(87.5)	24(100)	8.0371	0.15
Artisan	21(12.3)	150(87.7)	171(100)		
Salaried worker	14(11.1)	112(88.9)	126(100)		
Trading	52(13.6))	330(86.4)	382(100)		
Unemployed	29(21.3)	107(78.7)	136(100)		
Others	6(10.5)	51(89.5)	57(100)		
Ethnicity					
Dagomba	105(15.2)	586(84.8)	691(100)	3.8963	**0.05**
Other ethnicity	20(9.8)	185(90.2)	205(100)		
Gravidity					
Primigravidae	61(22.7)	208(77.3)	269	25.8450	**<0.001**
Secundigravidae	16(7.8)	189(92.2)	205		
Multigravidae	48(11.4)	374(88.6)	422		
Parity					
Nulliparous	64(21.1)	239(78.9)	303	19.9092	**<0.001**
Primiparous	18(9.2)	178(90.8)	196		
Multiparous	43(10.8)	354(89.2)	397		

4.3.2 Association between baseline characteristics and Stillbirth

Table 4.3.2 below shows the association between the baseline characteristics and the prevalence of stillbirth. It was realized from the study that, there was an association between stillbirth and educational level (X^2=10.8023; p<0.013 and occupation (X^2=20.1602; p<0.001) but there was no association between stillbirth and the type of hospital the women attended ANC, maternal age, religion, ethnicity, marital status, gravidae, parity, trimester at which the woman reported to the ANC and residence.

Regarding the educational level, women without formal education delivered the highest stillbirth babies (12.7%) compared to tertiary level graduates (5.5%). Moreover, pregnant women who were farmers had the highest stillbirth deliveries (26.8%) compared to salaried workers (4.1%). Stillbirth was high in primigravidae (12.2%) as compared to secundigravidae (9.3%).

Table 4.3.2 Association between baseline characteristics and Stillbirth

Variable	Stillbirths n (%) 117(10.2)	1029(89.8)	N (%) 1146	Test statistic (Pearson chi2) X^2	P-value
Hospitals	**Yes**	**No**			
TTH	23(8.0)	265(92.0)	288	2.7839	0.43
Central	37(10.9)	304(89.1)	341		
West	46(11.6)	349(88.4)	395		
SDA	11(9.0)	111(91.0)	122		
Age (years)					
<24	41(10.5)	351(89.5)	392	5.1377	0.16
25-29	41(11.0)	331(89.0)	372		
30-34	16(6.7)	224(93.3)	240		
35+	19(13.4)	123(86.6)	142		
Marital status					
Married	110(10.4)	951(89.6)	1061	0.3903	0.53
Single	7(8.2)	78(91.8)	85		
Religion					
Christian	12(9.6)	113(90.4)	125	0.0568	0.81
Muslim	105(10.3)	916(89.7)	1021		
Residence/locality					
Rural	20(12.8)	136(87.2)	156	1.4582	0.48
Peri-urban	23(10.4)	198(89.6)	221		
Urban	74(9.6)	695(90.4)	769		
Educational level					
No school	71(12.7)	488(87.3)	559	10.8023	**0.013**
Primary	26(10.5)	221(89.5)	247		
Secondary	11(6.2)	166(93.8)	177		
College/tertiary	9(5.5)	154(94.5)	163		
Occupation					
Farmer	11(26.8)	30(73.2)	41	20.1602	**<0.001**
Artisan	22(9.9)	200(90.1)	222		
Salaried worker	6(4.1)	142(95.94)	148		
Trading	58(11.6)	444(88.4)	502		
Unemployed	14(8.5)	151(91.5)	165		
Others	6(8.8)	62(91.2)	68		
Ethnicity					
Dagomba	88(10.0)	795(90.0)	883	0.2487	0.62
Other ethnicity	29(11.0)	234(89.0)	263		
Gravidity					
Primigravidae	42(12.2)	303(87.8)	345	2.00819	0.35
Secundigravidae	24(9.3)	235(90.7)	259		
Multigravidae	51(9.4)	491(90.6)	542		
Parity					
Nulliparous	47(12.2)	337(87.8)	384	3.1012	0.21
Primiparous	20(8.1)	228(91.9)	248		
Multiparous	50(9.7)	464(90.3)	514		
Trimester					
1st Trimester (0-12 weeks)	51(10.3)	444(89.7)	495	0.9669	0.62
2nd Trimester (13-24 weeks)	64(10.4)	550)89.6)	614		
3rd Trimester (25-to term)	2(5.4)	35(94.6)	37		

4.4 Association of reported ITN/IPTp-SP use and maternal and neonatal health outcomes

4.4.1 Association of reported ITN/IPTp-SP use and Malaria prevalence at 36 weeks

The relationship between other preventive measures and malaria prevalence was assessed and presented in Figure 4.1. It was realized that, from the bar chart, there was an association between the two (X^2=26.7546; p<0.001). The overall prevalence of malaria was 25.9 %. Out of this, pregnant women who neither used ITN nor IPTp-SP (38.8%) had the highest prevalence of malaria compared to those who combine the use of ITN and IPTp-SP (18.4%). There was not much difference in the prevalence of malaria between the pregnant women who either used ITN (30.6%) or IPTp-SP (27.7%).

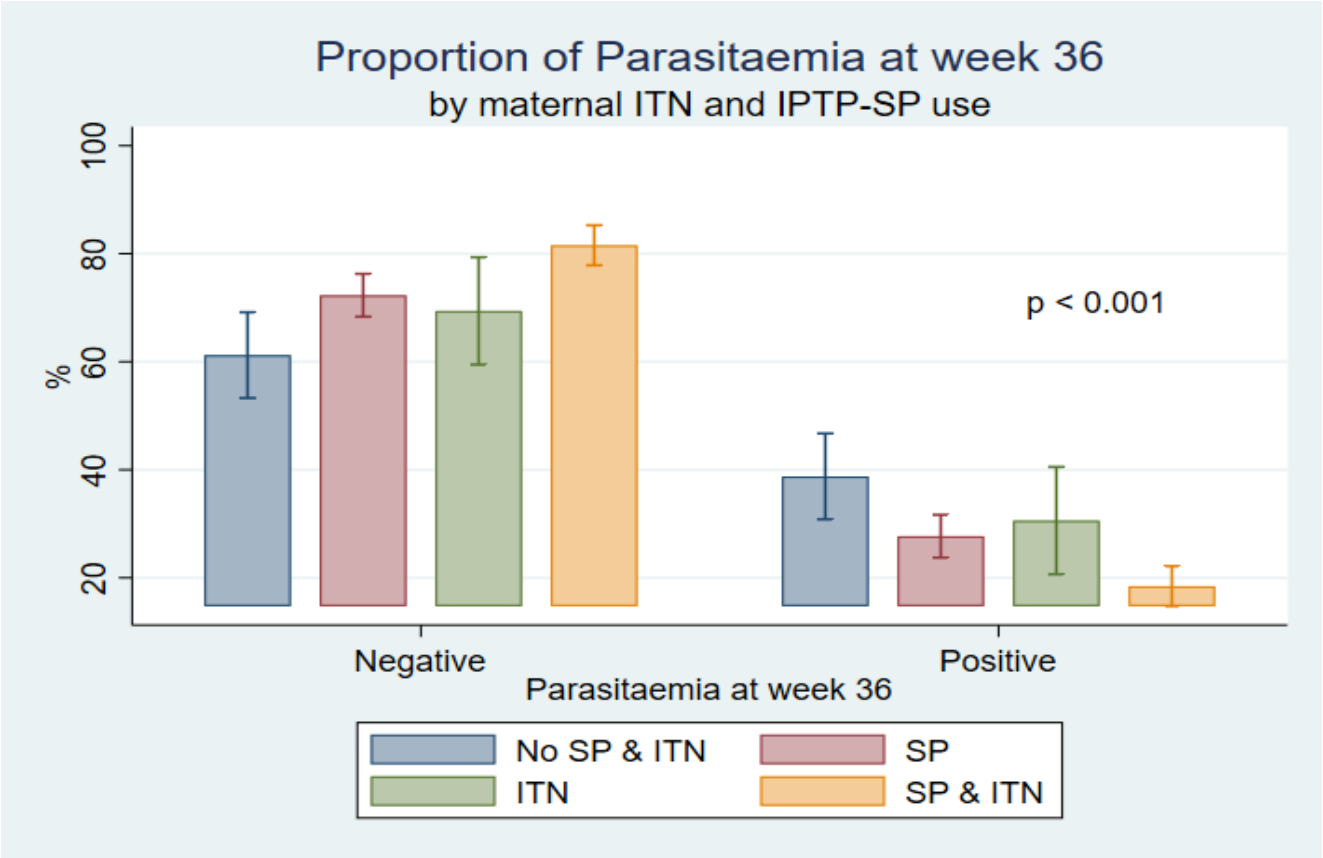


Figure 4.1: malaria prevalence at 36 weeks by maternal ITN and IPTp-SP use

4.4.2 Association of ITN/IPTp-SP use and maternal anaemia at 36 weeks

The second primary maternal outcome that was assessed was the relationship between other preventive measures and maternal anaemia is presented in figure 4.2. It was found that, there was an association between the two (X^2=16.0672; p=0.001). The overall prevalence of anaemia was 717/1146(62.6%) among the respondents at 36 weeks of gestation. The prevalence of anaemia among the pregnant women who neither used SP nor ITN was 77.6% as compared to those who combined the usage of ITN and SP was 58.4%.

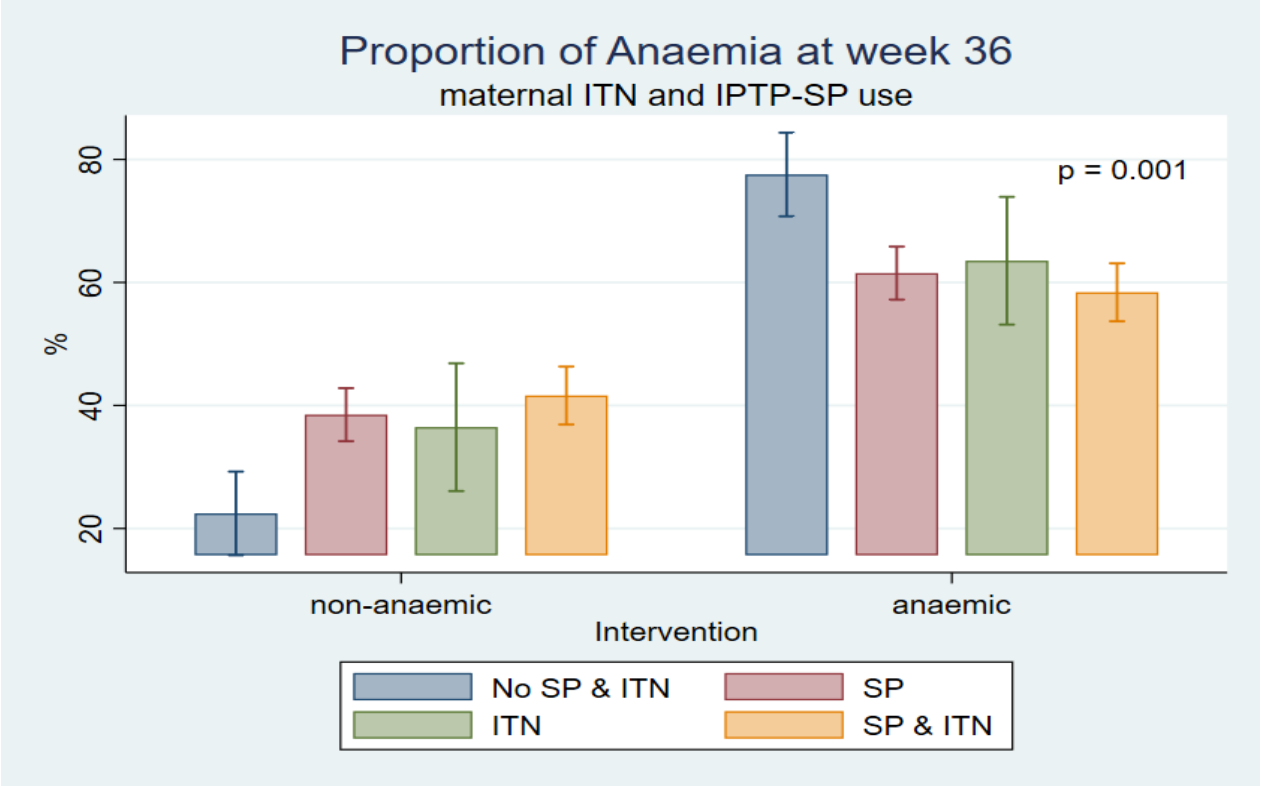


Figure 4.2: Prevalence of anaemia at 36 weeks by maternal ITN and IPTp-SP use

4.4.3 Association of ITN/IPTp-SP use and neonatal outcomes at 36 weeks (LBW and stillbirth)

The relationship between the reported use of ITN/IPTp-SP and low birth weight was assessed and presented in Table 4.4.3. It was found that**,** undoubtedly, the use of either ITN or SP during pregnancy was associated with low birth weight (X^2=32.0245; p<0.001). From the table, it could be seen that, pregnant women who took SP and at the same time slept in ITN

during the current pregnancy had 10.9% of prevalence of low birth weight recorded as compared to those who did not take ITN/IPTp-SP nor slept under ITN (32.0%) during pregnancy. In the bivariate analysis, there was an association between the use of ITN/IPTp-SP and stillbirth (X^2=22.8468; P<0.001) but ownership of ITN (p=0.21) and use of ITN (p=0.99) were not predictors of stillbirth. The prevalence of stillbirth among women who used only IPTp-SP was 8.6% as compared to pregnant women who did not use any intervention (21.1%).

Table 4.4.3 Maternal ITN/IPTp-SP use and neonatal health outcomes (LBW and stillbirth)

Preventive measure	**Low birth weight n (%)**		**N (%)**	**Test statistic (Pearson Chi2)**	**P-value**
	<2.5kg	**≥2.5k**			
Reported ITN/IPTp-SP use					
No ITN nor SP	33(32.0)	70(68.0)	103		
Only SP	48(12.0)	353(88.0)	401		
Only ITN	8(13.1)	53(86.9)	61		
SP and ITN	36(10.9)	295(89.1)	331		
Total	**125(14.0)**	**771(86.0)**	896	32.0245	**<0.001**
Reported ITN use					
Use ITN	43(11.9)	318(88.1)	361		
Do not use ITN	26(11.9)	193(88.1)	219		
Total	**69(11.9)**	**511(88.1)**	580	0.0002	0.99
	Stillbirth				
	Yes	**No**			
Reported ITN/IPTp-SP use					
No ITN nor SP	31(21.1)	116(78.9)	147		
Only SP	42(8.6)	449(91.4)	491		
Only ITN	10(11.8)	75(88.2)	85		
SP and ITN	34(8.0)	389(92.0)	423		
Total	**117(10.2)**	**1029(89.8)**	1146	22.8468	**<0.001**
Reported ITN use					
Use ITN	40(8.5)	432(91.5)	472		
Do not use ITN	30(10.9)	244(89.1)	274		
Total	**70(9.4)**	**676(90.6)**	746	1.2482	0.26

4.5 MULTIVARIABLE LOGISTIC REGRESSION MODEL OF PREDICTORS FOR MATERNAL AND NEONATAL OUTCOMES

4.5.1 Multivariable logistic regression model of predictors for maternal malaria prevalence

Table 4.5.1 below presents predictors for maternal malaria prevalence. The multivariable analysis showed that maternal age was a risk factor for malaria infection at 36 weeks of gestation. Pregnant women who were between 30-34 years and 35 years and above were 46% (aOR 0.54 CI (0.31-0.94), p=0.03) and 47% (aOR 0.43, 95% CI 0.22-0.84, P = 0.01) less likely to develop malaria infection respectively as compared to pregnant women below 25 years.

Similarly, pregnant women with primary education (aOR 0.60, 95% CI (0.37-0.92), p=0.02) and tertiary education (aOR 0.42, 95% CI (0.23-0.77), p=0.005) were better protected than those with no formal education from getting malaria infection. From the table, it was seen that, pregnant women who combined the use of ITN and IPTp-SP (aOR 0.52, 95% CI (0.31-0.89), p=0.02) were 48% less likely to get malaria infection as compared to pregnant women who used no intervention (ITN or IPTp-SP). Again, pregnant women who were anaemic at the time of registration did not influence the malaria infection at 36 weeks (aOR 0.93; CI 0.66-1.32; p=0.69), however, anaemia at 36 weeks of gestation was strongly associated with malaria infection at 36 weeks of gestation. Pregnant women who were anaemic at 36 weeks of gestation were 2.43 times more likely to get malaria infection (aOR 2.43; 95% CI 1.66-3.57; p <0.001).

Table 4.5.1 Multivariable logistic regression model of predictors for maternal malaria infection

Variable	Parasitaemia at 36 weeks					
	cOR	**95% CI**	**P-value**	**aOR**	**95% CI**	**P-value**
Age (years)						
<25	1.00	**Ref**				
25-29	0.72	0.53-1.01	0.06	0.79	0.51-1.23	0.29
30-34	0.64	0.44-0.93	**0.02**	0.54	0.31-0.94	**0.03**
≥35	0.69	0.44-1.07	0.10	0.43	0.22- 0.84	**0.01**
Residence						
Rural	1.00	**Ref**				
Urban	0.70	0.48-1.01	0.06	0.81	0.51-1.29	0.38
Peri-urban	0.74	0.47-1.16	0.19	1.07	0.63-1.85	0.79
Education						
No school	1.00	**Ref**		1.00		
Primary	0.67	0.47-0.94	0.02	0.60	0.37-0.92	**0.02**
secondary	0.66	0.44-0.97	0.04	0.69	0.42-1.12	0.13
Tertiary	0.34	0.21-0.55	**<0.001**	0.42	0.23- 0.77	**0.005**
Religion						
Islam	1.00	**Ref**				
Christianity	0.69	0.43-1.09	0.11	0.77	0.41-1.45	0.41
Ethnicity						
Dagomba	1.00	**Ref**				
Others	1.08	0.79-1.47	0.65	0.76	0.47-1.23	0.26
Trimester at ANC registration						
1st trimester	1.00	**Ref**				
2nd trimester	1.28	0.97-1.68	0.08	0.98	0.69-1.39	0.91
3rd trimester	1.81	0.89-3.67	0.10	1.34	0.56-2.27	0.51
Reported ITN/SP use						
No SP/ITN	1.00	**Ref**		1.00		
Only SP	0.60	0.41-0.89	**0.011**	0.82	0.50-1.37	0.46
Only ITN	0.70	0.39-1.23	0.211	0.96	0.46- 2.00	0.92
Both SP &ITN	0.36	0.24-0.54	**<0.001**	0.52	0.31- 0.89	**0.02**
Anaemia at registration						
No	1.00	**Ref**		1.00		
Yes	1.44	1.10-1.88	**0.009**	0.93	0.66-1.32	0.69
Anaemia at 36wks						
No	1.00	**Ref**				
Yes	3.20	2.32-4.39	**<0.001**	2.43	1.66-3.57	**<0.001**
LBW						
≥2.5kg	1.00	**Ref**				
<2.5kg	1.38	1.00-1.91	**0.05**	1.39	0.88-2.19	0.14

4.5.2 Multivariable logistic regression model of predictors for maternal anaemia

Table 4.5.2 below shows multivariable logistic regression and risk factors for maternal anaemia. Multivariable logistic regression showed a correlation between age and anaemia at 36 weeks of gestation in all the age groups, however, the type of residence was not correlated with anaemia at 36 weeks of gestation. Pregnant women who were between the ages of 30-34 years were 55% less likely to have maternal anaemia (aOR 0.45; 95%CI 0.27-0.75; p=0.002), compared to those who were below 25 years old. Pregnant women who were tertiary graduates were 60% less likely to have maternal anaemia (aOR 0.4; 95%CI 0.25-0.67; p<0.001), compared to those with no formal education.

There was an association between the trimester at which women attended ANC and anaemia. Pregnant women who first attended ANC in the third trimester had 3.45 times more risk of maternal anaemia (aOR 3.45; 95%CI 1.38-8.64; p=0.008) compared to those who were enrolled during the first trimester of pregnancy. The use of only SP, only ITN and combined use of ITN and SP did not protect the pregnant women against anaemia.

Pregnant women who were anaemic during the time of registration is 3.36 times more at risk of anaemia at 36 weeks of gestation (aOR 3.36; 95%CI 2.40-4.71; p<0.001) compared to those who were not anaemic during the time of registration. Similarly, there is an association between pregnant women who had malaria infection at 36 weeks of gestation and anaemia in the multivariable analyses. Pregnant women with malaria infection at 36 weeks of gestation had 2.35 times more risk of maternal anaemia at 36 weeks of gestation (aOR 2.35; 95%CI 1.54-3.53; p<0.001) compared to those without malaria infection at 36 weeks of gestation. Statistically, there was no association between having low birth weight and anaemia

(aOR1.19; CI0.74-1.91; p=0.48) compared to those who were not anaemic. Pregnant women who used antihelminthics had no protection against maternal anaemia.

Table 4.5.2 Multivariable logistic regression model of predictors for maternal anaemia

Variable	Anaemia at 36 weeks					
	cOR	**95% CI**	**P-value**	**aOR**	**95% CI**	**P-value**
Age (years)						
<25	1.00	Ref				
25-29	0.68	0.51-0.92	**0.01**	0.62	0.41-0.94	**0.03**
30-34	0.57	0.41-0.79	**0.001**	0.45	0.27- 0.75	**0.002**
≥35	0.64	0.43-0.95	**0.03**	0.51	0.28-0.95	**0.03**
Residence						
Rural	1.00	**Ref**				
Urban	0.49	0.33-0.72	**<0.001**	0.74	0.46-1.21	0.23
Peri-urban	0.61	0.39-0.96	0.034	1.04	0.59-1.83	0.91
Education						
No school	1.00	**Ref**				
Primary	0.71	0.52-0.97	**0.03**	0.61	0.39-0.95	**0.03**
secondary	0.66	0.46-0.93	**0.02**	0.79	0.49-1.30	0.36
Tertiary	0.39	0.28-0.56	**<0.001**	0.40	0.25-0.67	**<0.001**
Religion						
Islam	1.00	**Ref**				
Christianity	0.58	0.39-083	**0.003**	0.82	0.47-1.42	0.48
Ethnicity						
Dagomba	1.00	**Ref**				
Others	1.03	0.77-1.23	0.51	1.26	0.83-1.90	0.28
Trimester at ANC registration						
1st trimester	1.00	**Ref**				
2nd trimester	1.50	1.17-1.91	**0.001**	1.30	1.00-1.69	**0.05**
3rd trimester	3.97	1.63-9.68	**0.002**	3.45	1.38-8.64	**0.008**
Reported ITN/SP use						
No SP/ITN	1.00	**Ref**		1.00		
Only SP	0.41	0.26-0.65	**<0.001**	0.69	0.40-1.19	0.19
Only ITN	0.44	0.24-0.81	**0.008**	0.55	0.25-1.18	0.13
Both SP &ITN	0.36	0.22-0.56	**<0.001**	0.65	0.37-1.14	0.14
Reported ITN use						
No	1.00	**Ref**				
Yes	1.61	0.69-1.27	0.68	1.47	0.70-3.07	0.31
Use of antihelminthics						
No	1.00	**Ref**				
Yes	0.92	0.60-1.42	0.71	1.34	0.74-2.40	0.33
Anaemia at registration						
No	1.00	**Ref**				
Yes	4.49	3.48-5.80	**<0.001**	3.32	2.36-4.66	**<0.001**
MPs at registration						
No	1.00	**Ref**				
Yes	0.57	0.31-1.06	0.08	0.78	0.34-1.82	0.57
MPs at 36 wks						
No	1.00	**Ref**				
Yes	3.20	2.33-4.39	**<0.001**	2.35	1.56-3.56	**<0.001**
LBW						
≥2.5kg	1.00	**Ref**				
<2.5kg	1.48	1.08-2.03	**0.02**	1.19	0.74-1.91	0.48

4.5.3 Multivariable logistic regression model of predictors for birth weight

Table 4.5.3 below shows multivariable logistic model predicting birth weight. The multivariable analysis showed that women who were 30-34 years old were 60% less likely to deliver low birth weight babies (aOR 0.40 95% CI (0.20-0.79), p=0.008) compared to those below the age of 25 years.

Also, all the levels of education were predictors of birth weight. Primary, secondary and tertiary educated pregnant women were 46% (aOR 0.54; 95% CI (0.31-0.94), p=0.03), 59% (aOR 0.41 95% CI (0.21-0.80), p=0.009) and 55% (aOR 0.45 95% CI (0.21-0.97), p=0.04) less likely of delivering low birth weight babies respectively compared to pregnant women without formal education.

In the multivariable analysis, there was no relationship between religion (aOR 0.93 95% CI (0.39-2.21), p=0.87) and birth weight. Pregnant women who were anaemic at the time of ANC registration were 55% more likely to deliver babies with low birth weight (aOR 1.55; 95% CI 0.99-2.41, p=0.05) compared to those who were not anaemic.

Pregnant women who took only IPTp-SP (aOR0.31; 95% CI (0.17-0.54), p<0.001), or slept in only ITN (aOR0.30; 95% CI (0.12-0.74), p=0.009) and those who combined the use of IPTp-SP and ITN (aOR0.27; 95% CI (0.15-0.49), p<0.001) were all protected from delivering babies with low birth weight compared to those who used no intervention. However, the use of both ITN and IPTp-SP gave a better protection than the use of only ITN or only IPTp-SP.

Gravidity was a predictor of low birth weight. Secundigravidae and multigravidae were 60% (aOR 0.40; 95% CI 0.25-0.62; p<0.001) and 53% (aOR 0.47; 95% 95% CI 0.33-0.67; p<0.001) less likely to deliver low birth weight babies respectively compared to primigravidae. Examining parity and birth weight, the relationship remained significant among the multiparous women (aOR 0.15; 95%CI 0.03-0.71; p=0.02) in the multivariable

analysis. Multiparous were 85% less likely to deliver babies with low birth weight compared to the nulliparous.

Table 4.5.3 Multivariable logistic regression model of predictors for birth weight

Variable	Low birth weight					
	Unadjusted Analysis			Adjusted Analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (years)						
<25	**1.00**	**Ref**				
25-29	0.80	0.56-1.14	0.22	0.98	0.60-1.61	0.93
30-34	0.51	0.33-0.80	**0.003**	0.40	0.20-0.79	**0.008**
≥35	0.87	0.55-1.42	0.62	0.80	0.41-1.56	0.58
Residence						
Rural	1.00	**Ref**				
Urban	0.60	0.36-1.00	**0.05**	0.84	0.48- 1.49	0.56
Peri-urban	0.52	0.28-0.99	**0.05**	0.68	0.34- 1.37	0.28
Education						
No school	1.00	**Ref**				
Primary	0.72	0.49-1.05	0.08	0.54	0.31-0.94	**0.03**
secondary	0.52	0.32-0.83	**0.006**	0.41	0.21-0.80	**0.009**
Tertiary	0.46	0.28-0.77	**0.003**	0.45	0.21-0.97	**0.04**
Religion						
Islam	1.00	**Ref**				
Christianity	0.55	0.31-0.96	**0.04**	0.74	0.29-1.88	0.53
Ethnicity						
Dagomba	1.00	**Ref**				
Others	1.14	0.36-1.00	**0.05**	1.35	0.73-2.50	0.34
Reported ITN/SP use						
No SP/ITN	1.00	**Ref**				
Only SP	0.26	0.18-0.39	**<0.001**	0.31	0.17- 0.54	**<0.001**
Only ITN	0.24	0.12-0.47	**<0.001**	0.30	0.12- 0.74	**0.009**
Both SP &ITN	0.22	0.15-0.34	**<0.001**	0.27	0.15- 0.49	**<0.001**
Anaemia at registration						
No	1.00	**Ref**				
Yes	1.93	1.41-2.64	**<0.001**	1.55	0.99-2.41	0.05
Anaemia at 36						
No	1.00	**Ref**		1.00		
Yes	1.48	1.08-2.03	**0.02**	1.26	0.78-2.05	0.35
MPs at registration						
No	1.00	**Ref**		1.00		
Yes	1.37	0.64-2.94	0.42	2.35	0.79-7.02	0.13
MPs at 36						
No	1.00	**Ref**		1.00		
Yes	1.38	1.00-1.91	**0.05**	1.47	0.93-2.29	0.10
Gravidae						
Primigravidae	1.00	**Ref**		1.00		
Secundigravidae	0.40	0.26-0.61	**<0.001**	0.40	0.25-0.62	**<0.001**
multigravida	0.52	0.37-0.72	**<0.001**	0.47	0.33-0.67	**<0.001**
Parity						
Nulliparous	1.00	**Ref**		1.00		
Primiparous	0.42	0.28-0.65	**<0.001**	0.74	0.20-2.72	0.66
Multiparous	0.53	0.34-0.74	**<0.001**	0.15	0.03-0.71	**0.017**

4.5.4 Multivariable logistic regression model of predictors for stillbirth

There was no statistical relationship between maternal age and stillbirth, however, older women 35 years and above and women between 25-29 were 45% and 33% more likely to deliver stillbirth babies respectively as compared to women who were below 25 years. Tertiary education is a predictor for stillbirth. Pregnant women with tertiary level of education were 58% less likely to deliver stillbirth babies and the level of significance was at the borderline (aOR 0.42, 95% CI 0.17-1.01, *P*=0.05) compared to pregnant women with no formal education. Pregnant women who attended ANC during the third trimester of their pregnancy had reduced odds of having stillbirths (aOR 0.21; CI 0.43-1.01; p=0.05 (see table 4.5.4).

There was a strong association between anaemia at registration and stillbirth. Pregnant women with anaemia at the time of ANC registration had 2.68 times increased odd of delivering a stillborn baby (aOR 2.68; 95% CI 1.59-4.53; p<0.001) as compared to those without anaemia at the time of registration. Low birth weight was greater than 7-fold increase in the odds for stillbirths (aOR 7.60; 95%CI 4.84-11.94; p<0.001) after all the confounding variables were controlled compared to babies with birthweight 2500g and above.

Table 4.5.4 Multivariable logistic regression model of predictors for stillbirth

Variable	Univariate regression			Multilevel regression		
stillbirth	**cOR**	**95% CI**	**P-value**	**aOR**	**95% CI**	**P-value**
Age (years)						
<25	1.00	**Ref**				
25-29	1.06	0.67-1.68	0.80	1.33	0.72-2.39	0.36
30-34	0.61	0.34-1.12	0.12	0.98	0.45-2.16	0.97
≥35	1.32	0.74-2.37	0.35	1.45	0.64-3.20	0.38
Residence						
Rural	1.00	**Ref**				
Urban	0.72	0.43-1.23	0.47	0.90	0.49-1.65	0.73
Peri-urban	0.79	0.42-1.49	0.23	0.95	0.46-1.97	0.23
Education						
No school	1.00	**Ref**				
Primary	0.81	0.50-1.30	0.38	0.91	0.53-1.57	0.73
secondary	0.46	0.24-0.88	**0.02**	0.55	0.26-1.45	0.11
Tertiary	0.40	0.20-0.82	**0.01**	0.42	0.17-1.01	**0.05**
Religion						
Islam	1.00	**Ref**				
Christianity	0.93	0.49-1.74	0.81	1.60	0.58-4.41	0.37
Ethnicity						
Dagomba	1.00	**Ref**				
Others	1.13	0.72-1.75	0.62	1.16	0.66-2.03	0.61
Trimester at ANC registration						
1st trimester	1.00	**Ref**				
2nd trimester	1.01	0.69-1.49	0.95	0.69	0.44-1.10	0.12
3rd trimester	0.50	0.12-2.13	0.35	0.21	0.43-1.01	**0.05**
Reported ITN/SP use						
No SP/ITN	1.00	**Ref**		1.00		
Only SP	0.35	0.21-0.58	**<0.001**	0.69	0.38-1.25	0.22
Only ITN	0.50	0.23-1.08	0.08	1.22	0.50-2.98	0.66
Both SP &ITN	0.33	0.19-0.56	**<0.001**	0.70	0.37-1.32	0.27
Anaemia at registration						
No	1.00	**Ref**				
Yes	2.91	1.86-4.56	**<0.001**	2.68	1.59-4.53	**<0.001**
Anaemia at 36						
No	1.00	**Ref**				
Yes	1.52	1.00-2.31	**0.05**	0.90	0.54-1.51	0.69
MP at registration						
No	1.00	**Ref**				
Yes	1.98	0.61-6.45	0.26	2.18	0.60-7.86	0.24
MP at 36						
Negative	1.00	**Ref**				
Positive	1.56	1.04-2.34	**0.03**	1.26	0.78-2.03	0.35
LBW						
≥2.5kg	1.00	**Ref**		1.00		
<2.5kg	2.90	1.89-4.52	**<0.001**	7.60	4.84-11.94	**<0.001**
Antihelminthics						
No	1.00	**Ref**				
Yes	0.72	0.39-1.34	0.30	0.95	0.47-1.94	0. 89

4.6 The effectiveness of IPTp-SP on maternal health (objective I)

Women who delivered before 36 weeks were excluded from the analyses of the prevalence of malaria and anaemia at 36 weeks of gestation, in all 35 women were excluded and 1146 pregnant women were used in the analysis.

4.6.1 Malaria prevalence at 36 weeks in relation to IPTp-SP dose taken

As shown in Table 4.6.1, the overall prevalence of malaria prevalence among the study participants was 25.9% in all the stratifications (no SP, <3 and ≥3). Out of the study respondents used in the analysis of the malaria prevalence (1146), 20.2% women did not take SP while 79.8% women took one or more doses of SP. The prevalence of malaria was 35.8% among the pregnant women who did not take SP compared to those who took at least one (1) dose of SP (23.4%). From the table, it could be seen that there was an association between SP uptake and malaria infection (p<0.001).

Again, it could be seen that, malaria prevalence decreased with increased dose of SP. Pregnant women who used of at least three (3) doses of SP had the lowest prevalence of malaria (16.9%) compared to those who took one (1) or two (2) doses pf SP (30.9%) and those who did not take any SP (35.8%). There was statistical association between the number of doses of SP a woman takes and malaria prevalence in pregnancy (p<0.001).

Table 4.6.1 Malaria prevalence in relation to IPTp-SP dose taken

Variable	**Mps at 36 weeks n (%)**		**N (%)**	**Test statistic (Pearson chi2)**	**P-value**
	297(25.9)	**849(74.1)**	**1146**	X^2	
Reported SP use	**Positive**	**Negative**			
Did not take SP	83(35.8)	149(64.2)	232(100)	**14.7283**	**<0.001**
Taken SP	214(23.4)	700(76.6)	914(100)		
SP doses					
No SP	83(35.8)	149(64.2)	232(100)	**37.8570**	**<0.001**
<3	132(30.8)	296(69.2)	428(100)		
≥3	82(16.9)	404(83.1)	486(100)		

4.6.2 Prevalence of anaemia in relation to IPTp-SP dose taken

Table 4.6.2 below shows the proportion of pregnant women with anaemia at 36 weeks. The overall prevalence of anaemia was 62.6% which was quite on a higher side**.** The prevalence of anaemia among the pregnant women who did not take any SP was 72.8% compared to those who had taken at least one (1) dose of SP 60.0%**.**

It was seen that, the number of times the pregnant women took the SP during pregnancy had effect on the haemoglobin level of the woman ($p<0.001$). Prevalence of anaemia in the no SP group, <3 SP group and ≥3 SP group were 72.8%, 66.6% and 42.4% respectively (Table 4.6.2). It was seen that, the prevalence of anaemia was high irrespective of reported use of IPTp-SP during pregnancy.

Table 4.6.2 Prevalence of anaemia in relation to IPTp-SP dose taken

Variable	**anaemia at 36 weeks n (%)**		**N (%)**	**Test statistic (Pearson chi2)**	**P-value**
	717(62.6)	**429(37.4)**	**1146**	X^2	
Reported SP use	**Yes**	**No**			
No SP	169(72.8)	63(27.2)	232(100)	**12.0461**	**0.001**
Took SP	549(60.0)	366(40.0)	914(100)		
SP doses					
No SP	169(72.8)	63(27.2)	232(100)	**28.2421**	**<0.001**
<3	285(66.6)	143(33.4)	428(100)		
≥3	263(54.1)	223(45.9)	486(100)		

4.7 The effectiveness of IPTp-SP on birth outcomes (objective II)

4.7.1 Prevalence of low birth weight in relation to IPTp-SP dose taken

There was an association between SP use and birthweight. Birth weight improved with increased SP uptake (X^2 =35.6293; $p<0.001$). The pregnant women who did not take any SP during pregnancy recorded 24.8% of LBW as compared to those who took 3 or more doses of SP (7.1%) (see table 4.7.1).

Out of the 37.8% pregnant women who took one (1) or two (2) doses of SP, 83.5% gave birth to babies with birth weight ≥2.5kg while 16.5% gave birth to babies with low birth weight. There was a better outcome among pregnant women who took three or more doses of SP; 92.9% gave birth to babies with ≥2.5kg while 7.1% gave birth to babies with <2.5kg (see table 4.7.1).

Table 4.7.1 Prevalence of low birth weight in relation to IPTp-SP dose taken (37 completed weeks of gestation)

Variable	**Birth weight n (%)**		**N**	**Test statistic (Pearson chi2)**	**P-value**
	125(14.0)	**771 (86.0)**	**896**	X^2	
	<2.5kg	**≥2.5kg**			
Reported SP use					
No SP	41(24.8)	124(75.2)	165(100)	35.6293	**<0.001**
took SP	84(11.5)	647(88.5)	731(100)		
SP dosage					
No SP	41(24.8)	124(75.2)	165(100)	32.13	**<0.001**
<3	56(16.5)	283(83.5)	339(100)		
≥3	28(7.1)	364(92.9)	392(100)		

4.7.2 Prevalence of stillbirth in relation to IPTp-SP dose taken

There was a relationship between reported SP use and stillbirth (X^2=17.6734; p<0.0001). Among the pregnant women who took SP (914), majority (91.7%) gave birth to live babies while only 8.3% delivered stillborn babies. Further, out of the 232 pregnant women who did not take SP during pregnancy, 191(82.3%) gave birth to live babies while 41(17.7%) had stillbirths. Statistically, there was no significant relationship between the number of SP doses a pregnant woman took and stillbirth (X^2=1.3917; p=0.24), however, there was a decrease in SB with increasing intake of SP doses (see table 4.7.2).

Table 4.7.2 Prevalence of stillbirth in relation to IPTp-SP dose taken

Variable	Stillbirths		N	Test statistic (Pearson chi2)	P-value
	117(10.2)	**1029(89.8)**	**1146**	X^2	
Reported SP use	**Yes**	**No**			
No SP	41(17.7)	191(82.3)	232(100)	17.6734	<0.001
took SP	76(8.3)	838(91.7)	914(100)		
SP dosage					
No SP	41(17.7)	191(82.3)	232(100)	**1.3917**	**0.238**
<3	41(9.6)	387(90.4)	428(100)		
≥3	35(7.4)	451(92.6)	486(100)		

4.8 The association between IPTp-SP use, maternal health (maternal parasitaemia and maternal anaemia) and neonatal health (low birth weight and stillbirth) (objective III)

Table 4.8 below presents analysis of the various maternal and neonatal birth outcomes and reported SP use. Pregnant women who reported that, they took three (3) or more doses of SP had some protection against malaria infection and had improved birth weight. The use of ≥3 doses of IPTp-SP was associated with 56% decrease in the risk of malaria infection (aOR 0.44; 95%CI 0.27-0.70; p=0.001) compared to those who did not take any IPTp-SP. Again, pregnant women who took ≥3 doses were 63% less likely to deliver low birth weight babies (aOR 0.37;95%CI 0.21-0.68; p=0.001) as compared to those who did not take SP.

The use of ≥3 doses of IPTp-SP did not protect pregnant women against maternal anaemia (aOR 0.89; 95%CI 0.55-1.45; p=0.65) and stillbirths (aOR 1.15; 95%CI 0.55-2.42; p=0.71) compared to those who did take SP. Although taking ≥3 doses of SP was not statistically significant in reducing the odds of stillbirths, however, pregnant women who took three or more doses of SP had 15% increased risk of stillbirth babies (aOR 1.15; 95%CI 0.55-2.42; p=0.71).

Table 4.8 Multivariable analysis between IPTp-SP and maternal and neonatal outcomes

Variable	Univariate regression			Multivariable regression		
	cOR	95% CI	P-value	aOR	95% CI	P-value
Maternal health outcomes						
Malaria infection at 36 wks						
No SP	1.00	**Ref**		1.00		
<3 doses	0.80	0.57-1.12	0.20	0.96	0.63-1.47	0.86
≥3 doses	0.36	0.25-0.52	**<0.001**	0.44	0.27-0.70	**0.001**
Anaemia at 36 weeks						
No SP	1.00	**Ref**		1.00		
<3 doses	0.70	0.49-1.01	0.06	1.03	0.63-1.69	0.91
≥3 doses	0.42	0.30-0.60	**<0.001**	0.89	0.55-1.45	0.65
Neonatal outcomes						
LBW						
No SP	1.00	**Ref**				
<3 doses	0.56	0.39-0.80	**0.002**	0.84	0.50-1.42	0.52
≥3 doses	0.24	0.16-0.35	**<0.001**	0.37	0.21-0.68	**0.001**
Stillbirth						
No SP	1.00	**Ref**				
<3 doses	0.51	0.32-0.81	**0.005**	0.55	0.26-1.18	0.12
≥3 doses	0.38	0.24-0.62	**<0.001**	1.15	0.55-2.42	0.71

4.9 Mean percentage content of Sulphadoxine (S) and Pyrimethamine (P) in sampled tablets using the HPLC method (objective IV)

The USP NF 29 Acceptance criteria for Sulphadoxine is between 90.0-110% representing 450mg to 550 mg and for pyrimethamine, it was 22.5mg to 27.5 mg. Twenty-three (23) different samples of SP were analysed. Out of the twenty-three products analysed, 6/23(26.1%) products fell within the acceptable range with respect to content of the ingredient as stipulated by the USP NF 29 (see table 4.9).

Table 4.9 Mean Percentage content of Sulphadoxine (S) and Pyrimethamine (P) in sampled tablets using the HPLC method.

The actual estimated amount of Sulphadoxine and pyrimethamine, all in milligrams, are indicated in parenthesis.

Sample Code	Sulphadoxine (%) (500 mg) *	Pyrimethamine (%) (25 mg) *
SP 1	88 (440)	74 (18.5)
SP 2	96 (480)	80 (20.0)
SP 3	92 (460)	81 (20.3)
SP 4	90 (450)	75 (18.8)
SP 5	88 (440)	74 (18.5)
SP 6	96 (480)	80 (20.0)
SP 7	92 (460)	81 (20.3)
SP 8	90 (450)	75 (18.8)
SP 9	94 (470)	97 (24.3)
SP 10	82 (410)	91 (22.8)
SP 11	98 (490)	96 (24.0)
SP 12	96 (480)	97 (24.3)
SP 13	97 (485)	83 (20.8)
SP 14	97 (485)	96 (24.0)
SP 15	98 (490)	91 (22.8)
SP 16	94 (470)	82 (20.5)
SP 17	95 (475)	86 (21.5)
SP 18	96 (480)	82 (20.5)
SP 19	92 (460)	83 (20.8)
SP 20	83 (415)	86 (21.5)
SP 21	85 (425)	92 (23.0)
SP 22	97 (485)	98 (24.5)
SP 23	94 (470)	88 (22.0)

USP NF 29 Acceptance criteria: 90.0-110.0 % representing (450 mg to 550 mg) for Sulphadoxine (S) and (22.5 mg to 27.5 mg) for pyrimethamine (P). For these products to be accepted as of good quality product, both the S and P must satisfy this requirement/specification.

* - mean of three replicate determinations

CHAPTER FIVE

5.0 DISCUSSION

This chapter discusses the findings of the study in more details by linking research questions, objectives, key variables, literature review and results.

5.1 General baseline characteristics of the study participants

5.1.1 Socio-demographic characteristics

The majority of the participants were married, young reproductive women, who practised Islam and of urban residence. Most of them were Dagombas, who had no formal education and engaged in petty trading. These findings were consistent with previous studies in Ghana and elsewhere in Kenya (Haruna *et al.*, 2019; Ibrahim *et al.*, 2017; Tesfaye *et al.*, 2017). In the Ghanaian studies, 37-37.8% of pregnant women were between the ages of 20 to 29 years in Yendi and Sunyani municipalities respectively; similar to the 34.1% of women aged less than 24 years old in the current study. However, unlike the Benin studies, this study recorded almost half of the respondents with no formal educational background (49.5%) as against 56.0% (Huynh *et al.*, 2011) . The divergence may reflect differences between both countries educational policies and socio-cultural acceptability of such policies. In Ghana, education is free from Kindergarten up to the Senior High School level and, as such, the policy might have contributed to the lower levels of illiteracy.

The educational level (primary to tertiary) (50.5%) observed in this study was comparable to a study in the Sunyani municipality (56.5%) (Ibrahim *et al.*, 2017). Further, respondents with college or tertiary education were lower (14.0%) and similar to a Hohoe study (11.9%) (Kweku *et al.*, 2017) unlike a study done in Nigeria that had 22.8% college or tertiary educational level (Isah, Isah, Thairu, & Agida, 2017). Women with no formal education (49.5%) were more than a study conducted by Kweku *et al.*, (2017) in Hohoe (9.8%). In the

current study, maternal education was a risk factor for malaria in pregnancy, though not associated with the risk of MiP among pregnant women living in Lagos, Nigeria, where a high literacy rate (67%) consistent with the current findings (50.5%) increases practices that lower MiP risk (Agomo *et al.*, 2013).

Previously published studies report of higher percentage of married women (≥90%) among study participants as found in the current study (92.8%) (Florey, 2013). Ultimately, the young reproductive study population like the Sunyani study (90.3%) were largely in some form of employment (80.0%), unlike their compatriots in other parts of Sub-Saharan Africa who were unemployed (Ibrahim *et al.*, 2017). Therefore, in this study, it emerged that pregnant population could overcome perennial barriers that restrict expectant mothers from accessing ANC services to improve maternal and neonatal health (Manu *et al.*, 2017). Several recent studies that have investigated the determinants of ANC attendance and MiP prevention, especially in malarial Africa, concluded that marital status, religion and ethnicity had no relationship with MiP (Ibrahim *et al.*, 2017; Rassi *et al.*, 2016; Dahiru & Oche, 2015) which was consistent with the current study.

5.1.2 Reproductive health history of participants

In this study cohort, pregnant women of all ages had equal access to antenatal clinic in the Tamale Metropolitan area. Majority of the pregnant women had an average experience of not more than two previous pregnancies with less adverse outcomes such as miscarriages and abortions. In this setting, most pregnancies resulted in successful deliveries and babies survived beyond the neonatal ages. Antenatal care visits commenced mostly at the very early stages of gestation ranging from 2 weeks to as late as 34 weeks with a mean of 15.3.

The observed that pregnant women of all ages had equal access to antenatal clinic in the Tamale Metropolitan area; suggesting that pregnant women in this setting appreciated the need for antenatal care and considered the health prospects of using antenatal services (Yakob *et al.*, 2019). This was consistent with earlier studies in Benin and Congo (Nsibu *et al.*, 2016; Huynh *et al.*, 2011). Generally, knowledge of malaria prevention in pregnancy had increased in malaria-endemic Africa due to intensified educational campaigns (Agomo & Oyibo, 2013). Hence, many pregnant women now appreciate the detrimental effects of malaria infection on both pregnant women and their babies (Vala *et al.*, 2014). So, most pregnant women now patronize antenatal clinics to access safe motherhood interventions for healthy birth outcomes (Sumankuuro *et al.*, 2016).

The majority of the pregnant women had an average experience of not more than two previous pregnancies, with less adverse outcomes such as miscarriages and abortions. This finding is similar to a previous study which reported high number of births, five births or more, among women in Northern Ghana. It is, therefore, not surprising that, the study observed an average of two previous pregnancy experiences among the respondents since pregnancy precedes birth. Additionally, ANC coverage is high (96%) in Ghana and pregnant women make at least one visit to the antenatal clinic during pregnancy (Sumankuuro *et al.*, 2016). Antenatal care lectures in low-and-middle income countries like Ghana involve talks on nutrition, potential problems with pregnancy or childbirth, child care and prevention or detection of diseases during pregnancy. Therefore, pregnancies in countries of high ANC attendance as reported in Ghana are often associated with lesser pregnancy complications like miscarriages, abortions and neonatal deaths (Mbuagbaw, Medley, Aj, Richardson, & K, 2016). The low reports of miscarriages, abortions and neonatal deaths might suggest that pregnant women in the area were served with standard and quality antenatal care (Yakob *et*

al., 2019; Tesfaye *et al.*, 2017;). Relatedly, significant proportions of deliveries in the Northern Region were known to be conducted under skilled supervision, which is associated with successful deliveries and improved child survival (Sumankuuro *et al.*, 2016).

In this study, concerning the reproductive health history, most pregnancies (93.8%) resulted in successful deliveries and many babies (97.8%) survived beyond the neonatal ages. This was contrary to what was reported by a previous study that accessed child survival within 24 hours after birth in Ghana. According to the study, 54% of Ghanaian neonates did not survive after the first day of birth (Baqui *et al.*, 2016).

The current study on the other hand, found 21.9% (167/762) child deaths among women who had had previous births. Though the study did not determine the ages at which the deaths occurred, the comparably lower experiences of child death among the participants might imply that child survival in the study area was high. Since, antenatal care utilisation and skilled supervision deliveries were high in the region, most pregnant women not unexpectedly had access to effective neonatal care to prevent or reduce infant deaths within the first 24 hours of life (Baqui *et al.*, 2016; Sumankuuro *et al.*, 2016).

Antenatal care visits on the average commence earlier during pregnancy (2weeks) with instances as late as 34 weeks. The study observation suggests that during pregnancy, most women in the study region visit the ANC at periods when they cannot be served IPTp-SP and largely remain unprotected from malaria infections. The finding is similar to a previous study in Mali, where early initiation of ANC was a common practice among the pregnant women. The practice or habit of seeking antenatal care earlier in pregnancy promotes multiple return visits for the delivery of continuous focused antenatal care services (Hill *et al.*, 2014).

However, the persistence of such health seeking behaviour promotes late visits among teenage (<18 years old) and elderly (> 34 years old) expectant mothers because of being stigmatized for early and late conception respectively.

Notwithstanding, younger reproductive population (an average age of 26 years old), similar to that found in the current study (~27 years old) responded positively to antenatal care services (Nsibu *et al.*, 2016).

In this study area, 45.1% and 47.6% were multiparous and multigravidae respectively and visited the ANC for the first time during the second trimester. This differs from a recently published study conducted in Ghana by Haruna *et al.*, which found 18.0% multiparity (Haruna *et al.*, 2019). This could be due to two reasons. Comparably, the current sampled a larger population (1,181) than the population (140) studied by Haruna *et al.*, which might have increased the chance of sampling more multiparous and multigravidae. Secondly, this current study geographical area is noted for a high number of births among women which is consistent with a study done in the Upper West Region of Northern Ghana (Sumankuuro *et al.*, 2016). This reflected in the highest number of birth parities observed in the study (birth parity of nine), which differed from that of Haruna and colleagues, who did not observe birth parities above seven (Haruna *et al.*, 2019). However, multiparous and multigravidae women have dominated findings of many current malaria in pregnancy studies in Africa (Igboeli *et al.*, 2018; Williams *et al.*, 2016; Ndam *et al.*, 2015; Florey, 2013; Huynh *et al.*, 2011).

Majority (64.7%) of the pregnant women in the study area owned ITNs and 44.0% of the pregnant women were using it every evening. The finding is comparable with a previous study conducted in the middle belt of Ghana (Kintampo) which found 57.2% ownership of

ITNs (Manu *et al.,* 2017). This may suggest that the free distribution of ITNs to pregnant women in Ghana has improved access and obtaining ITNs might not be problematic for Ghanaian women unlike Cameroonian women with 33.7% ITN ownership and 16.9% usage (Odom *et al.,* 2017). However, the increased access did not correspond to improved affinity of bed net usage, which has been a persistent challenge in Ghana and other Sub-Saharan African countries (Manu *et al.,* 2017; Odom *et al.,* 2017). In recent years, ITN use in the country had been low (47%) and almost all (80%) pregnant women lacked interest in sleeping under bed nets and resorted to other preventive mosquito repellents (Manu *et al.,* 2017). Importantly, the study observed high bed net usage (68.5%) among ITN owners but most users (56.0%) slept in the nets once a while. This might imply that pregnant women in the study area had gradually accepted the use of ITNs as the primary method to repel mosquitoes and consciously sleep under bed nets to protect themselves and their babies against malaria infections.

The prevalence of malaria parasitaemia at first ANC or registration visit was low (4.7%) but anaemia among the pregnant women was high (54.1%) in this current study. The recorded malaria prevalence was lower than the range reported by previous studies in Hohoe (20.3%) and Bekwai (19.0%) (Asamoah *et al.,* 2018; Kweku *et al.,* 2017). Importantly, the reported malaria prevalence (4.7%) was among the lowest prevalence observed in Ghana compared to 20.3% malaria prevalence in Hohoe (Kweku *et al.,* 2017). This might be due to the interaction of two concurrent events. Firstly, the successful implementation and sustenance of the two main malaria interventions in pregnancy (IPTp with SP and ITN distribution) (Omer *et al.,* 2017). The pregnant women in the study area made early visits to the ANC after conception, a behavior that promoted focused antenatal care and access to IPTp-SP (Hill *et al.,* 2014). Secondly, ITN ownership and usage were high (>60%) in this study population,

indicating that the concept of administering IPTp-SP and ITNs through antenatal care service was well founded and widely accepted by a greater number of the pregnant population. A well-established IPTp-SP and ITN systems reduce the prevalence of malaria infections among pregnant women (Orish, Onyeabor, Boampong, Afoakwah, Nwaefuna, Acquah, Sanyaolu, Iriemenam, *et al.*, 2015). Further research is required to explain why the relatively low ITN ownership (68.5%) and usage (56.0%) in this study yielded lower malaria prevalence (4.70%) than the higher percentages (95.2% ownership and 86.5% usage) reported by Kweku *et al.*, (20.3%) in the Volta region. However, most of the participants of their study attended first ANC late during pregnancy (24 weeks) than the participants (15 weeks) of this study. Hence, the pregnant women might have remained largely unprotected and highly vulnerable to malaria infections before visiting the ANC to access IPTp-SP which was first given at week 16 (Kweku *et al.*, 2017).

Secondly, the MiP programmes (IPTp-SP and ITN use) might have interacted with other on-going malaria interventions that had intensified ACT and ITN use in the general population. The prevalence of anaemia was high (54.1%) among the women. The anaemia prevalence found in this study was less than the prevalence of anaemia (60.3%) reported in the Hohoe municipality of Ghana (Kweku *et al.*, 2017) and the 88% reported in India (Sohail *et al.*, 2015). The difference might be due to differences in malaria prevalence and degree of parasite pathogenesis. Malaria prevalence in the Hohoe study was higher (20.30%) than the malaria prevalence recorded at registration in the current study (4.7%) and might have caused more anaemia in the women compared to the current study. Therefore, malaria might not be the main cause of anaemia among the study participants since anaemia in pregnancy can be the result of multifactorial factors like malnutrition and socio-economic status other than malaria alone (Mosha *et al.*, 2014). Furthermore, the Indian study recorded more *Plasmodium vivax* infections (86%) and P. vivax malaria pathologically causes less malarial anaemia

complications than *P. falciparum* parasites strengthening the point that it was due to the afore mentioned factors (McLean *et al.*, 2015).

5.2 Association between baseline characteristics and maternal and neonatal health outcomes

5.2.1. Association between baseline characteristics and malaria prevalence at 36 weeks of gestation

In this setting, maternal education and occupation were risk factors for malaria parasitaemia at 36 weeks of gestation. The prevalence of late gestational malaria infection (within the third trimester) varied with higher maternal education and had reliable employment income such as being a salaried worker.

These findings are not consistent with findings by Mbu *et al.,* from Cameroon, which found parity to be a risk factor but not maternal education and occupation. The disparity could be due to differences in the impact of maternal education and employment. For instance, poverty rate is high (40%) among Cameroonian pregnant women; thus women of diverse educational standards co-exist in the same deprived communities (Mbu *et al.*, 2014a). Hence, pregnant women were subjected to similar environmental conditions that favoured infectivity and maternal educational differences only protected against early infections (in the first and second trimester) (Sohail *et al.*, 2015; Mbu *et al.*, 2014b). However, majority (84.8%) had some form of employment and could afford to live in 'decent' neighborhoods with relatively improved environmental elements that discourage vector survival and early gestational infectivity. Nevertheless, effectiveness of ITN was compromised in 'urbanized-neighborhoods' because of proliferate use of mosquito repellants (sprays and coils) among pregnant women. Therefore, vectors develop sophistications in their biting pattern (Agomo & Oyibo, 2013). It appeared that the biting sophistication fully evolved in the third trimester and exposed the current study pregnant women cohort to high malaria prevalence (25.9%) at

36 weeks of gestation. Late gestation malaria parasitaemia (third trimester) produced insufficient levels of antibodies to prevent the onset of malaria in pregnancy (Fried *et al.*, 2018; Gavina *et al.*, 2018; McLean *et al.*, 2017). Apparently, higher maternal education and having a reliable source of employment income such as being a salaried worker might have been impactful in reducing the risk of malaria infections during late pregnancy. This was in agreement with several previous studies (Odom *et al.*, 2017; Manu *et al.*, 2017; Sohail *et al.*, 2015; Feng *et al.*, 2010). Educated women are better subscribers of malarial interventions and show good compliance to ITNs and often complete their IPTp-SP dosage course (Odom *et al.*, 2017; Agomo & Oyibo, 2013). Similarly, salaried working women have the financial capacity to overcome the constraints that hinder continuous maternity care throughout gestation (Manu *et al.*, 2017).

The findings of this study confirmed earlier evidence that IPTp with SP ingestion does not prevent new malaria infections in pregnant women enrolled on the programme (Moore *et al.*, 2017; Cohee *et al.*, 2014). However, this study was the first in the country to provide evidence of new malaria infections in pregnant women who had benefitted from the 2014 revised IPTp-SP policy. Importantly, the study findings indicated that the new IPTp-SP policy could not protect pregnant women from late pregnancy (third trimester) malaria infections which had dire implications on birth outcomes.

In this study setting, irrespective of the trimester at which a woman made her first visit to the ANC, pregnant women of all gravidities and parities remained vulnerable to malaria infections during the course of pregnancy. The current results suggest that, the 2014 revised WHO IPTp-SP policy might not be effective in protecting women against malaria infections during pregnancy. The lack of protection from ingesting IPTp-SP against malaria have been attributed to the influence of poor SP uptake, reinfections and drug quality (Cohee *et al.*, 2016; Yeboah *et al.*, 2016; Mosha *et al.*, 2014). This may underscore the need to review drug

quality issues, improve uptake and implement additional interventions to treat the new infections that occurred after IPTp-SP administration. According to Nkoka *et al.*, 2018, early ANC visit (first trimester) is required to receive the recommended doses (≥3 doses) of IPTp-SP in order to stay protected from malaria (Nkoka *et al.*, 2018).

5.2.2 Association between baseline characteristics and anaemia prevalence at 36 weeks of gestation

Factors like maternal age, marital status, religion, residence, educational level and occupation were related with anaemia at 36 weeks of gestation. The prevalence of anaemia at 36 weeks of gestation was higher in younger maternal age, single women, Muslims, rural residents, illiterates and low- or no-income earners. These findings are consistent with results of a study in Volta region (Kweku *et al.*, 2017), Ashanti region (Ampofo *et al.*, 2018) and Northern region (Adokiya, Aryeetey, Yost, Jones, & Wilson, 2019). According to Ampofo *et al.*, 2018, such socio-demographic characteristics increased the risk of loss to follow-up and subsequent ANC visits, thereby, negatively influencing the adherence level to health interventions applied at the ANC (Ampofo *et al.*, 2018). Potentially, this might have limited the significance of continuous maternity care and increased the risk of anaemia among the women at the later stages of pregnancy (at 36 weeks of gestation). In Northern Ghana, certain occupations (i.e., farming) confine families to reside in the outskirts of communities where access to health care is limited. These families usually have poor nutritional health because their subsistence depends on farm produce which is seasonal compared to the families of salaried workers who have secured supplies of nutritional diversity. Additionally, the initiation and re-attendance of antenatal clinic depended on successful graduation from certain cultural and religious rites performed by the in-laws of pregnant women. For example, the elderly member of the husband's family must publicly declare the pregnancy before

women can attend ANC (Adokiya *et al.*, 2019). This might have interrupted the effectiveness of ANC services in reducing the risk of anaemia throughout gestation, especially in illiterates and younger aged women who have had no experience with the use of ITN and IPTp-SP. It was imperative that education on ITN and IPTp-SP be strengthened throughout pregnancy.

The study discovered that, late ANC visit (third trimester) made the women vulnerable to anaemia. This finding is similar to what was found in the study done in Nigeria (Idowu *et al.*, 2005). However, this finding was contrary to other previous studies in Kenya by Okube *et al.*, which found age and occupation as risk factors for anaemia; Omer *et al.*, reported that, peripheral and placental malaria, younger age and antenatal care visits were risk factors among Sudanese women and Owusu-Boateng *et al.*, found an association between the trimester at first ANC attendance and IPTp-SP use (Omer *et al.*, 2017; Owusu-Boateng & Anto, 2017; Okube, Mirie, Odhiambo, Sabina, & Habtu, 2016). According to Nkoka *et al.*, 2018, early ANC visit (first trimester) was required to receive the recommended doses (≥3 doses) of IPTp-SP in order to stay protected from anaemia (Nkoka *et al.*, 2018). Regardless, IPTp-SP use among pregnant women in the Sekondi-Takoradi metropolis, SP use was found not to be associated with improved haemoglobin levels (Orish *et al.*, 2015).

5.2.3 Association between baseline characteristics and birth weight

Socio-demographic predictors of low birth weight included type of health facility, maternal age, religion, educational level and ethnicity. The prevalence of low birth weight was high in non-governmental health facilities (24.2%), younger maternal age (30.6%), Muslims (26.64%) illiterates (31.5%) and non-Dagombas (27.0%) (i.e., women of other ethnicities). The study data revealed that the type of health facility where women sought antenatal service contributed to the risk of low-birth-weight deliveries. Pregnant women who delivered at the

Seventh Day Adventist Hospital (24.2%) had higher prevalence of low birth compared to those who delivered at the Tamale Teaching Hospital (9.1%). This is consistent with a study done in Botswana which found the place of birth as a risk factor for LBW (Letamo & Majelantle, 2001). This is also similar to a study in Jordan where government health facilities operate on homogenous health system aimed at replicating comparable outcomes across board (Mohammed et al., 2019). The prevalence of low birth weight was higher among SDA hospital participants (24.2%) (the only Christian-based health facility) than in the three government facilities in this study (TTH, TCH and TWH). However, the Tamale Teaching Hospital recorded the lowest prevalence although it was the main tertiary level facility where most complicated maternity related cases are referred to. This suggests that on-going upgrade programmes and projects aimed at modernizing the Tamale Teaching Hospital (which began in 2010) might have improved emergency intervention systems and positively impacted on maternity care.

The finding of this current study indicated that younger maternal age (<24 years old) contributed to low birth weight. This is different from studies done in Jordan (Mohammed *et al.,* 2019) and Thailand (McGready *et al.,* 2012), where older maternal age (≥30 years old) was a high risk for low birth weight independently. However, the finding correlated with a recent study in Nigeria which indicated that younger maternal age is a predictor for LBW (Igboeli *et al.,* 2018). This might be the result of the level of social changes between the geographical areas. In many regions outside Africa, age for marriage has shifted to later years (around 35 years old) and so women give birth at periods when they are prone to pregnancy complications which increased the risk of adverse birth outcomes like low birth weight (Mohammed *et al.,* 2019). Being of younger maternal age increases the risk of malaria

infections in the first and third trimesters which exacerbate maternal anaemia during pregnancy and induced low birth weight (Igboeli *et al.*, 2018; Omer *et al.*, 2017).

The current study is also consistent with an earlier study in the country which found maternal education as an important risk factor for low birth weight (Tampah-naah *et al.*, 2016). Unlike the previous study, the present study found illiterates to be highly vulnerable to low birth weight than their educated colleagues. The discrepancy might be attributed to the type of study design. The current study was hospital-based whilst Tampah-naah *et al.*, conducted a population-based cluster survey. So, the current study might have sampled more literates because the educated are likely to patronize health facilities that are supervised by trained professionals. Again, pregnant women with no formal education in this current study recorded higher prevalence of other important risk factors of low birth weight like malaria parasitaemia (31.5%) and anaemia (68.9%) compared to their educated counterparts with 13.5% prevalence of malaria and 46.6% of anaemia prevalence.

The present study also showed that ethnicity increased the risk of low birth weight. The prevalence of LBW among Dagombas was 15.2% as compared to the other ethnic groups, which was 9.8%. This finding is consistent with a study in Ghana (Fosu *et al.*, 2016a) and Democratic Republic of Congo (Moise *et al.*, 2017). This would buttress the hypothesis that some cultural practices contribute to malnutrition. In Northern Ghana, especially among the Dagombas, greater portions of certain nutrient rich diets such as meat, eggs and fish are reserved for the husbands. Pregnant women are denied the opportunity to improve their nutrition and that of the growing foetus contributing to high risk of low birth weight (Moise *et al.*, 2017). Low birth weight in Ghana has been postulated to be an issue of ethno-cultural orientation than an area of geographic challenge (Fosu *et al.*, 2016a). The findings of this

current study indicated that religion was a social risk factor of low birth weight among the study cohort. In the study setting, the Dagomba tribe was predominant over the other tribes and majority of them were Muslims. The tenets of the Islamic religion were inseparably ingrained into the cultural system as one traditional body such that almost every Dagomba was, by default, a Muslim. Therefore, it was possible that cultural orientation did not work in isolation to influence the risk of low birth weight among the study participants but might have had some level of religious undertone. The problem of low birth weight in the country might be the interaction of ethnicity, culture and religion. Hence, the study proposes that low birth weight might be a socio-cultural challenge than a matter of ethno-cultural orientation.

Low birth weight is predominantly the result of Intra Uterine Growth Restriction (IUGR) during pregnancy, being caused by maternal, placental and foetal health complications during pregnancy. The pathophysiology of IUGR is explained by two theories: 1. symmetrical IUGR, where placental structure and function become impaired because of pathological consequences of malaria infections early in pregnancy (first trimester). 2. asymmetrical IUGR, where nutrient supply to the foetus through the placenta became insufficient during late pregnancy (third trimester) (Cutland *et al.,* 2017). The study data revealed high malaria parasitaemia (25.9%) late in pregnancy (week 36). This suggests that malaria parasitaemia at 36 weeks of gestation might be the underlying cause of low birth weight among the study cohort. Since, late parasitaemia result in active placental infections and were of short duration to cause significant damage to placental integrity, nutrient transfer and create low birth weight (Odongo *et al.,* 2016).

In this study, adverse birth outcomes such as low birth weight were gravidity and parity dependent. Primigravidae and nulliparous women were more susceptible to low-birth-weight deliveries. These findings are consistent with results of studies in malaria endemic Sub-

Saharan Africa (Igboeli *et al.,* 2018; Omer *et al.,* 2017). Malarial anaemia, non-malarial anaemia and preeclampsia were among the reported risk factors of LBW in this region. In Sudan, LBW was mainly because of poor compliance to malarial preventive practices which escalated the risk of malarial anaemia (Omer *et al.,* 2017). However, since 2010, compliance to reviewed malaria chemoprophylaxis policy in Nigeria did not reduce the risk of malarial anaemia in primigravidae and Nulliparous women (Igboeli *et al.,* 2018). The recorded prevalence of LBW (22.7%) in the primigravidae and in the nulliparous women (21.1%) in this current study was higher than the national estimate (8.3%) (Reproductive and Child Health Report, 2013). This finding perhaps stresses the risk of LBW in primigravidae and nulliparous women. Additionally, the results suggest that malaria chemoprophylaxis policy may not be the effective mechanism to eliminate the excess risk of LBW in highly vulnerable groups. Further research into innovative methods that improve non malarial anaemia is required to supplement current standard remedies. Notwithstanding, the persistent surplus of LBW risk probably highlights the importance of packaging non-malarial anaemia interventions and malarial control programmes as one product.

5.2.4 Baseline characteristics and stillbirth rate

The study findings indicated that socio-demographic factors like maternal education and occupation influenced the risk of stillbirth. The prevalence of stillbirth was high among illiterates (12.7%) and farmers (26.8%). This is consistent with a previous study conducted in the West Gonja municipality of the Northern region. Here, housewives, but not farmers, were found to have high prevalence (73.9%) of stillbirths (Sutaa, Azongo, & Kubio, 2016). The differences in these results may be due to differences in geographical economy and the periods when the study data were collected. Tamale is a cosmopolitan city and doubles as the regional capital with higher economic activity than West Gonja, whose economy relied on the

markets of Tamale; wherefore, employment rates might be higher than West Gonja municipality. Moreover, Sutaa *et al.,* reviewed data from 2009-2013 while the current study collected post 2013 data. As of that time, a greater part of the population were farmers (Sutaa *et al.*, 2016). It was possible that the economic dynamics had changed such that most people might have found themselves busy with some other forms of employment. Furthermore, the study findings of high stillbirth prevalence among farmers (26.8%) and uneducated women (12.7%) are in agreement with a previous study (Framers 29.8% and no education 25.5%) in Asante Akim South district of the Ashanti region (Alhassan, Ayikai, Alidu, & Yakong, 2016).

Again, it was seen in this cohort that, adverse birth outcomes (stillbirths) were gravidity and parity dependent although it was not found to be statistically significant. Primigravidae and nulliparous women were more susceptible to having a stillbirth delivery. These findings are similar to findings of other studies in malaria endemic Sub-Saharan Africa (Igboeli *et al.*, 2018; Omer *et al.,* 2017).

According to an earlier hypothesis, stillbirth is the product of three interactions that might be of: 1. Maternal origin (e.g. maternal age, health), 2. Foetal and placental origin (e.g. foetal growth restriction, placental insufficiency) or 3. The activation of a stressor (venocaval compression from maternal sleep position) (Warland & Mitchell, 2014). The current study supports this hypothesis although, maternal sleeping position was not measured. Accordingly, the study findings revealed that the health of primigravidae and nulliparous women, placental processes and foetal growth might have been badly compromised to effectuate the high stillbirth outcomes (10.2%). Therefore, future studies should investigate the events that might have contributed to the poor health status and the ensuing excess stillbirth rates (~11.00%) in these two groups (primigravidae and nulliparous women). Regardless, health care should be

reinforced in these two groups by resorting to segregated rather than universal antenatal health care delivery. For example, primigravidae educational lectures could be held separately from the rest of expectant mothers at the antenatal level in order to emphasize relevance and participation.

5.3 Association between ITN/IPTp-SP use and maternal and neonatal health outcomes

5.3.1 Association between ITN/IPTp-SP use and maternal health outcomes (malaria and anaemia) at 36 weeks

The prevalence of malaria at 36 weeks of gestation was high among pregnant women who neither used ITN nor IPTp-SP (38.8%). Malaria prevalence was higher in ITN users (30.6%) compared to SP users (27.7%) and both SP and ITN users (18.4%). Sleeping under ITN, at least, once a while protected against malaria, p=0.001. The results were higher than the findings of previous studies in Ghana and Nigeria. Malaria prevalence was 10.50% among ITN users in the Ashanti region of Ghana. Malaria prevalence was 7.2%, 8.6% and 4.5% among ITN, SP and both SP and ITN users respectively in Nigeria (Asamoah *et al.*, 2018; Agomo & Oyibo, 2013). The difference in prevalence could be attributed to changes in geographical locations, level of adherence and reduced parasite clearance. The utilisation of malaria in pregnancy interventions in Sub-Saharan Africa was influenced by the individual, the health provider, the system and/or community factors. These factors affect the intake of IPTp-SP and women often do not take the full doses required to treat infections and provide adequate prophylaxis (Odom *et al.*, 2017). The study data confirmed the existence of differences in the protective effect of ITNs and SP. However, SP may still be protective at the individual and community level, unlike in Malawi, where high ITN coverage like that recorded in this setting (>60.0%) masked the effect of SP at the community level (Feng *et al.*, 2010). This probably explained why irregular use of ITN (sleeping under bed nets once awhile) still protected against malaria. The current study findings suggest that the combined use of ITN and IPTp-SP provided additional protection against late gestational (36 weeks of

gestation) peripheral malaria infections (18.4%). In malaria endemic Africa, combining IPTp-SP with ITN utilisation provide synergistic protection against malaria in pregnancy (Feng *et al.*, 2010).

Likewise, it was discovered in this current study that, the prevalence of anaemia at 36 weeks of gestation was high among pregnant women, who neither used ITN nor IPTp-SP (77.5%) as described for malaria parasitaemia. Anaemia prevalence was higher in ITN users (63.5%) compared to SP users (61.5%) and both SP and ITN users (58.4%). Owning and sleeping under ITN, at least, once a while, did not protect against anaemia, p=0.684. This was similar with a previous study in Malawi where ITN use did not reduce the risk of maternal anaemia (*Feng et al.*, 2010). It appears that using ITNs alone or SP or irregular use of ITN combined with IPTp-SP did not protect against anaemia in late pregnancy (36 weeks of gestation). This might provide empirical evidence in the current study setting that using the two interventions provided no additive benefit against maternal anaemia in pregnancy. Importantly, the utilisation of ITN or IPTp-SP or both protected against malaria but not anaemia. This suggests that these interventions might still be protective against malaria in pregnancy in the study context. It is possible that factors, other than malaria, might be responsible for increased risk of anaemia late in pregnancy. Further research is required to provide answers to the deficiencies related with intervention use and the increased risk of anaemia during late gestation.

5.3.2 Association of ITN/IPTp-SP and maternal health outcomes (Low Birth Weight and Stillbirth) At 36 Weeks

The prevalence of low birth weight was high among pregnant women who neither used ITN nor IPTp-SP (32.0%). Low birth weight prevalence was higher in ITN users (13.1%)

compared to SP users (12.0%) and both SP and ITN users (10.9%). Pregnant women who owned ITN had some level of protection against low birth weight, p=0.02. Other studies elsewhere agreed with these findings (Muanda *et al.,* 2015; Feng *et al.,* 2010). A meta-analysis of antimalarial drugs used for chemoprophylaxis prevention of malaria in pregnancy showed a 27% reduction in the risk of low birth weight compared to non-users (Muanda *et al.,* 2015). The combined use of IPTp-SP and ITN provided better protection against LBW than using only ITN or IPTp-SP (Feng *et al.,* 2010). This study observed ~20.07% reduction in the risk of low birth weight with IPTp-SP and comparable prevalence of LBW with ITN (12.0% vrs 13.1%). This suggests that the protective effect of bed nets against LBW had not changed over the years. The Ghana prevalence of low birth weight is 14.0%, which was higher than rates recorded with the use of ITN (13.1%) and IPTp-SP (12.0%). Potentially, the two interventions might still be effective in protecting women against LBW in the country. Previous studies associate the risk of low birth weight with malaria parasitaemia and maternal anaemia (Omer *et al.,* 2017; Muanda *et al.,* 2015; Feng *et al.,* 2010). Detectable malaria parasitaemia in pregnancy is responsible for placental malaria and adverse birth outcomes (Kapisi *et al.,* 2017). Acute and chronic placental malaria infections increase the risk of maternal anaemia, poor foetal growth and low birth weight (Lufele *et al.,* 2017; Odongo *et al.,* 2016). The findings of this current study revealed that, the combined use of ITN and IPTp-SP protected pregnant women against malaria infection but not maternal anaemia during pregnancy. This meant or implies that the late gestational anaemia recorded in the present study was not because of malaria. It also suggested that malaria might have influenced birth weight in a way that did not affect maternal haemoglobin level. In Malawi, placental malaria acquired through detectable peripheral parasitaemia late in pregnancy such as in the 36th week reported by the current study had minimal impact on placental architecture, function, foetal nutrition, foetal growth and birth weight (Odongo *et al.,* 2016).

It is possible that the impact of the late gestational malaria infections was grave on the pregnant women in this setting.

The prevalence of stillbirth was high among pregnant women who neither used ITN nor IPTp-SP (21.1%). Stillbirth prevalence was higher in ITN users (11.8%) compared to SP users (8.6%) and both SP and ITN users (10.2%). Ownership and sleeping under an ITN did not protect against stillbirth, p=0.26. Several studies have established a link between malaria and stillbirth (Moore *et al.*, 2017; Taylor and Kuile, 2017). Malaria infections acquired during pregnancy that increased the risk of pregnancy can be grouped as antenatal infections, placental infections and maternal infections at delivery (S. M. Taylor & Kuile, 2017). Therefore, malaria related interventions such as the utilisation of ITN and IPTp-SP reduce the risk of antepartum (death in utero) and intrapartum (death during labour) stillbirths (Moore *et al.*, 2017). The figures of this study revealed that, taking IPTp-SP might be the best method to protect pregnant women against malarial stillbirth, especially in the study context. For example, the prevalence of stillbirth among non-SP users (21.1%) was almost thrice that of SP users (8.6%). It can be deduced that IPTp-SP might be more efficient in protecting pregnant women against stillbirth than ITN since the combined use of both interventions did not show any protective synergy. The prevalence of stillbirths among those who used only SP (8.6%) was less than using only ITN (11.8%) or combining the use of ITN with SP (10.2%). Moreover, the present study findings indicated that both ownership and good adherence of ITN (sleeping under) did not protect against stillbirth, p=0.26.

It is feasible that IPTp-SP treated infections acquired in early trimester and prevented the detection of chronic and sub-patent infections (asymptomatic) late in gestation and decreased the risk of antepartum stillbirth (Moore *et al.*, 2017; Feng *et al.*, 2010).

5.4 Multivariate regression of risk factors and maternal and neonatal health outcomes

5.4.1 Multivariate regression of predictors for maternal health outcomes

The present study findings showed that socio-demography was not an independent predictor of malaria parasitaemia at 36 weeks of gestation. The current study revealed that, age and educational level were risk factors for malaria infection after adjusting for confounders and it is consistent with the findings of Sohail *et.al*., 2015. Maternal age (30 years and above) protected against late gestational (36 weeks of gestation) malaria infection. Pregnant women who had attained primary education (aOR 0.60; 95%CI 0.37-0.92; p= 0.02) and tertiary education (aOR 0.42; 95%CI 0.23-0.77; p= 0.005) were 40% and 58% less likely of late gestational peripheral malaria infection respectively. Anaemia at 36 weeks of gestation was associated with 2.40 times increased odds of malaria infection at 36 weeks of gestation, (aOR 2.40 CI 1.58-3.64, p<0.0001).

In this current study, anaemia at 36 weeks of gestation was associated with primary and tertiary education but not secondary level education. Being a primary or tertiary graduate protected against anaemia at 36 weeks of gestation. Primary graduates were 39% (aOR 0.61 CI (0.39-0.95) p=0.03) and tertiary graduates were 60% (aOR 0.40 CI (0.25-0.67) p<0.001), less likely to develop anaemia at 36 weeks of gestation. Women with peripheral malaria infection at 36 weeks of gestation were 2.35 times more likely to have anaemia at 36 weeks of gestation, (aOR 2.35 CI 1.56-3.56, p<0.0001).

The study has shown in a Chi square analysis that maternal education and occupation were the socio-demographic risk factors of late gestational malaria in pregnancy. However, sub-group analysis revealed that maternal age; 30 years and above (30-34 years; aOR 0.54, CI 0.31-0.94 p= 0.03 and those 35 years and above; aOR 0.43, CI 0.22-0.84 p= 0.014) protected

the pregnant women against late gestational (36 weeks of gestation) peripheral parasitaemia as compared to those below 25 years.

Also, concerning educational levels, primary (aOR 0.60; 95%CI 0.37-0.92; p=0.02) and tertiary (aOR 0.42; 95%CI 0.23-0.77; p=0.005), were associated with 40% and 58% less likelihood of late gestational peripheral malaria infection respectively as compared to those with no formal education. The elimination of maternal occupation, sustenance of maternal education and re-appearance of maternal age after adjusting for confounders may suggest variable levels of immunity, knowledge and compliance to malaria preventive methods late in pregnancy. Older women have established immunity through previous pregnancies and stay partially protected from malaria (Kweku *et al.,* 2017). Moreover, pregnant women above thirty (30) years old are over 200% more likely to utilise ANC services (Dahiru & Oche, 2015). It appeared that partial immunity and commitment to utilise ANC services might have conferred 46% and 57% protection against late gestational peripheral malaria infections among the older women; and those between 30 and 35 years and 35 years and above respectively in the study cohort. Formally educated women were more empowered to readily make independent decisions and commence ANC early (in the first trimester) in pregnancy. This increases their capacity to utilise full ANC services like IPTp-SP and ITNs as compared to uneducated women (Uppadhaya *et al.,* 2017).

Early ANC visit promotes timely treatment and clearance of malaria parasites before women enter the third trimester. By the third trimester, women restrict their movement, activity and minimize late evening outings, which protect them from mosquito bites and infection likelihood decreases by 41.0% times (Kweku *et al.,* 2017). Future studies are required to confirm the observations in this study setting. Notwithstanding, previous studies have shown

that educated women are better subscribers of malarial interventions and show good compliance to ITNs and often complete their IPTp-SP dosage course (Odom *et al.*, 2017; Agomo & Oyibo, 2013). It is true that education increases the advantage of having salary employment and living in cosmopolitan cities like Tamale, where rampant infrastructural developments and high knowledge on malaria prevention alter the ecology of mosquito breeding sites and eliminate the effect of socio-demographic-specific risks (Dahiru & Oche, 2015; Agomo & Oyibo, 2013; Cot *et al.*, 1993). Additionally, education, especially, higher maternal education influenced having a reliable source of employment income such as being a salaried worker; and overcome the constraints of continuous maternity care to positively impact on the risk reduction of malaria infections during late pregnancy (Manu *et al.*, 2017; Odom *et al.*, 2017; Sohail *et al.*, 2015; Feng *et al.*, 2010). Further, employed women and women with lower socio-economic status consider expenditure on days of medical and ANC review as loss of daily wage (Uppadhaya *et al.*, 2017). It can be adduced, therefore, that knowledge on the dangers of late gestational malaria infections is more aligned with older age and education but not occupation.

Pregnant women with anaemia at 36 weeks of gestation were 2.40 times more likely to have microscope detectable peripheral malaria parasitaemia at 36 weeks of gestation, aOR 2.40 CI 1.58-3.64, $p<0.0001$. According to reviewed studies, the current study was the first to assess the relationship of anaemia at 36 weeks and malaria parasite presence in the maternal peripheral blood at 36 weeks of gestation. It was known that active involvement of pregnant women in interpreting their anaemia and malaria test results motivated ANC re-attendance to observe potential changes in haemoglobin and malaria parasitaemia results. However, the enthusiasm was short-lived (4-8 weeks after enrolment) and revisits to the ANC were inexplicably interrupted (Ampofo *et al.*, 2018). Perhaps, the loss of commitment to re-attend

ANC, negatively impacted on adherence to nutrient supplement intake in the last months of pregnancy, particularly around week 20-30 of gestation (WHO, 2004; WHO, 2009). This might have badly affected IPTp-SP consumption and increased anaemia and malaria risk in the pregnant women cohort around 36 weeks of gestation. Not too long ago, high malaria (24.2%) and anaemia prevalence (80.0%) similar to the findings of this study (25.9% and 62.6% for malaria and anaemia respectively) were observed in Ghanaian women at the last ANC visit (just before delivery) (Tarkang & Adjuik, 2017). This might reaffirm that malaria remains an important component of the multi-factorial complex (malnutrition, other infections and socio-economic factors) that cause anaemia in malarial Africa (Omer *et al.*, 2017; Mosha *et al.*, 2014), especially in late pregnancy (around 36 weeks of gestation).

The current study also showed that, age was a risk factor for maternal anaemia in pregnancy. All the different age groups in the study were predictors for anaemia and it was in agreement with a study conducted by Bam, in 2009, however, this was different from studies by Adam *et al.*, in Eastern Sudan in 2005 (Bam, 2009; Adam *et al.*, 2005).

Anaemia at 36 weeks of gestation was associated with primary and tertiary education but not secondary level education. Being a primary or tertiary graduate protected against anaemia at 36 weeks of gestation. Primary graduates were 39% (aOR 0.61 CI (0.39-0.95) p=0.03) and tertiary graduates were 60% (aOR 0.40 CI (0.25-0.67) p<0.001), less likely to develop anaemia at 36 weeks of gestation compared to those without formal education. The current study observed that anaemia at 36 weeks of gestation was strongly associated with primary and tertiary education but not secondary level education. Several studies had shown the importance between educational status, ANC utilisation and anaemia in pregnancy (Ampofo *et al.*, 2018; Abubakari *et al.*, 2017; Amentie *et al.*, 2015). Pregnant women were required to make eight visits to the ANC for IPTp-SP malaria prophylaxis intake, assessment and

management of detectable pregnancy complications (Owusu-Boateng & Anto, 2017). However, obtaining improved health outcome like anaemia depends on health provider compliance to interventions and adherence of pregnant women to ANC recommendations and treatment (Ampofo *et al.*,2018). Ampofo *et al.*, 2018, proposed that actively involving pregnant women in understanding their maternity care test results such as haemoglobin concentration reports can potentially improve maternal health outcomes. It can be inferred that maternal literacy level might mediate the translation of antenatal care test results into women's adherence to ANC recommendations and treatment for improved health status.

The present study findings showed that being a primary or tertiary graduate protected against anaemia at 36 weeks of gestation. This may be explained by difference of ANC utilisation levels. ANC service was the major intervention to improve the health of pregnant women in areas where the general health status of women was poor like Ghana. A study in Ethiopia that assessed ANC utilisation factors among women of child bearing age found high ANC attendance among literates than illiterates (Amentie *et al.*, 2015). ANC utilisation was over 3.18 times higher in educated women compared to the uneducated. Nevertheless, ANC attendance was highest (7.6 times) among secondary school and tertiary graduates. ANC utilisation is strongly related with maternal educational status in Northern Ghana (Abubakari et al., 2017). The study indicated that primary graduates were 39% (aOR 0.61 CI (0.39-0.95) p=0.03) and tertiary graduates were 60% (aOR 0.40 CI (0.25- 0.67) p<0.001), less likely to develop anaemia at 36 weeks of gestation as compared to those without formal education. This may imply that adherence to ANC recommendations and treatment of anaemia among secondary school graduates was sub-optimal. This is critical to public health preventive measures against anaemia in pregnancy. Further inquiry is needed to determine the factors contributing to the sub-optical care of women with secondary school education.

It was observed that, obstetric characteristics such as gravidity, trimester at first ANC and parity were not associated with the risk of malaria at 36 weeks of gestation. This is consistent with previous studies which found that, gravidity was not a predictor of malaria infection (Helegbe *et al.,* 2018; Kweku *et al.*, 2017; Agomo & Oyibo, 2013). Further, in the Northern Ghana, trimester at first ANC was also not predictor of malaria infection (Helegbe *et al.*, 2018). The lack of association might hint at a loss of gravidity or parity specific acquired immunity in this study setting. A possible explanation might be, the women could have experienced some episodes of malaria infection before their first ANC visit such that they were no longer different in terms of the levels of specific immunity based on gravidity (Agomo & Oyibo, 2013). Hence, acquired immunity was so balanced that seeking early ANC services might not have affected any advantageous protection from malaria infection at 36 weeks of gestation. Acquired immunity in malaria endemic areas like Tamale accumulates after subsequent infections and pregnancies. An earlier study in the Tamale Metropolis indicated that two implemented malaria interventions (ITN and IRS) had not achieved desirable targets. Hence, the Tamale area recorded consistent high malaria cases every month of the year among pregnant women (Helegbe *et al.*, 2018). Since malaria transmission intensity remains high every year in the metropolis, the pregnant women, irrespective of the gravidity, parity and trimester they visited the ANC might have been equally vulnerable to malaria in pregnancy at any stage of gestation.

In this current study, women who attended their first ANC (first enrollment) in the third trimester was associated with 3.45 increased odds of anaemia at 36 weeks of gestation, aOR 3.45; 95%CI (1.38-8.64) p=0.008. This is comparable to a study in Hohoe municipality where those who attended their first ANC in the second trimesters were 1.39 times more likely to have anaemia after adjusting for confounders (aOR=1.39; 95%CI 1.01-1.90, p=0.04) (Kweku

et al., 2017). Again, the findings of this study is not consistent with a recent study in Savelugu Municipality in the Northern region where parity was related with anaemia rather than trimester (Adokiya et al., 2019). The disparity could have been due to differences in the determinants of anaemia. Kweku *et al.*, 2017, found a strong relationship between malaria infection, trimester and anaemia. For instance, the malarial pregnant women in their study were 1.70 times more likely to be anaemic. On the other hand, Adokiya *et al.*, 2019, found that parity was associated with higher odds of moderate/severe anaemia (aOR=2.13, CI: 1.28-3.54); such that women with no previous experience of birth were 2.13 times more likely to be moderately/severely anemic. There was no association between malaria, trimester and anaemia. Although the current study did not measure the spaces between births, women with well-spaced birth intervals were less susceptible to anaemia in pregnancy (Kassa, Muche, Berhe, & Fekadu, 2017).

It was possible that anaemia among the study participants was not because of malaria parasitaemia in pregnancy. So, the use of malaria control methods like ITN and even the recently upgraded IPTp-SP policy might have minimally impacted anaemia. This suggests that other anaemia intervention measures applied at the ANC addressed the trimester risk differences as the women progressed in gestation. It was possible that the threat of anaemia in pregnant women as trimester progresses were minimized. This implied antenatal clinics in the study setting served as efficient platforms to administer interventions that control anaemia in pregnancy. Pregnant women were supplied with folic acid at the ANC to produce adequate red blood cells and prevent anaemia. However, good compliance to folic acid treatment is required to significantly improve folate deficiency (Moya-Alvarez, Ouédraogo, Accrombessi, & Cot, 2018). Again, the women might have actively participated in antenatal anaemia and malaria point-of-care testing which probably facilitated the management of anaemia (Ampofo

et al., 2018). Therefore, these factors that might have contributed to the efficiency need to be strengthened in order to sustain its long-term effect.

Pregnant women with peripheral malaria parasites at 36 weeks of gestation were 2.35 times more likely to have anaemia at 36 weeks of gestation, aOR 2.35 CI 1.56-3.56, p<0.0001 compared to pregnant women without peripheral parasitaemia at 36 weeks of gestation. This was consistent with a previous study in the Hohoe municipality where malaria infected women were 1.70 times more likely to have anaemia, aOR 1.70 CI 1.24-2.31, p=0.0001 (Kweku *et al.*, 2017). However, behavioural changes of the women in the third trimester (week 36 of gestation) minimized their exposure to mosquito bites and highly reduced the likelihood of malaria. This could be that though, the study participants rightfully modified their behaviour, their homes were not protected against mosquitoes. Women in Northern Ghana live in houses made with mud walls and thatch roofs and tend to be frequently exposed to malaria infections, which might predispose them to anaemia (Ahenkorah *et al.*, 2016). It is important that Indoor Residual Spraying, which has been halted for a while in the North, be reactivated to improve malaria protection in the area.

Again, pregnant women with anaemia at the time of enrollment is 3.32 times more likely to have maternal anaemia at 36 weeks of gestation. this finding is consistent with a study done in Tanzania which found that, anaemia at the time of enrollment is a predictor of anaemia during late gestation (Finkelstein *et al.*, 2011). This could be that, the IPTp-SP that pregnant women took during pregnancy might not have protected them against maternal anaemia, because the prevalence of anaemia at registration (54.1%) was less than what was found at 36 weeks of gestation (62.6%).

5.4.2 Multiple regression analysis of risk factors and birth outcomes

In this current study, maternal age (30-34 years) was strongly associated with low birth weight. Women 30-34 years old were 60% less likely to deliver low birth weight babies (aOR 0.40; 95%CI (0.20-0.79); p=0.008) compared to pregnant women below 25 years of age. Education was also strongly associated with the lower odds of low birth weight, that is, primary, secondary and tertiary educated women were at 46%, 59% and 55% less likely respectively of delivering low birth weight babies; (aOR 0.54 95% CI (0.31-0.94), p=0.03) for primary, (aOR 0.41 95% CI (0.21-0.80), p=0.009) for secondary and tertiary education as compared to pregnant women without formal education. Secundigravidae and multigravidae were 60% and 53% less likely to deliver low birth weight babies, aOR 0.40 CI (0.25-0.62) p<0.001, aOR 0.47 CI (0.33-0.67) p<0.001, respectively as compared to primigravidae. Multiparous women were 85% less likely to deliver low birth weight babies, aOR 0.15 CI (0.03-0.71), p=0.02 as compared to nulliparous. Anaemia at registration was associated with 1.55 times borderline increased odds of low birth weight, aOR 1.55 CI 0.99-2.41, p=0.05 compared to pregnant women without anaemia at enrollment.

Socio-demography was not an independent predictor of stillbirth. Being anaemic at registration increased the likelihood of stillbirth by 2.56 times, aOR 2.56 CI 1.35-4.83, p<0.001 as compared to pregnant women without anaemia at registration or enrollment. Low birth weight fetuses were 7.60 times more likely to die in the uterus before birth or during childbirth (stillbirth), aOR 7.60 CI 4.84-11.94, p<0.0001 as compared to birth weight of 2500g or above.

The findings of this study revealed that older maternal age and education protected against low-birth-weight outcomes. This was comparable with studies in other regions of Ghana and

Africa; babies of younger women had lower mean birth weight compared to babies of older women in the Central Region (Afriyie, Bedu-addo, Asiamah, & Boateng, 2016; Prah, Ameyaw, Afoakwah, & Kudom, 2016), Volta Region (Schuler, Edward, & Agbozo, 2019; Afeke et al., 2017; Agbozo *et al.*, 2016) and DR Congo (Moise *et al.*, 2017). This emphasized the fact that younger women in Ghana still experience adverse birth outcomes in spite of increased antenatal care coverage. Poor antenatal care, poor financial position and nutritional status are common occurrences of younger women (Afriyie *et al.*, 2016). According to Schuler *et al.*, 2019, low birth weight was a function of poor diet, ailments and heavy work load. Poverty affects the quality of diet and immunity to diseases. Poverty and low birth weight were major concerns in the Northern territories more than the Southern districts of Ghana (Fosu *et al.*, 2016a).

Several previous studies found education to be a predictor of low birth weight (Zeidan, 2019; Tampah-naah *et al.*, 2016; Ngwira & Stanley, 2015; Nobile, Raffaele, Altomare, & Pavia, 2015; Silvestrin *et al.*, 2013; Chang, 2002). The findings of this current study indicated that, education is a predictor of LBW and all levels of maternal education protected mothers delivering LBW babies. Pregnant women with secondary education were better protected (59% less likely) as compared to those with primary education (46% less likely) and it is consistent with a Portuguese study which found that high maternal education showed 33% protective effect against LBW (Silvestrin *et al.*, 2013). However, the findings of this study are contrary to a study done in Italy, they reported that, mothers with less education are likely to give birth to LBW (Nobile *et al.*, 2015); in Malawi study, they found secondary education to be a predictor of LBW (Ngwira & Stanley, 2015). Women without formal education were advantaged to give birth to normal weight babies because of certain social and environmental factors (Tampah-naah *et al.*, 2016). This current study recorded high employment rate and

improved socio-economic position among educated women and was not perhaps surprising as different measures of socioeconomic disadvantages are associated with adverse birth outcomes such as LBW (Liu *et al.*, 2008; Dibben *et al.*, 2006). Again, pregnant women with some form of education are more likely to adhere to health messages because of their social circumstances and also for allowing wise use of medical care (Leigh, 1983).

In this current study, anaemia at registration was associated with 1.55 times borderline increased odds of low birth weight, (aOR 1.55 CI 0.99-2.41, p=0.05) as compared to pregnant women without anaemia at the time of registration. It is known that good antenatal behaviour like attending ANC at least four times positively affects low birth weight risk factors like maternal nutrition, maternal weight gain in pregnancy, anaemia and regular medical checkups. The repeated visits enable healthcare providers to precondition pregnant women to align with good pregnancy care practices, recognize danger signs and the need to make immediate contact with their healthcare staff (Meiriza *et al.,* 2018; Uppadhaya *et al.*, 2017; Haque *et al.*, 2015). Even so, women must possess adequate knowledge on pregnancy care to correlate ANC attendance with observance of healthy lifestyles (Meiriza *et al.,* 2018). It seemed that either the impact of anaemia-related remedies in the study setting was sub-optimal during the third trimester of pregnancy, especially around 36 weeks of pregnancy. Or that the presence of anaemia instigated certain cardiovascular medical conditions, which invoked poor foetal development and growth, and increased the odds of low birth weight by 1.55 times (Meiriza *et al.,* 2018). It was important that women's ANC seeking behaviour and adherence to administered counselling as well as health worker compliance to medical actions during ANC visits, particularly in the last trimester of pregnancy be investigated in the study setting. For the time being, approaches that promote pregnant women adaptation to preventive lifestyles such as increased community support for women education and healthy

pregnancy awareness campaigns could be strengthened (Meiriza *et al.*, 2018; Haque *et al.*, 2015).

The study reported that, socio-demographic characteristics such as maternal age, residence, education, religion and ethnicity were not independent predictors of stillbirth. This differed from a study in the Eastern region which indicated that, maternal age and type of residence (closeness to a referral health facility) were predictors of stillbirth (Asare and Laar, 2016). The distinction may be related to differences in the levels of antenatal care. For example, stillbirth rates were high among non-ANC attendees and obstetric cases referred from peripheral health facilities. All the pregnant women in the current study utilised the ANC for maternity care and resided in the Tamale Metropolis where four standard health facilities were available to manage complications. This explains why there was high intrapartum (death during labour) stillbirth rate among older women (≥35years old) in the previous study, whose reproductive health probably was comparably weaker than the young adults (an average age of 26 years old) in this study. All the same, the present study was comparable to a previous study conducted in Thai-Myanmar border, that recorded antepartum (death in utero) and intrapartum (death during labour) stillbirths (Moore *et al.*, 2017). Since, the study participants were ANC attendees, it is possible that malaria infections might have influenced the stillbirth rate. Antenatal, placental and maternal malaria infections during pregnancy and delivery increases the risk of stillbirth (S. M. Taylor & Kuile, 2017). Moreover, the current study also recorded high detectable symptomatic falciparum malaria infections in the third-trimester (36 weeks of gestation). The risk of this late gestation infections as had been revealed earlier by the current study data was not associated with socio-demography. In low malaria endemic settings, late gestational malaria contribute to antepartum stillbirth (Moore *et al.*, 2017).

Tamale is a malaria endemic area but the present study did not determine the relative contribution of malaria to antepartum or intrapartum stillbirths. Future research can determine the relation between malaria and antepartum or intrapartum stillbirth.

The study data showed that gravidity and parity were strongly associated with reduced odds of low birth weight after adjusting for covariates. Secundigravidae and multigravidae were 60% and 53% less likely to deliver low birth weight babies, aOR 0.40 CI (0.25-0.62) p<0.001, aOR 0.47 CI (0.33-0.67) p<0.001, respectively. Multiparous women were 85% less likely to deliver low birth weight babies, aOR 0.15 CI (0.03-0.71) p=0.02. The use of SP and ITN are also predictors of birthweight. Elsewhere, low birth weight was also associated with being primigravidae and malaria treatment in Thailand (Rijken *et al.,* 2014), parity and the intake of IPTp-SP in the Volta region of Ghana (Agbozo *et al.,* 2016), ANC visit and trimester at first ANC in Ethiopia (Shiferaw, Yallew, & Tiruneh, 2018). Pregnancy-related malarial immunity is only developed at first pregnancy and becomes the principal defense fountain during later pregnancies. Hence, primigravidae are at a greater risk of malaria induced low birth weight than secundigravidae and multigravidae (McLean *et al.*, 2015).

Possibly, the improved knowledge of the detrimental effects of malaria during pregnancy among women (Vala *et al.,* 2014), which has increased ANC attendance and encouraged them to practise safe motherhood methods for healthy birth outcomes (Sumankuuro *et al.,* 2016), had positively affected parity.

This study recorded high number of previous surviving births, which was captured in the data as high parity size among the women as in other published studies (Igboeli *et al.*, 2018; Williams *et al.*, 2016; Sumankuuro *et al.*, 2016; Ndam *et al.*, 2015; Florey, 2013). The desire of expectant mothers to see their babies in good health and always survive after delivery

might have reduced the risk of low-birth-weight outcomes in women of high parity. The knowledge of potential threats to babies' survival shapes women's perception, attitude and commitment towards the utilisation of preventative interventions (Onyeneho *et al.,* 2015). The high protectiveness conferred by parity (85%) against low birth weight in the current study suggests that the pregnant women might have desirably used all available interventions. This was different from reports in other parts of Africa. For example, Mozambican women prefer to use ITNs (62.5%) over IPTp-SP (12.5%), iron supplements (9.1%) and antihelminthics (2.3%). A situation which has badly affected acceptability and adherence to malaria and anaemia interventions. Consequentially, pregnant women are not well protected from the risk of low birth weight which is a known outcome of malaria and anaemia in pregnancy (Vala *et al.,* 2014). On the contrary, in Ghana, subscription to malaria and non-malarial anaemia interventions like iron supplementation and antihelminthics is mandatory for all pregnant women. Since 2005, the combined contributions of these interventions have reduced the risk of bad birth outcomes by 23% (Asundep *et al.,* 2014). Recently, Ghanaian women have supplemented standard interventions with methods like the use of mosquito repellents, wearing protective clothing and the practice of good environmental hygiene to control malaria (Manu *et al.,* 2017). It is possible that such behavior could maximize protection against the risk of low birth weight which is as high as the 85% recorded among high parity women in this study.

It was observed that being anaemic at registration increased the likelihood of stillbirth by 2.56 times, aOR 2.56 CI 1.35-4.83, p<0.0001. Moreover, low birth weight babies were 7.60 times more likely to die in the uterus before birth or during childbirth (stillbirth), aOR 7.60 CI 4.84-11.94, p<0.0001 and compared to babies with birth weight 2.5kg or more.

The findings of the current study are consistent with an earlier report in Ghana that anaemia during pregnancy facilitates foetal under development and co-existence of low birth weight and stillbirth (Agbozo *et al.,* 2016). Stillbirth risk is multifactorial (direct, indirect and intermediate factors) and vulnerability is the result of a cumulative or interactive effect of risk factors (Jones, 2019). Anaemia promotes utero-placental nutrient insufficiency during pregnancy (Cutland *et al.,* 2017), which orchestrates Intrauterine Growth Retardation (IUGR) and hampers foetal weight gain and generate low birth weight (Hartman and Rogerson, 2010). Poor nutrition and foetal growth restriction are important causes of stillbirth. The results of this study emphasized that anaemia and low birth weight are still critical risk factors of stillbirth. Therefore, health managers should beef-up strategies that enforce: 1. uptake of multiple micro-and-macro nutrient supplements (Smith *et al.,* 2017); 2. prompt reporting and monitoring of changes in foetal movement as well as blood pressure checks (Christou *et al.,* 2019).

5.5 Effectiveness of IPTp-SP and maternal health outcomes (objective I)

5.5.1 Malaria prevalence in relation to IPTp-SP dose taken

In this setting where malaria is endemic, almost half of the pregnant women (42.4%) took doses of SP which were up the levels up to the new World Health Organisation (WHO) acceptable doses of three or more. The proportion (prevalence) of malaria at 36 weeks of gestation was higher in non-SP users (35.8%) than in women dosed with at least two (30.8%) or three or more SP doses (16.9%).

The moderate coverage (42.4%) of increased IPTp-SP dosing (three or more doses) in this current study was consistent with reports in Tanzania (40.6-52.6) (Ndeserua *et al.,* 2015), Burkina Faso (49.2%)(Scott *et al.,* 2019). Again, the results agreed with previous studies in the Western Region of Ghana (47.7%) (Orish *et al.,* 2015). However, the measured

percentage or reported use of SP was higher (42.4%) than published ranges in Uganda (7.0-8.0%) (Abeku *et al.,* 2015), North-western Tanzania (6.0%) (Mpogoro *et al.,* 2014) and The Gambia (3.7%) (Scott *et al.,* 2019). This may be due to differences of implementation challenges, procurement bottle-necks, variations in geographical malaria transmission intensity, health worker delays and irregular subscription of pregnant women unto the IPTp-SP services (Ndam *et al.,* 2015; Orish *et al.,* 2015; Mpogoro *et al.,* 2014; Mosha *et al*., 2014; Mbu *et al.,* 2014). The IPTp-SP policy has been saddled with frequent shortages of SP which has denied pregnant women on antenatal appointments access to the programme drug (SP) in many parts of malaria endemic Sub-Saharan Africa (Mpogoro *et al.,* 2014). So, women tend to be inconsistent with their visits to the antenatal clinic and have contributed to inequalities of SP supply (Orish *et al.,* 2015). The moderate coverage (42.4%) of increased (three or more) SP dosing in the Sub-Saharan malarial Africa as recorded in the current study may suggest that pregnant women in the region recognised the need to take sufficient (three or more) SP doses to remain protected from malaria infections until delivery. In high malaria transmission intensity countries like Ghana, increased SP dosing (at least three doses) is required to protect pregnant women against gestational malaria (Ndam *et al.,* 2015; Mosha *et al.,* 2014). This may explain why almost half (42.4%) of the pregnant women saw the need to take their SP intake to at least three doses.

The post IPTp-SP malaria prevalence (25.9%) in the current study is inconsistent with published percentages in Benin (4-16%) (Ndam *et al.,* 2015), Nigeria (7.7%) (Agomo & Oyibo, 2013) and Ghana (7.9-11.2%) (Anto *et al.,* 2019; Yeboah *et al.,* 2016). However, the reported malaria prevalence (25.9%) is similar with a previous study in the Hohoe municipality (20.3%) (Kweku *et al.,* 2017). These results suggest that the SP which were being used were found to be marginally lower than the recommended doses. In a similar

study conducted in 2009 but published in 2016, the IPTp-SP served pregnant women in the Central Region of Ghana possessed poor bioavailability and dissolution characteristics and were ineffective to treat and provide malaria prophylaxis (Yeboah *et al.*, 2016). The prolonged (since 2009) administration of substandard programme SP might be responsible for the rising levels of SP failure and prevalence of malaria in pregnancy. This may have important implications on the prevalence of malaria parasitaemia among pregnant women, which has remained unchanged since 2009 (Kweku *et al.*, 2017).

The prevalence of malaria at 36 weeks of gestation was higher in non-SP users (35.8%) than in women dosed with two (30.8%) or more SP doses (16.9%). This agreed with a previous study in Takoradi (Ghana) by Orish *et al.*, and other published results elsewhere in malaria endemic Africa (Orish *et al.*, 2015; Mpogoro *et al.*, 2014; Mosha *et al.*, 2014;). For instance, in the Western region of Ghana malaria prevalence was higher with one SP dose (20.7%) than, at least, two doses (13.7%) (Orish *et al.*, 2015). Also, in Tanzania, non-IPTp-SP users recorded higher malaria prevalence in pregnancy (41.7-43.1%) than women that took two (25.3-36.8%) and at least three (14.7-15.4%) SP doses (Mpogoro *et al.*, 2014; Mosha *et al.*, 2014). Looking at the trend, the study results obviously reinforce the fact that, increased dosing of SP (three or more doses) could provide better protection against malaria during pregnancy (Scott *et al.*, 2019), especially third trimester infections. The current study findings also confirm that malaria in pregnancy continues to be a perennial public health burden across Sub-Saharan Africa (Ndeserua *et al.*, 2015), even in the context of IPTp-SP chemoprophylaxis. Therefore, strategies that maximize the effect and coverage of three or more SP doses should be more enhanced in the antenatal system. For example, co-morbidity infections like HIV and other pathogenic infections that occur during pregnancy should be given equal clinical importance as malaria (Ndeserua *et al.*, 2015). Also, IPTp-SP delivery at

antenatal clinics could be designed to monthly target specific pregnant groups (Mosha *et al.*, 2014).

5.5.2 Anaemia prevalence in relation to IPTp-SP dose taken

The overall prevalence of anaemia in this study (62.6%) was not consistent with previous studies in Benin (14.0-16.3%) (Ouédraogo *et al.*, 2012). This may be due to the types of study designs; prospective observational versus experimental, which used different sampling methods of recruitment. In the study, respondents were randomly sampled out of the numbers of pregnant women available during each visit while Ouedraogo *et al.*, randomized participants based on age and body mass index which are important factors of haemoglobin concentration. Nevertheless, the results are consistent with recent studies in Ho municipality (60.3%) (Kweku *et al.*, 2017), in Cape Coast municipality (73.5%) (Yeboah *et al.*, 2016), in Sudan (58.9%) (Omer *et al.*, 2017), and in India (72.9%) (Sohail *et al.*, 2015). These findings suggest that pregnancy-related anaemia is still high and the 2014 reviewed malaria control methods (IPTp with SP) may not provide adequate protection against maternal anaemia. This may confirm the etiology that anaemia in pregnancy is multifactorial that involve malaria infectivity and other factors like nutrition (Mosha *et al.*, 2014). Therefore, other supplementary methods are required to combat anaemia in pregnancy.

The prevalence of anaemia at 36 weeks of gestation was higher (72.8%) among pregnant women who did not take SP compared to those that had taken less than three doses (66.6%) and at least three doses (54.1%). This is inconsistent with previous studies in the Sekondi/Takoradi Metropolis of Ghana and Tanzania, where similar anaemia prevalence was observed in both SP users and non-users. For example, in the Ghana study, anaemia prevalence was 36.2% among SP users and 31.8% in non-SP users. Likewise, in Tanzania, published ranges of anaemia prevalence in SP users was 46.2-61.0% and 27.3-56.0% in non-

users. However, the findings were similar to earlier works in the Hohoe municipality of Ghana and other parts of West Africa. For example, taking additional SP dose of more than two, significantly reduced malaria parasite density and increased protection against anaemia by 57% (Kweku *et al.,* 2017). Relatedly, in other parts of West Africa, anaemia prevalence with less than three SP doses ranged higher (48-54%) compared to that of three or more doses (24-29%) (Scott *et al.,* 2019). The difference may be due to variations of dosage completion, compromised drug quality, growing drug resistance, variable parasite transmission intensity and weakened pregnancy-specific malarial immunity. In malaria endemic Africa, contrary factors such as poor dosage completion, sub-standard drug quality, increased drug resistance and weakened immunity constrict the therapeutic and prophylactic potency of SP. Hence, peripheral blood parasite densities expand and invoke active placental infections late in pregnancy (Odongo *et al.,* 2016; Mpogoro *et al.,* 2014).

It was stated earlier in this study that the anaemia recorded in the study cohort was not due to malaria infections. Additionally, the effect of non-malarial anaemia interventions like iron and folate supplementation were not controlled in this study but rather the effect of antihelminthics on anaemia was controlled. Unfortunately, the antihelminthics (aOR 1.34. CI 0.74-2.40, p=0.3) did not offer any protection against anaemia among the pregnant women and this is consistent to what Mosha *et al.,* found in their study. Thereupon, the influence of non-malarial anaemia interventions in the SP induced pregnant women of the current study cohort could not be ignored.

However, exposure to antihelminthics, iron and folate supplementation showed negligible impact on maternal anaemia during pregnancy in both SP dosed and non-dosed pregnant women (Mosha *et al.,* 2014). Meanwhile, the IPTp-SP doses taken by the study participants appeared to have protected against anaemia and the effect improved with increased SP

dosing. Notwithstanding, the results also suggested that increased SP dosing with three or more doses may not have protected against anaemia at 36 weeks through reduced risk of late gestational malaria infections. Since anaemia prevalence observed under three or more SP dosing (54.1%) at 36 weeks was the same as what was recorded at registration (54.1%). Moreover, parasitaemia at registration was less (4.7%) than the prevalence seen after the participants had taken three or more SP doses (16.9%). Wherefore, the study hypothesized that, taking three or more IPTp-SP doses did not enhance the antimalarial activity of the drug, either for therapy or prophylaxis. The finding is consistent with previous evidence (in the Western region of Ghana) of the lack of enhanced protection against anaemia in pregnancy associated with increased SP dosing under three or more doses (Orish *et al.,* 2015). This may hint at growing changes of contrary factors that constrict the therapeutic and prophylactic potency of SP administered under IPTp in the country, and also confirm earlier reports of changing malaria epidemiology in Africa (Baraka *et al.,* 2015). It is possible that changes in malaria epidemiology, especially in pregnancy in the study context might have well evolved. This might have dire implications on malaria control in pregnancy. Additional research is required to profile the impact of the changes on malarial control strategies as well as other pregnancy-related health interventions.

5.6 Effectiveness of IPTp-SP and neonatal health outcomes (OBJECTIVE II)

5.6.1 Prevalence of Low birth weight in relation to IPTp-SP dose taken

Adverse birth outcomes such as low birth weight was also high, 14.0%. High prevalence of low birth weight has been reported among pregnant women of high malaria parasitaemia and anaemia in Sub-Saharan Africa (Igboeli *et al.,* 2018; Omer *et al.,* 2017; McGready *et al.,* 2012). The recorded high percentage of malaria parasitaemia (25.9%) and anaemia (62.6%) among the participants, which are risk factors of low birth weight and stillbirth.

In malaria endemic Africa, most incidence of LBW are the direct consequence of high malaria parasitaemia among pregnant women which induce maternal anaemia, Intra Uterine Growth Retardation and poor foetal weight gain (Hartman and Rogerson, 2010; Saba *et al.*, 2008). In Ghana, the prevalence of low birth weight was 14.0% in 2016 but this varied among the regions (Fosu *et al.*, 2016b). In the Volta region, prevalence varied between 7.2 and 9.7% (Agbozo *et al.,* 2016; Afeke *et al.,* 2017), 7.7% in Central region (Prah *et al.*, 2016) and 14% in the Ashanti region (Asamoah *et al.,* 2018). The current study reported prevalence (14.0%) was higher than the prevalence of LBW in the Volta and Central (the lowest in the country) regions but comparable with what was recorded in the Ashanti region and the national rate (14.0%). This may imply that health indicators in this deprived region had improved, since Ashanti region has better economy and double as the hub of Ghana's natural resources (Afeke *et al*., 2017).

The prevalence of low birth weight among pregnant women who did not use IPTp-SP was higher (24.9%) in comparison with women dosed with less than three SP doses (16.5%) and at least three SP doses (7.1%). This was inconsistent with studies conducted elsewhere in Tanzania where low birth weight prevalence under increased SP dosing (at least one dose SP) did not differ (3.8-5.5%) with that of SP non-users (5.3-16.7%) (Mosha *et al.,* 2014). Nevertheless, the findings corresponded with low-birth-weight prevalence ranges in other parts of the West African sub-region. Thus, 0-10% under three or more IPTp-SP doses and 10-15% with less than two SP doses (Scott *et al.,* 2019). The disparity may be the result of variations in malaria transmission intensity, malarial pathology, and low birth weight mediatory processes. In Tanzania, unlike many parts of malarial Africa, variable parasite transmission intensity influence malaria pathology and prematurity rather than anaemia to generate low birth weight (Mosha *et al.,* 2014). Additionally, low birth weight prevalence is

lower (2.2-6.3%) and significantly related with prematurity but not with placental malaria. So, IPTp-SP intake regardless the dose, has no impact on low birth weight prevalence (Ndeserua *et al.*, 2015).

Significant improvement of low-birth-weight prevalence was observed with increased IPTp-SP dosing, particularly under three or more SP doses. This suggests that IPTp-SP potentially mitigated the dangerous effects of peripheral malaria infections that occurred during the later weeks of pregnancy (around 36 weeks) in the study participants. This might have modified malarial pathology and low birth weight mediatory processes like anaemia and prematurity (Ndeserua *et al.*, 2015; Mosha *et al.*, 2014). In East Africa, excess risk of active placental malaria infections and low birth weight were found among pregnant women who had taken IPTp-SP in Uganda (Odongo *et al.*, 2016). The current study provides evidence for the first time in the country's post 2014 WHO reviewed IPTp-SP policy that, the policy change has reduced the prevalence of low birth weight. Additional research is, however, needed to confirm the period of SP protection and other promoting factors. Regardless, the current study proposes that IPTp-SP educational lectures be intensified in the third trimester to enhance uptake in the later weeks of pregnancy (before 36 weeks) to improve protection against low-birth-weight deliveries.

5.6.2 Prevalence of stillbirth in relation to IPTp-SP dose taken

The prevalence of stillbirth (10.2%) in this current study is higher compared to Greater Accra region, which recorded stillbirth prevalence of 6.2% (Larysa *et al.*, 2017). The study might affirm the sharp difference in prevalence of low birth weight between the two geographic areas, which was high in the North compared to the South (Fosu *et al.*, 2016a). Elsewhere, low birth weight increased the risk of stillbirth deliveries by five-fold (Afeke *et al.*, 2017). The current study findings indicated that malaria and anaemia in pregnancy as well as low

birth weight and stillbirth deliveries are still high above the national targets after the introduction of the WHO IPTp-SP policy review in 2014. This may have important implications on standard methods that aim at improving safe motherhood and child survival, considering the simmering appearance of SP-resistant malaria parasite strains in Ghana (Orish *et al.*, 2015).

The prevalence of stillbirth was greater among pregnant women who did not take SP (17.7%) compared to women that had taken one or two doses (9.6%) and reduced more than two-fold under at least three SP doses (7.4%). To the best of my knowledge, this study is the first in Africa and outside Africa to explain the impact of variable IPTp-SP doses on stillbirth pregnancy outcome after the WHO revised IPTp-SP policy in 2014. Literature review revealed limited published stillbirth prevalence ranges in the context of pregnancy-related malaria and IPTp-SP antimalarial activity. Probably, this study findings may expand the volume of limited studies on the subject of IPTp-SP intake and stillbirth deliveries (Goldenberg and Thompson, 2003). However, stillbirth prevalence was higher among non-IPTp-SP users and pregnant women under one dose in Hohoe municipality of Ghana (Agbozo *et al.*, 2016). Malaria-related stillbirth prevalence outside Africa was estimated to be lower (4.5%), especially in the Thai-Myanmar border area (Moore *et al.*, 2017).

This might underscore that differences of antenatal services, frequency of antenatal visits, efficiency of obstetric emergency support systems, type of malaria infectivity, malarial disease pathology and changes of stillbirth intermediary factors, affect IPTp-SP use and stillbirth prevalence. It is possible therefore, that the pregnant women in the study area timely experienced continuous and quality antenatal content throughout pregnancy which might have improved IPTp-SP relationship with stillbirth (Christou *et al.*, 2017). Also, the antimalarial potency of IPTp-SP, tended to suppress the detrimental effects of late

asymptomatic malaria triggered through peripheral infections in the third trimester, which may have tentatively reduced low birth weight incidence and minimized the risk of stillbirth outcome (Asamoah *et al.*, 2018; Moore *et al.*, 2017). Nominally, it appeared that additional SP doses potentially empowered the antimalarial action of IPTp-SP against asymptomatic infections in late pregnancy (around 36 weeks) and the prevalence of stillbirth outcome. Hereafter, clinical trials could be considered to interpret the prospects of increased protective antimalarial activity under high dosage of three or more IPTp-SP doses. Henceforth, current methods that encourage pregnant women to seek prompt and frequent antenatal care such as free maternal care, should be reinforced to sustain high malaria and stillbirth protection throughout pregnancy. Besides, available maternity medical emergency systems and antenatal services should be strengthened, especially uptake of IPTp-SP in the third trimester.

5.7 The association between IPTp-SP doses and maternal health (maternal malaria and anaemia) and neonatal health (low birth weight and stillbirth) (objective III)

5.7.1 Association between IPTP-SP and malaria parasitaemia at 36 weeks of gestation

IPTp-SP utilisation was associated with dose-dependent protection against the odds of peripheral malaria infection at 36 weeks of gestation. Lower SP dose (less than three) was associated with 4.0% while higher SP dose (three or more) was associated with 56%, (p=0.001), reduced odds of late gestational (36 weeks) peripheral malaria infection. Increased IPTp-SP dosing was not associated with dose-dependent protection against the odds of maternal anaemia in the later weeks of gestation (around 36 weeks), p=0.65. Higher IPTp-SP dosing with three or more doses corresponded with increased likelihood (63%) of protection against low birth weight (aOR=0.37, 95% CI 0.21-0.68, p=0.001). Increasing IPTp-SP doses from two to three or more showed no dose-dependent protection against the likelihood of stillbirth outcome (aOR 1.15 CI 0.55-2.42 p=0.71).

IPTp-SP utilisation showed dose-dependent protection against the odds of peripheral malaria infections at 36 weeks of gestation. Intake of lower doses (1-2) provided 4.0% less likelihood while higher doses of three or more provided 56% less likelihood (p=0.001), of late gestational (36 weeks) peripheral malaria. This corresponded with earlier studies in Tanzania where high SP doses (three or more) was associated with 60-80% reduced odds of third trimester malaria parasitaemia (Mpogoro *et al.,* 2014; Mosha *et al.*, 2014). The findings of this study also agreed with previous studies in Ghana (Orish *et al.,* 2015), and within the West African sub-region where protective efficacy of SP was greater under three or more doses (63-72% reduced likelihood) compared to doses below three (13-36% reduced likelihood) (Scott *et al.*, 2019). This may reiterate the position of malarial authors that higher SP doses (three or more) provide better protection against malaria during pregnancy (Scott *et al.*, 2019; Orish *et al.,* 2015; Kimberly *et al.*, 2015; Mpogoro *et al.*, 2014; Mosha *et al.*, 2014).

It appeared that protection against malaria increased from 4.0% with two SP doses to 56% under at least three SP doses. This suggests that the malarial immunity of the study participants may have remained optimal after three or more IPTp-SP doses. This contradicted with a previous observation in Beninese pregnant women where immunity dropped to sub-optimal levels post IPTp-SP with two doses. Probably, shortfalls in available preventive methods, pregnancy induced plasma expansion and limited parasite exposure during the periods of IPTp-SP services had minimal impact on host malarial immunity. Therefore, standard levels of antibody activity might have been maintained against blood stage and placental parasite binding proteins under high (at least three) SP doses (Ndam *et al.*, 2015). The study affirms that the WHO revised IPTp-SP policy (implemented in Ghana in 2014), which recommend the intake of, at least, three SP doses, might be beneficial against the odds

of malaria infections during pregnancy, especially around 36 weeks (aOR0.44; 95%CI 0.27-0.70; P=0.001).

Further analysis showed that the protective efficacy of SP under three or more doses tended to be shifted closer to the lowest bracket of protection range. That is, 56% versus 60-80% in Tanzania (Mpogoro *et al.,* 2014; Mosha *et al.,* 2014), and 56% versus 63-72% in the West African sub-region (Scott *et al.,* 2019). This might imply that prevailing factors such as high parasite transmission intensity, sub-optimal uptake of high SP doses and the timing of SP intake could abruptly shorten the antimalarial influence of at least three SP doses in the study area. Thus, the antimalarial protective potency of three or more doses of IPTp-SP in the study area might be short lived. Meaning, pregnant women could still be in danger of late malaria infections (around 36 weeks) and maternal anaemia at a period when iron and folate are in high demand prior to delivery (Fleming, 1989). Wherefore, antenatal lectures should aim at encouraging iron and folate intake, especially during 20-30 weeks of gestation (WHO, 2018). In addition to this, pragmatic and innovative methods are needed to sustain the long-term prophylactic effect of the new WHO IPTp-SP policy, which advocates the intake of at least three SP doses. Also, the study supports earlier proposals that individual SP doses be properly spaced (one month apart) with the last dose being taken within four weeks to delivery (Mpogoro *et al.,* 2018), in order to enhance SP efficacy until child birth. Again, IPTp-SP uptake targets could be set for antenatal clinics at the community level. For example, at least 84% of the pregnant women in the community of an antenatal clinic should have completed eight maternity care appointments and taken five SP doses annually (Yeboah *et al.,* 2016; Arinaitwe *et al.,* 2013). Appropriate research methods could properly profile the possible dose-dependent antimalarial depletion associated with IPTp-SP observed in the study area.

5.7.2 Association between IPTp-SP and anaemia at 36 weeks of gestation

Increased IPTp-SP dosing (three or more) was associated with 11.0% less likelihood of maternal anaemia in the later weeks of gestation (around 36 weeks), though the association was not statistically significant (aOR 0.89; CI 0.55-1.45; p=0.65). The current study findings correlated with a previous studies elsewhere in the West African sub-region (The Gambia, Burkina Faso, and Benin), Sekondi/Takoradi Metropolis of Ghana and in Tanzania where the measured association between higher SP doses (at least three) and dose-dependent protection from maternal anaemia was not statistically significant (Scott *et al.*, 2019; Ndeserua *et al.*, 2015; Orish *et al.*, 2015; Mosha *et al.*, 2014). This might be indicative of the fact that, IPTp-SP under high dosage (at least three doses) did not protect the pregnant women in this study against anaemia. Earlier authors have asserted that improvements of haemoglobin concentration in pregnancy before delivery (particularly around 36 weeks) was not related with IPTp-SP utilisation (Orish *et al.*, 2015; Mosha *et al.*, 2014). The investigators of the current study suggest that dosing pregnant women beyond two doses of IPTp-SP might not safeguard them from the odds of maternal anaemia in the later weeks of pregnancy (36 weeks).

Kweku *et al.*, (2017), demonstrated a dose-dependent potency of IPTp-SP among Ghanaian pregnant women who took variable doses of SP in the Hohoe municipality of Ghana. They found that women that had taken at least three SP doses under IPTp were 54% less likely to develop anaemia in pregnancy (Kweku *et al.*, 2017). The disparity might be related to differences of parasite reduction associated with the consumption of at least three SP doses. For instance, malaria prevalence before IPTp-SP was higher (20.3%) in their study compared to what was found in this current study (4.7%). So, additional SP doses taken (beyond two) correlated with reduced prevalence of malaria (18.9%) in their study. However, peripheral

malaria prevalence remained elevated (16.9% vrs 4.7%) under higher (three or more than three) SP doses in the current study, especially at 36 weeks. It can be inferred that the IPTp-SP investigated in the current study could not prevent new malaria infections (peripheral malaria infections). Meanwhile, parasite presence did not rapidly destroy red blood cells and drastically reduce haemoglobin concentration to worsen anaemia burden (Chen *et al.,* 2016), after the intake of three or more SP doses (54.1% vrs 54.1% at registration). Again, univariate regression analysis indicated that women that had taken three or more SP doses obtained 58% protection against the odds of anaemia at 36 weeks of gestation. Possibly, the new infections did not create maternal anaemia because the additional SP doses taken (after the first two doses) protected non-parasitized red cells against haemolysis.

The WHO reviewed IPTp-SP policy, which advocate for increased SP dosing with at least three doses, has the potential to protect pregnant women against peripheral parasitaemia-related intravascular haemolysis of red blood cells in the later weeks of pregnancy (36 weeks) but not anaemia caused by other factors.

Future research may investigate study the pathophysiological mechanisms that might have given rise to these observations. Notwithstanding, health planners should implement methods to address inadequate dosage completion, poor drug quality, increasing drug resistance and weakened immunity (Odongo *et al.,* 2016; Ndeserua *et al.,* 2015) to reinforce the potency period of higher SP doses (three or more) against peripheral malaria-related anaemia in pregnancy.

5.7.3 Association between IPTp-SP and Low Birth Weight

In this cohort of pregnant women, IPTp-SP intake was associated with dose-dependent protective efficacy against the odds of low-birth-weight delivery outcome. Protection

improved with the intake of higher doses (at least three SP doses). Women who had taken three or more SP doses were 63% less likely to deliver low birth weight babies, (aOR 0.37; CI 0.21-0.68; p=0.001), compared to those who took below three doses (aOR 0.84; CI 0.50-1.42; p=0.52). The current study findings were not consistent with previous studies which reported that, IPTp-SP use was not associated with reduced risk of low birth weight, in Tanzania by Mosha *et al.,* (2014) (aOR 0.7; CI 0.1-6.4; p=0.76); Ndeserua *et al.,* (2015) (p=0.73), Harrington *et al.,* (2011) and Mpogoro *et al.,* (2014) (aOR0.68; CI 0.22-2.14; p=0.49. Regardless, the study findings are consistent with published studies which reported that, intake of three or more doses of IPTp-SP was associated with improved birth weight (Mikomangwa *et al.*, 2019; Igboeli *et al.*, 2017; Gutman *et al.*, 2013b; Kayentao *et al.*, 2013). The disparity could be attributed to differences in geographical malaria transmission intensity, coverage of high IPTp-SP doses (at least three doses), timing of SP intake and frequency of antenatal visits. Variations of malaria transmission intensity alter low birth weight mediatory factors like placental malaria, anaemia and prematurity (Ndeserua *et al.*, 2015; Mosha *et al.*, 2014). Moreover, irregular antenatal visits and inconsistent IPTp-SP supplies limit the effect of high SP doses against the risk of malaria infections in the third trimester (34-36 weeks) and cause low birth weight delivery (Orish *et al.,* 2015; Mpogoro *et al.*, 2014).

Pregnant women who took three or more doses of IPTp-SP showed a dose-dependent protective efficacy against the odds of low birth weight (aOR 0.37; CI 0.21-0.68; p=0.001) delivery outcome in the study cohort. Pregnant women who took three or more doses had lower prevalence of LBW (7.1%) compared to those who took less than 3 doses (16.5%). This highlights the importance of addressing malaria infection during pregnancy in middle- and low-income West African countries like Ghana, as malaria prevention has a direct effect

on birth outcomes (Mosha *et al.,* 2014). In Nigeria, malaria chemoprophylaxis policy changed from chloroquine to IPTp-SP in 2010 resulting in increased risk of low birth weight (Igboeli *et al.,* 2018). Previous evidence in West Africa indicated that the protective potency of malaria chemoprophylaxis is complemented by optimal antibody activity after malarial chemotherapy (Ndam *et al.,* 2015). This study observed that women who had taken three or more SP doses were 63% less likely to deliver low birth weight infants, (aOR 0.37; CI 0.21-0.68; p=0.001) compared to those who took below three doses (aOR 0.84; CI 0.50-1.428; p=0.52). It can be inferred that, the WHO revised IPTp-SP policy, which promotes the intake of higher SP doses (at least three) maintained adequate immune activity after taking at least three doses. This possibly reduced the deleterious consequences of peripheral malaria infections before delivery (around 36 weeks) and the likelihood of low-birth-weight deliveries. The study results suggest that parasite presence in the peripheral blood, like in the placenta or in cord blood equally have detrimental effect on foetal survival since IPTp-SP activity (demonstrated a dose-dependent) protection against malaria parasitaemia and low birth weight (Bardajı *et al.,* 2010). The study found that, the 2014 IPTp-SP policy change from two SP doses to at least three SP doses in Ghana, significantly averted low birth weight deliveries. This study, therefore, encourages policy makers and health professionals especially at the antenatal clinics to institute measures that aim at mitigating policy implementation challenges, low coverage of at least three SP doses and poor documentation of IPTp services.

5.7.4 Association between IPTp-SP and Stillbirth

Lower SP doses (less than two doses) rather than higher (at least three) SP doses tended to show potential reduced odds of stillbirth delivery, though not statistically significant (aOR 0.55 CI 0.26-1.18 p=0.12). This finding was inconsistent with a previous study in the Hohoe municipality of Ghana where lower SP doses (one or two doses) was associated with 1.3-2.0

times increased likelihood of stillbirth delivery (Agbozo *et al.*, 2016). The differences in the results obtained may be related to differences in the coverage of IPTp-SP doses (at least three doses). Agbozo *et al.*, (2016) recorded lower coverage of SP dosing of at least two doses (12.5%) compared to the current study which recorded higher percentage (37.4%) compared to their findings which probably reduced the power of their study.

Previous evidence explained that effective antenatal practices that encourage consumption of variable SP doses (at least one SP doses), as observed in this study, eliminate the relationship between malaria and stillbirth (Moore *et al.*, 2017). It could be inferred that the uptake of two (37.4%) or more (42.4) SP doses as recorded in this study did not reduce the risk of stillbirth. This has the tendency to discourage uptake of the revised WHO IPTp-SP policy which support the intake of at least three SP doses. Such developments have important implications for malaria control in pregnancy. Since, new malaria infections that arise after three or more doses of IPTp-SP therapy (as observed in this study), create maternal anaemia, small for gestational age, low birth weight and invoke stillbirth delivery (Moore *et al.*, 2017; Agbozo *et al.*, 2016). Health planners should institute measures that discourages apathy and promote enhanced uptake of the revised WHO IPTp-SP policy.

The results of the study indicated that pregnant women who took less than three doses of IPTp-SP was associated with reduced odds of stillbirth, although the association was not statistically significant (aOR 0.55 CI 0.26-1.18 p=0.12), however, those who took at least three doses of SP increased the odds of stillbirth (aOR 1.15 CI 0.55-2.42 p=0.71). Probably, intake of two SP doses by the second trimester (13-24 weeks) minimally interfered with antibody responses in the peripheral blood, unlike in the placenta and may have cleared blood-stage parasites but the protection seemed to be short-lived. This might have negatively

impacted on the antimalarial-immunity interplay allowing for subsequent episodes of peripheral malaria infections (Odongo *et al.*, 2016; Ndam *et al.*, 2015). It could be conjectured that the extra SP doses taken after the two doses tended to modify the antimalarial-immunity interaction and further increased plasma binding inhibitory capacity. All the same, the modification seemed not to have any relationship with reductions of the likelihood of peripheral malaria infection and stillbirth, unlike with placental malaria and low birth weight (Ndam *et al.*, 2015).

The findings of the current study may hint that malaria-related stillbirths may be low in the study area such that minimum doses of IPTp-SP (less than three doses) might be needed to complement other antenatal care and obstetric factors to maximize protection against stillbirth pregnancy outcome. For instance, quality antenatal content and effectual obstetric support networks alleviate the risk of stillbirths (Christou *et al.*, 2017). Future malaria in pregnancy studies could estimate the efficacy of individual rather than the cumulative IPTp-SP doses taken such that women are assessed for malaria in-between the last and the next SP dose (Mosha *et al.*, 2014). Such analysis would properly help distinguish malaria-related stillbirths from non-malarial stillbirths. However, current strategies that ensure quality antenatal service and efficient obstetric medical emergency care systems should be enhanced.

5.8 Assessment of the adequacy of SP (objective IV)

The analyses of the SP for its adequacy revealed sub-optimal doses of SP that was not expected to completely get rid of the parasitaemia in the pregnant women. Almost three-quarters of the drug analysed did not meet the accepted criteria by the USP NF 29. This is consistent in a study done in Kenya by Amin *et al.*, (2005); 35.1% of the SP analysed did not meet the USP specifications for content. However, it was observed that a significant

proportion of the program drugs contained the right amount of Sulphadoxine but inadequate amount of the pyrimethamine. For complete protection against malaria parasites, a dose required an amount of 450 to 550mg of S and 22.5 to 27.5mg of P to successfully achieve that (The USP 2004). However, the content of the program drugs determined were in the range of 440 – 480mg of S and 18.5 to 20.3mg of P (The United States Pharmacopeia, 2009). Thus, some level of protection was achieved (56%). If pregnant women obtain the good quality SP products, it would be expected that a significant level of protection would be observed.

5.9 Summary

The majority of the participants were married (92.8%), young reproductive women (<24=34.1%), who practised Islam (89.2%) and of urban residence (66.6%). Most of them were Dagombas (77.1%), who had no formal education (49.5%) and engaged in petty trading (39.4%).

In this study area, 45.1% and 47.6% were multiparous and multigravidae respectively and visited the ANC for the first time during the second trimester (53.9%) Majority (64.7%) of the pregnant women in the study area owned ITNs and 44.0% of the pregnant women were using it every evening. Almost half of the pregnant women (42.4%) took SP levels (at least 3 doses) up to the revised WHO acceptable doses of ≥3.

In the study setting, maternal educational background and occupation were risk factors for malaria parasitaemia at 36 weeks of gestation. The prevalence of late gestational parasitaemia (within the third trimester) varied with higher maternal education and having a reliable employment income such as being a salaried worker. This implies that, higher maternal

education and having a reliable source of employment income such as being a salaried worker may have contributed to reducing the risk of malaria infections during late pregnancy.

Irrespective of the trimester at which a woman made her first visit to ANC, pregnant women of all gravidities and parities remained vulnerable to malaria infections during the course of pregnancy. Older maternal age and education protected against peripheral parasitaemia. Combining the use of ITN and IPTp-SP provided synergistic protection against malaria in pregnancy.

Age (all age groups) and maternal level of education were risk factors for maternal anaemia in pregnancy. Late reporting to the ANC (third trimester) was associated with increased odds of anaemia in pregnancy at 36 weeks of pregnancy. Pregnant women with anaemia at 36 weeks of gestation had higher odds of detectable peripheral malaria parasitaemia at 36 weeks of gestation. Women between the ages of 30 to 34 years and lower level of maternal education protected against LBW deliveries. Secundigravidae, multigravidae and multiparity were strongly associated with lower odds of LBW compared to primigravidae, nulliparity and primiparity. Sociodemographic characteristics were not associated with stillbirth deliveries but being anaemic at the time of registration and babies with birth weight below 2.5kg increased the likelihood of stillbirth.

The first objective sought to address the effectiveness of IPTp-SP on maternal health by assessing the prevalence of malaria and anaemia among pregnant women who had taken three or more doses of IPTp-SP at 36 weeks of gestation. it was discovered that, the prevalence of malaria and anaemia were 16.9% and 54.1% respectively among pregnant women who had taken three or more doses of IPTp-SP.

The second object sought to address the effectiveness of IPTp-SP on birth outcomes by assessing the prevalence of LBW and stillbirth among pregnant women who had taken three or more doses of IPTp-SP. At the end of the study, 7.1 % and 7.4% birth weight and still birth were recorded among the study participants.

The third objective was to establish the association between different doses of IPTp-SP and maternal (malaria infection, anaemia) and neonatal (birth weight, stillbirth) outcomes. Logistic regression was used to determine the odds of association. It was found that, pregnant women who reported uptake of three or more doses were 56% less likely of having malaria (aOR 0.44; CI 0.27-0.70; p=0.001) and 63% less likely to give birth to babies with low weight (aOR 0.37; CI 0.21-0.68; p=0.001). However, the effect of taking three or more doses did not translate into protection against maternal anaemia (aOR 0.89; CI 0.55-1.45; p=0.65) and stillbirth delivery (aOR 1.15; CI 0.55-2.42; p=0.71).

The last objective the study addressed was to find the adequacy of the SP dispensed to pregnant women and it was discovered that, almost three-quarters of the drug analysed did not meet the accepted criteria by the USP NF 29. However, it was observed that a significant proportion of the program drugs contained the right amount of Sulphadoxine but inadequate amount of the pyrimethamine.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

This chapter summarises the key findings of the study and the recommendations that have been made to the various stakeholders and interested parties.

6.1 Conclusion

Majority of the participants were married young reproductive women, who practised Islam and of urban residence. Most of them were literate. Pregnant women of all ages had equal access to antenatal care (ANC) in the Tamale metropolis. ANC visits on the average commenced earlier during pregnancy around 15 weeks with fewer instances (3.2%) as late as 34 weeks. This may suggest that, during pregnancy, most women in the study setting region visit the ANC at periods where they cannot be served IPTp-SP and largely remained unprotected from malaria. It was found in the current study that; almost half of the pregnant women (42.4%) took SP levels (at least 3 doses) up to the revised WHO acceptable doses of three or more.

Objective I

The prevalence of malaria (16.9%), anaemia (54.1%) were high among the pregnant women despite the high reported use of three or more doses of SP (42.4%).

Objective II

Low birth weight (LBW) and stillbirth recorded in this study among the pregnant women who reported uptake of three or more doses of SP were 7.1% and 7.4% respectively.

Objective III

It could be concluded that, the 2014 IPTp-SP policy change from two SP doses to at least three SP doses in Ghana, significantly reduced malaria prevalence and averted low birth weight deliveries. However, the use of three or more doses of IPTp-SP intake did not provide protection against maternal anaemia and stillbirth. This might provide empirical evidence in the current study setting that using the two interventions provided no additive benefit against maternal anaemia in pregnancy and stillbirth.

Objective IV

Lastly, the analysis of the SP for its adequacy revealed a lower than the ideal doses of SP being given to the pregnant women during antenatal clinic in the Northern Ghana.

6.2 Recommendations

The Ministry of Health (MOH)

1. The Ministry of Health should strengthen interventions in the prevention of malaria and anaemia among pregnant women and adverse neonatal outcomes such as Low birth weight and Stillbirth.
2. The Ministry of Health should replicate this study in the other regions of Ghana.
3. There is the need to conduct further research to provide answers to the deficiencies related to the use of the intervention and the increased risk of anaemia during late gestation.
4. This study, therefore, recommends policy makers and health professionals especially at the antenatal clinics to institute measures that aim at mitigating policy implementation challenges, low coverage of at least three SP doses and poor documentation of IPTp services.

Food and Drug Authority (FDA)

5. Effective and regular monitoring of SP programme drugs by the Food and Drug Authority (FDA), Ghana should be done.

District Directorate of Health Service

6. There is the need to establish more antenatal clinics at the community level so that the volunteers could help in the administration of the IPTp-SP at the community level
7. The current study proposes that IPTp-SP educational lectures be intensified in the third trimester to enhance uptake in the later weeks of pregnancy (before 36 weeks) to improve protection against low-birth-weight deliveries.
8. After thorough evaluation, the DDHS should strengthened other measures that that help prevent anaemia in pregnancy such as intensifying education on three key areas: iron and folate uptake from conception of pregnancy until delivery to improve iron status; the need for women to complete their SP dosages to reinforce the protective potency accrued under the new IPTp-SP policy and counselling on nutrition at the antenatal clinic
9. IPTp-SP uptake targets could be set for antenatal clinics at the community level; i.e., at least 84% of the pregnant women in the community should complete eight maternity care appointments and take five SP doses annually.

Recommendations for future research

10. Further research is required to provide answers to the deficiencies related to the use of intervention (SP) and the increased risk of anaemia during late gestation and innovative methods that improve non-malarial anaemia required to supplement current standard remedies.

11. Future studies should investigate the events that might have contributed to the poor health status and the ensuing excess stillbirth rates (~11.00%) in primigravidae and nulliparous women and to determine the relation between malaria and antepartum or intrapartum stillbirth.
12. Appropriate research methods could properly profile the possible dose-dependent antimalarial depletion associated with IPTp-SP observed in the study area.

REFERENCES

Abeku, T. A., Helinski, M. E. H., Kirby, M. J., Kefyalew, T., Awano, T., Batisso, E., … Meek, S. R. (2015). Monitoring changes in malaria epidemiology and effectiveness of interventions in Ethiopia and Uganda : Beyond Garki Project baseline survey. *Malaria Journal*, 1–15. https://doi.org/10.1186/s12936-015-0852-7

Aberese-Ako, M., Magnussen, P., Ampofo, G. D., & Tagbor, H. (2019). Health system, socio-cultural, economic, environmental and individual factors influencing bed net use in the prevention of malaria in pregnancy in two Ghanaian regions. *Malaria Journal*, *18*(1), 363. https://doi.org/10.1186/s12936-019-2994-5

Abubakari, A., Agbozo, F., & Abiiro, G. A. (2017). *Factors associated with optimal antenatal care use in Northern region , Ghana Factors associated with optimal antenatal care use in*. *0242*(November). https://doi.org/10.1080/0363 0242.2017.1372842

Accrombessi, M., Yovo, E., Cottrell, G., Agbota, G., Gartner, A., Martin-Prevel, Y., … Briand, V. (2018). Cohort profile: Effect of malaria in early pregnancy on fetal growth in Benin (RECIPAL preconceptional cohort). *BMJ Open*, *8*(1), 1–13. https://doi.org/10.1136/bmjopen-2017-019014

Acheampong, K., Appiah, S., Baffour-Awuah, D., Saka Arhin, Y., & Author, C. (2018). Prevalence of Anemia among Pregnant Women Attending Antenatal Clinic of a Selected Hospital in Accra, Ghana. *International Journal of Health Sciences & Research (Www.Ijhsr.Org)*, *8*(January), 186. Retrieved from www.ijhsr.org

Action, A., To, P., & Preventable, E. (n.d.). *Every newborn 1*.

Adam, I., Khamis, A. H., & Elbashir, M. I. (2005). Prevalence and risk factors for anaemia in pregnant women of eastern Sudan. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *99*(10), 739–743. https://doi.org/10.1016/j.trstmh.2005.02.008

Adokiya, M. N., Aryeetey, R., Yost, M., Jones, A. D., & Wilson, M. L. (2019). *Determinants of anemia among pregnant women in northern Ghana*. 1–29.

Afeke, I., Mac-ankrah, L., Jamfaru, I., Amegan-aho, K. H., Mbroh, H. K., Lokpo, S. Y., … Orish, V. N. (2017). *Maternal Age , Low Birth Weight and Early Neonatal Death in Tertiary Hospital in the Volta Region of Ghana*. 254–262. https://doi.org/10.4236/ ojped.2017.74029

Afriyie, J., Bedu-addo, K., Asiamah, E. A., & Boateng, S. T. (2016). *Low birth weight among adolescents at Cape Coast Metropolitan Hospital of Ghana*. *5*(12), 4242–4247.

Agan, T., Ekabua, J. E., Udoh, A. E., Ekanem, E. I., Efiok, E. E., & Mgbekem, M. A. (2010). Prevalence of anemia in women with asymptomatic malaria parasitemia at first antenatal care visit at the University of Calabar Teaching Hospital, Calabar, Nigeria. *International Journal of Women's Health*, *2*(1), 229–233. https://doi.org/10.2147/ijwh.s11887

Agbozo, F., Lecturer, M. P., Abubakari, A., Der, J., Lecturer, M. P., & Jahn, A. (2016). *Prevalence of low birth weight , macrosomia and stillbirth and their relationship to associated maternal risk factors in Hohoe Municipality , Ghana*. *40*, 200–206.

Agomo, C. O., & Oyibo, W. A. (2013). Factors associated with risk of malaria infection among pregnant women in lagos, nigeria. *Infectious Diseases of Poverty*, *2*(1), 1–8.

https://doi.org/10.1186/2049-9957-2-19

Ahenkorah, B., Nsiah, K., & Baffoe, P. (2016). Sociodemographic and Obstetric Characteristics of Anaemic Pregnant Women Attending Antenatal Clinic in Bolgatanga Regional Hospital. *Scientifica, 2016*, 13–16. https://doi.org/10.1155/2016/4687342

Ahmed, R., Singh, N., Kuile, F. O., Bharti, P. K., Singh, P. P., Desai, M., … Terlouw, D. J. (2014). *Placental infections with histologically confirmed Plasmodium falciparum are associated with adverse birth outcomes in India : a cross-sectional study*. *13*(1), 1–12. https://doi.org/10.1186/1475-2875-13-232

Akotsen-Mensah, C. (2014). Management of insects in Ghana. *Journal of Ghana Science*, *11*(5), 201–242.

Alhassan, A., Ayikai, L. A., Alidu, H., & Yakong, V. N. (2016). *Stillbirths and associated factors in a peri-urban District in Ghana*. *5*, 23–31.

Alim, A., Bilal, N. E., Abass, A. E., Elhassan, E. M., Mohmmed, A. A., & Adam, I. (2015). Complement activation, placental malaria infection, and birth weight in areas characterized by unstable malaria transmission in central Sudan. *Diagnostic Pathology*, *10*(1), 4–9. https://doi.org/10.1186/s13000-015-0275-3

Amentie, M., Abera, M., & Abdulahi, M. (2015). *Utilization of Antenatal Care Services and Influencing Factors among Women of Child Bearing Age in Assosa District, Benishangul Gumuz Regional State, West Ethiopia*. *15*(2).

Amin, A. A., Snow, R. W., Kokwaro, G. O., & Amin, A. A. (2005). The quality of sulphadoxine-pyrimethamine and amodiaquine products in the Kenyan retail sector Europe PMC Funders Group. *J Clin Pharm Ther*, *30*(6), 559–565. https://doi.org/10.1111/j.1365-2710.2005.00685.x

Aminu, M., Unkels, R., Mdegela, M., Utz, B., Adaji, S., & van den Broek, N. (2014). Causes of and factors associated with stillbirth in low- and middle-income countries: a systematic literature review. *BJOG : An International Journal of Obstetrics and Gynaecology*, *121*, 141–153. https://doi.org/10.1111/1471-0528.12995

Ampofo, G. D., Tagbor, H., & Bates, I. (2018). Effectiveness of pregnant women's active participation in their antenatal care for the control of malaria and anaemia in pregnancy in Ghana: A cluster randomized controlled trial ISRTCTN88917252 ISRTCTN. *Malaria Journal*, *17*(1), 1–15. https://doi.org/10.1186/s12936-018-2387-1

Ankomah, A., Adebayo, S. B., Arogundade, E. D., Anyanti, J., Nwokolo, E., Ladipo, O., & Meremikwu, M. M. (2012). Determinants of insecticide-treated net ownership and utilization among pregnant women in Nigeria. *BMC Public Health*, *12*(1), 105. https://doi.org/10.1186/1471-2458-12-105

Anto, F., Agongo, I. H., Asoala, V., Awini, E., & Oduro, A. R. (2019). Intermittent Preventive Treatment of Malaria in Pregnancy: Assessment of the Sulfadoxine-Pyrimethamine Three-Dose Policy on Birth Outcomes in Rural Northern Ghana. *Journal of Tropical Medicine, 2019*. https://doi.org/10.1155/2019/6712685

Arinaitwe, E., Ades, V., Walakira, A., Ninsiima, B., Mugagga, O., Patil, T. S., … Dorsey, G. (2013a). *Intermittent Preventive Therapy with Sulfadoxine- Pyrimethamine for Malaria in Pregnancy : A Cross- Sectional Study from Tororo , Uganda*. *8*(9), 6–11. https://doi.org/10.1371/journal.pone.0073073

Arinaitwe, E., Ades, V., Walakira, A., Ninsiima, B., Mugagga, O., Patil, T. S., … Dorsey, G. (2013b). Intermittent Preventive Therapy with Sulfadoxine-Pyrimethamine for Malaria in Pregnancy: A Cross-Sectional Study from Tororo, Uganda. *PLoS ONE*, *8*(9). https://doi.org/10.1371/journal.pone.0073073

Asamoah, G. D., Gideon, D., Edzeamey, F. J., Ephraim, R. K., Sampong, B. B., Gborgblorvor, D., & Wiredu, O. K. (2018). Asymptomatic malaria and its effect on parturients who received intermittent preventive treatment, a cross sectional study of the Bekwai District Ghana. *GSC Biological and Pharmaceutical Sciences*, *4*(2), 007–016. https://doi.org/10.30574/gscbps.2018.4.2.0054

Asundep, N. N., Jolly, P. E., Carson, A. P., Turpin, C. A., Zhang, K., Wilson, N. O., … Tameru, B. (2014). *NIH Public Access*. *4*(5), 582–594. https://doi.org/10.9734/IJTDH/2014/7573.Effect

Axame, W. K., Kweku, M., Amelor, S., Kye-Duodu, G., Agboli, E., Agbemafle, I., … Newton, B. (2016). Ownership and Utilization of Long Lasting Insecticide Treated Nets (LLIN) and Factors Associated to Non-utilization Among Pregnant Women in Ho Municipality of Ghana. *Central African Journal of Public Health*, *2*(1), 35–42. https://doi.org/10.11648/j.cajph.20160201.16

Bam, V. B. (2009). *Control of pregnancy-associated malaria through community involvement in rural Ghana By*. (June).

Baqui, A. H., Mitra, D. K., Begum, N., Hurt, L., Soremekun, S., Edmond, K., … Manu, A. (2016). *Neonatal mortality within 24 hours of birth in six low- and lower-middle-income countries*. (July 2015), 752–758.

Baraka, V., Ishengoma, D. S., Fransis, F., Minja, D. T. R., Madebe, R. A., Ngatunga, D., & Van Geertruyden, J. P. (2015). High-level Plasmodium falciparum sulfadoxine-pyrimethamine resistance with the concomitant occurrence of septuple haplotype in Tanzania. *Malaria Journal*, *14*(1), 1–9. https://doi.org/10.1186/s12936-015-0977-8

Bardají, A., Sigauque, B., Bruni, L., Romagosa, C., Sanz, S., Mabunda, S., … Menéndez, C. (2008). Clinical malaria in African pregnant women. *Malaria Journal*, *7*, 1–7. https://doi.org/10.1186/1475-2875-7-27

Bardajı, A., Sigauque, B., Sanz, S., Aponte, J. J., Mene, C., & Alonso, P. L. (2010). *Malaria Prevention with IPTp during Pregnancy Reduces Neonatal Mortality*. *5*(2), 1–6. https://doi.org/10.1371/journal.pone.0009438

Berry, I., Walker, P., Tagbor, H., Bojang, K., Coulibaly, S. O., Kayentao, K., … Cairns, M. (2018). Seasonal dynamics of malaria in pregnancy in West Africa: Evidence for carriage of infections acquired before pregnancy until first contact with antenatal care. *American Journal of Tropical Medicine and Hygiene*, *98*(2), 534–542. https://doi.org/10.4269/ajtmh.17-0620

Black, R. E., Alderman, H., Bhutta, Z. A., Gillespie, S., Haddad, L., Horton, S., … Webb, P. (2013). Maternal and child nutrition: building momentum for impact. *The Lancet*, *382*(9890), 372–375. https://doi.org/10.1016/S0140-6736(13)60988-5

Boudová, S., Divala, T., Mawindo, P., Cohee, L., Kalilani-Phiri, L., Thesing, P., … Laufer, M. K. (2015). The prevalence of malaria at first antenatal visit in Blantyre, Malawi declined following a universal bed net campaign. *Malaria Journal*, *14*(1). https://doi.org/10.1186/s12936-015-0945-3

Boudová, S., Divala, T., Mawindo, P., Cohee, L., Phiri, L. K., Thesing, P., … Laufer, M. K. (2015). The prevalence of malaria at first antenatal visit in Blantyre , Malawi declined following a universal bed net campaign. *Malaria Journal*, 1–6. https://doi.org/10.1186/s12936-015-0945-3

Bouyou-akotet, M. K., Nzenze-afene, S., Ngoungou, E. B., Kendjo, E., Owono-medang, M., Obono-obiang, G., … Kombila, M. (2010). *Burden of Malaria during Pregnancy at the Time of IPTp / SP Implementation in Gabon*. *82*(2), 202–209. https://doi.org/10.4269/ajtmh.2010.09-0267

Brabin, B. J., & Johnson, P. M. (2005). Placental malaria and pre-eclampsia through the looking glass backwards? *Journal of Reproductive Immunology*, *65*(1), 1–15. https://doi.org/10.1016/j.jri.2004.09.006

Cates, J. E., Westreich, D., Unger, H. W., Bauserman, M., Adair, L., Cole, S. R., … Lusingu, J. P. A. (2018). Intermittent preventive therapy in pregnancy and incidence of low birth weight in malaria-endemic countries. *American Journal of Public Health*, *108*(3), 399–406. https://doi.org/10.2105/AJPH.2017.304251

Chang, Y. K. Y. W. P. (2002). *Phys i cal and Social Pre dic tors for Pre-Term Births and Low Birth Weight Infants in Tai wan*. *10*(2), 83–89.

Chen, I., Clarke, S. E., Gosling, R., Hamainza, B., & Killeen, G. (2016). *" Asymptomatic " Malaria : A Chronic and Debilitating Infection That Should Be Treated*. 1–11. https://doi.org/10.1371/journal.pmed.1001942

Christou, A., Dibley, M. J., Hafiz, M., Adela, R., Murtaza, S., Hofiani, S., … Greenow, C. R. (2019). *Understanding country - specific determinants of stillbirth using household surveys : The case of Afghanistan*. (November 2018), 28–44. https://doi.org/10.1111/ppe.12530

Christou, A., Dibley, M. J., & Raynes-greenow, C. (2017). *Beyond counting stillbirths to understanding their determinants in low- and middle-income countries : a systematic assessment of stillbirth data availability in household surveys*. *22*(3), 294–311. https://doi.org/10.1111/tmi.12828

Cisse, M., Sangare, I., Lougue, G., Bamba, S., Bayane, D., & Guiguemde, R. T. (2014). Prevalence and risk factors for Plasmodium falciparum malaria in pregnant women attending antenatal clinic in Bobo-Dioulasso (Burkina Faso). *BMC Infectious Diseases*, *14*(1), 1–7. https://doi.org/10.1186/s12879-014-0631-z

Clerk, C. A., Bruce, J., Greenwood, B., & Chandramohan, D. (2009a). The epidemiology of malaria among pregnant women attending antenatal clinics in an area with intense and highly seasonal malaria transmission in northern Ghana. *Tropical Medicine & International Health : TM & IH*, *14*(6), 688–695. https://doi.org/10.1111/j.1365-3156.2009.02280.x

Clerk, C. A., Bruce, J., Greenwood, B., & Chandramohan, D. (2009b). The epidemiology of malaria among pregnant women attending antenatal clinics in an area with intense and highly seasonal malaria transmission in northern Ghana. *Tropical Medicine and International Health*, *14*(6), 688–695. https://doi.org/10.1111/j.1365-3156.2009.02280.x

Cohee, L. M., Kalilani-phiri, L., Boudova, S., Joshi, S., Mukadam, R., Seydel, K. B., … Laufer, M. K. (2014). *Submicroscopic malaria infection during pregnancy and the impact of intermittent preventive treatment*. *13*(1), 1–9. https://doi.org/10.1186/1475-

2875-13-274

Cohee, L. M., Phiri, L. K., Mawindo, P., Joshi, S., Adams, M., Kenefic, L., … Laufer, M. K. (2016). Parasite dynamics in the peripheral blood and the placenta during pregnancy - associated malaria infection. *Malaria Journal*, 1–8. https://doi.org/10.1186/s12936-016-1541-x

Consortium, C., & Alessandro, D. (2018). *Community-based Malaria Screening and Treatment for Pregnant Women Receiving Standard Intermittent Preventive Treatment With Sulfadoxine-Pyrimethamine : A Multicenter (The Gambia , Burkina Faso , and Benin) Cluster-randomized Controlled Trial*. https://doi.org/10.1093/cid/ciy522

Cot, M., Abel, L., Roisin, A., Barro, D., Yada, A., Carnavale, P., & Feingold, J. (1993). Risk factors of malaria infection during pregnancy in Burkina Faso. *The American Society of Tropical Medicine and Hygiene*, *48*(3), 358–364.

Cottrell, G., Mary, J. Y., Barro, D., & Cot, M. (2007). The importance of the period of malarial infection during pregnancy on birth weight in tropical Africa. *American Journal of Tropical Medicine and Hygiene*, *76*(5), 849–854. https://doi.org/10.4269/ajtmh.2007.76.849

Cutland, C. L., Lackritz, E. M., Mallett-moore, T., Bardají, A., Chandrasekaran, R., Lahariya, C., & Imran, M. (2017). Low birth weight : Case definition & guidelines for data collection , analysis , and presentation of maternal immunization safety data. *Vaccine*, *35*(48), 6492–6500. https://doi.org/10.1016/j.vaccine.2017.01.049

D'Almeida, T. C., Sadissou, I., Milet, J., Cottrell, G., Mondière, A., Avokpaho, E., … Garcia, A. (2017). Soluble human leukocyte antigen -G during pregnancy and infancy in Benin: Mother/child resemblance and association with the risk of malaria infection and low birth weight. *PLoS ONE*, *12*(2). https://doi.org/10.1371/journal.pone.0171117

Dahiru, T., & Oche, O. M. (2015). Determinants of antenatal care, institutional delivery and postnatal care services utilization in Nigeria. *Pan African Medical Journal*. https://doi.org/10.11604/pamj.2015.21.321.6527

Darko, A. G., Prince, A., Jonathan, E. F., & Kd, E. R. (2018). *Asymptomatic malaria and its effect on parturients who received intermittent preventive treatment , a cross sectional study of the Bekwai District Ghana GSC Biological and Pharmaceutical Sciences Asymptomatic malaria and its effect on parturients who rece*. (August). https://doi.org/10.30574/gscbps.2018.4.2.0054

Dégardin, K., Roggo, Y., & Margot, P. (2014). Understanding and fighting the medicine counterfeit market. *Journal of Pharmaceutical and Biomedical Analysis*. https://doi.org/10.1016/j.jpba.2013.01.009

Dellicour, S., Mcgready, R., Tinto, H., Mosha, D., Manyando, C., Rulisa, S., … Stergachis, A. (2017). *First-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia : A meta-analysis of observational studies*.

Desai, M., & Dellicour, S. (2012). Effects of malaria and its treatment in early pregnancy. *The Lancet Infectious Diseases*, *12*(5), 359–360. https://doi.org/10.1016/S1473-3099(11)70345-0

Desai, M., Gutman, J., Anne, L., Otieno, K., Juma, E., Ouma, P., … Williamson, J. (2016).

HHS Public Access. *386*(10012), 2507–2519. https://doi.org/10.1016/S0140-6736(15)00310-4.Intermittent

Desai, M., Gutman, J., Taylor, S. M., Wiegand, R. E., Khairallah, C., Kayentao, K., … Otieno, K. (2017). HHS Public Access. *Desai, Meghna Gutma*, *62*(3), 323–333. https://doi.org/10.1093/cid/civ881.Impact

Desai, M., Gutman, J., Taylor, S. M., Wiegand, R. E., Khairallah, C., Kayentao, K., … Ter Kuile, F. O. (2016). Impact of sulfadoxine-pyrimethamine resistance on effectiveness of intermittent preventive therapy for Malaria in pregnancy at clearing infections and preventing low birth weight. *Clinical Infectious Diseases*, *62*(3), 323–333. https://doi.org/10.1093/cid/civ881

Desai, M., ter Kuile, F. O., Nosten, F., McGready, R., Asamoa, K., Brabin, B., & Newman, R. D. (2007). Epidemiology and burden of malaria in pregnancy. *Lancet Infectious Diseases*, *7*(2), 93–104. https://doi.org/10.1016/S1473-3099(07)70021-X

Dfid. (2010). Malaria : Burden and Interventions Evidence Overview. *Department for International Development*, (December), 1–222. Retrieved from http://www.dfid.gov.uk /Documents/prd/malaria-evidence-paper.pdf

Dibben, C., Sigala, M., & Macfarlane, A. (2006). Area deprivation, individual factors and low birth weight in England: Is there evidence of an "area effect"? *Journal of Epidemiology and Community Health*, *60*(12), 1053–1059. https://doi.org/10.1136/jech. 2005.042853

Diema, K. K., Dodam, K. K., Aarah-Bapuah, M., & Asibi, A. J. (2017). Barriers to sustained use of the insecticide treated bed net in the upper east region of Ghana. *International Journal Of Community Medicine And Public Health*, *4*(2), 500. https://doi.org/10.18203/2394-6040.ijcmph20170280

Dimasuay, K. G., Gong, L., Rosario, F., Mcbryde, E., Spelman, T., Glazier, J., … Boeuf, P. (2017). *Impaired placental autophagy in placental malaria*. 1–20.

Elzahaf, R., & Omar, M. (2016). Prevalence of anaemia among pregnant women in Derna city, Libya. *International Journal of Community Medicine and Public Health*, *3*(7), 1915–1920. https://doi.org/10.18203/2394-6040.ijcmph20162065

Esu, E., Berens-Riha, N., Pritsch, M., Nwachuku, N., Loescher, T., & Meremikwu, M. (2018). Intermittent screening and treatment with artemether-lumefantrine versus intermittent preventive treatment with sulfadoxine-pyrimethamine for malaria in pregnancy: A facility-based, open-label, non-inferiority trial in Nigeria. *Malaria Journal*, *17*(1). https://doi.org/10.1186/s12936-018-2394-2

Feng, G., Simpson, J. A., Chaluluka, E., Molyneux, M. E., & Rogerson, S. J. (2010). *Decreasing Burden of Malaria in Pregnancy in Malawian Women and Its Relationship to Use of Intermittent Preventive Therapy or Bed Nets*. *5*(8). https://doi.org/10.1371/journal.pone.0012012

Feresu, S. A., Harlow, S. D., & Woelk, G. B. (2015). Risk factors for low birthweight in Zimbabwean women: A secondary data analysis. *PLoS ONE*, *10*(6), 1–17. https://doi.org/10.1371/journal.pone.0129705

Filler, S. J., Kazembe, P., Thigpen, M., Macheso, A., Parise, M. E., Newman, R. D., … Hamel, M. (2006). Randomized Trial of 2-Dose versus Monthly Sulfadoxine-

Pyrimethamine Intermittent Preventive Treatment for Malaria in HIV-Positive and HIV-Negative Pregnant Women in Malawi. *The Journal of Infectious Diseases*, *194*(3), 286–293. https://doi.org/10.1086/505080

Finkelstein, J. L., Mehta, S., Duggan, C. P., Aboud, S., Kupka, R., Msamanga, G. I., & Fawzi, W. W. (2011). *Predictors of anaemia and iron deficiency in HIV-infected pregnant women in Tanzania : a potential role for vitamin D and parasitic infections*. *15*(5), 928–937. https://doi.org/10.1017/S1368980011002369

Fitri, L. E., Jahja, N. E., Huwae, I. R., Nara, M. B., & Berens-Riha, N. (2014). Congenital malaria in newborns selected for low birth-weight, anemia, and other possible symptoms in maumere, Indonesia. *Korean Journal of Parasitology*, *52*(6), 639–644. https://doi.org/10.3347/kjp.2014.52.6.639

Fleming, A. F. (1989). Tropical obstetrics and gynaecology. 1. Anaemia in pregnancy in tropical Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *83*(4), 441–448. https://doi.org/https://doi.org/10.1016/0035-9203(89)90241-1

Florey, L. (2013). *Determinants of effective IPTp Delivery DHS ANALYTICAL STUDIES 39*. (September).

Fosu, M. O., Jackson, O. A. Y., & Twum, S. B. (2016a). *Application of Area to Point Kriging to Low Birth Weight Incidence in Ghana*. *15*(5), 1–9. https://doi.org/10.9734/BJAST/2016/25752

Fosu, M. O., Jackson, O. A. Y., & Twum, S. B. (2016b). *Bayesian and Frequentist Comparison : An Application to Low Birth Weight Babies in Ghana*. *16*(2), 1–15. https://doi.org/10.9734/BJAST/2016/25753

Francis, S. E., Malkov, V. A., Oleinikov, A. V., Rossnagle, E., Wendler, J. P., Mutabingwa, T. K., … Duffy, P. E. (2007). Six genes are preferentially transcribed by the circulating and sequestered forms of Plasmodium falciparum parasites that infect pregnant women. *Infection and Immunity*, *75*(10), 4838–4850. https://doi.org/10.1128/IAI.00635-07

Fried, M., & Duffy, P. E. (2017). *Malaria during Pregnancy*.

Fried, M., Kurtis, J. D., Swihart, B., Morrison, R., Pond-Tor, S., Barry, A., … Duffy, P. E. (2018). Antibody levels to recombinant VAR2CSA domains vary with Plasmodium falciparum parasitaemia, gestational age, and gravidity, but do not predict pregnancy outcomes. *Malaria Journal*, *17*(1), 1–14. https://doi.org/10.1186/s12936-018-2258-9

Garner, P., & Gülmezoglu, A. M. (2006). Drugs for preventing malaria in pregnant women. *The Cochrane Database of Systematic Reviews*, (4), CD000169. https://doi.org/10.1002/14651858.CD000169.pub2

Gavina, K., Gnidehou, S., Arango, E., Hamel-martineau, C., Mitran, C., & Agudelo, O. (2018). *crossm Clinical Outcomes of Submicroscopic Infections and Correlates of Protection of VAR2CSA Antibodies in a Longitudinal Study of Pregnant Women in Colombia*. *86*(4), 1–14.

Ghana Health Service. (2018). 2017 Annual Report National Malaria Control Programme. *Advances in Cancer Research*. https://doi.org/10.1016/S0065-230X(05)94002-5

Ghana Statistical Service. (2011). Ghana Multiple Indicator Cluster Survey with an Enhanced Malaria Module and Biomarker. In *Final Report*. https://doi.org/10.1017/CBO9781107415324.004

Global Burden of Disease Study 2017. (2017). Global Burden of Disease Study 2017. *The Lancet*.

Goldenberg, R. L., & Thompson, C. (n.d.). *The infectious origins of stillbirth*. 861–873. https://doi.org/10.1067/S0002-9378(03)00470-8

Gorard, S. (2010). *SAGE Handbook of Mixed Methods in Social & Behavioral Research* (2nd ed.). 2nd ed. https://doi.org/10.4135/9781506335193

Gutman, J., Mwandama, D., Wiegand, R. E., Ali, D., Mathanga, D. P., & Skarbinski, J. (2013a). Effectiveness of intermittent preventive treatment with sulfadoxine-pyrimethamine during pregnancy on maternal and birth outcomes in Machinga District, Malawi. *Journal of Infectious Diseases*, *208*(6), 907–916. https://doi.org/10.1093/infdis/jit276

Gutman, J., Mwandama, D., Wiegand, R. E., Ali, D., Mathanga, D. P., & Skarbinski, J. (2013b). Effectiveness of intermittent preventive treatment with sulfadoxine-pyrimethamine during pregnancy on maternal and birth outcomes in Machinga District, Malawi. *Journal of Infectious Diseases*, *208*(6), 907–916.

Guyatt, H. L., & Snow, R. W. R. (2004). Impact of malaria during pregnancy on low birth weight in sub-Saharan Africa. *Clinical Microbiology Reviews*, *17*(4), 760–769. https://doi.org/10.1128/CMR.17.4.760

Hamer, D. H., Mwanakasale, V., Macleod, W. B., Chalwe, V., Mukwamataba, D., Champo, D., … Gill, C. J. (2007). Two-dose versus monthly intermittent preventive treatment of malaria with sulfadoxine-pyrimethamine in HIV-seropositive pregnant Zambian women. *The Journal of Infectious Diseases*, *196*(11), 1585–1594. https://doi.org/10.1086/522142

Haque, S. M. R., Tisha, S., & Huq, N. (2015). *Poor Birth Size a Badge of Low Birth Weight Accompanying Less Antenatal Care in Bangladesh with Substantial Divisional Variation : Evidence from BDHS - 2011*. *5*(6), 184–191. https://doi.org/10.5923/j.phr.20150506.03

Harrington, W. E., Mutabingwa, T. K., Kabyemela, E., Fried, M., & Duffy, P. E. (2011). *Intermittent Treatment to Prevent Pregnancy Malaria Does Not Confer Benefit in an Area of Widespread Drug Resistance*. *53*, 2–8. https://doi.org/10.1093/cid/cir376

Hartman, T. K., Rogerson, S. J., & Fischer, P. R. (2010). The impact of maternal malaria on newborns. *Annals of Tropical Paediatrics*, *30*(4), 271–282. https://doi.org/10.1179/146532810X12858955921032

Hartman TK, Rogerson SJ, F. P. (2010). The impact of maternal malaria on newborns. *Ann Trop Paediatr. 2010;30(4):271-82.*, *30(4):271-*.

Haruna, U., Dandeebo, G., & Galaa, S. Z. (2019). *Improving Access and Utilization of Maternal Healthcare Services through Focused Antenatal Care in Rural Ghana : A Qualitative Study*. *2019*.

Health, A. (2013). *WHO Policy Brief for the Implementation of Intermittent Preventive Treatment of Malaria in Pregnancy using Sulfadoxine-Pyrimethamine (IPTp-SP)*. (October 2012), 1–12.

Helegbe, G. K., Aryee, P. A., Mohammed, B. S., Wemakor, A., Kolbila, D., Abubakari, A., … Ofosu, E. (2018). *Seroprevalence of Malaria and Hepatitis B Coinfection among Pregnant Women in Tamale Metropolis of Ghana : A Cross-Sectional Study*. *2018*.

Hill, J., Kayentao, K., Touré, M., Diarwara, S., Bruce, J., Smedley, J., … Webster, J. (2014). Effectiveness of antenatal clinics to deliver intermittent preventive treatment and insecticide treated nets for the control of malaria in pregnancy in Mali: A household survey. *PLoS ONE*, *9*(3). https://doi.org/10.1371/journal.pone.0092102

Hommerich, L., Oertzen, C. Von, Bedu-addo, G., Holmberg, V., Acquah, P. A., Eggelte, T. A., … Mockenhaupt, F. P. (2007). *implementation of intermittent preventive treatment in pregnancy*. *8*, 1–8. https://doi.org/10.1186/1475-2875-6-144

Hommerich, L., Von Oertzen, C., Bedu-Addo, G., Holmberg, V., Acquah, P. A., Eggelte, T. A., … Mockenhaupt, F. P. (2007). Decline of placental malaria in southern Ghana after the implementation of intermittent preventive treatment in pregnancy. *Malaria Journal*, *6*, 1–8. https://doi.org/10.1186/1475-2875-6-144

Hq, W. H. O. (2012). *WHO Evidence Review Group : Intermittent Preventive Treatment of malaria in pregnancy (IPTp) with Sulfadoxine - Pyrimethamine (SP)*. (September), 1–17.

Huynh, B. T., Fievet, N., Gbaguidi, G., Dechavanne, S., Borgella, S., Guézo-Mévo, B., … Cot, M. (2011). Influence of the timing of malaria infection during pregnancy on birth weight and on maternal anemia in Benin. *American Journal of Tropical Medicine and Hygiene*, *85*(2), 214–220. https://doi.org/10.4269/ajtmh.2011.11-0103

Ibrahim, H., Maya, E. T., Issah, K., Apanga, P. A., Bachan, E. G., & Noora, C. L. (2017). Factors influencing uptake of intermittent preventive treatment of malaria in pregnancy using sulphadoxine pyrimethamine in sunyani municipality, Ghana. *Pan African Medical Journal*, *28*, 1–12. https://doi.org/10.11604/pamj.2017.28.122.12611

Idowu, O. A., Mafiana, C. F., & Dapo, S. (n.d.). *Anaemia in pregnancy : a survey of pregnant women in Abeokuta ,*. 295–299.

Idris, Z., Chan, C. W., Kongere, J., Gitaka, J., Logedi, J., Omar, A., … Isozumi, R. (2016). High and Heterogeneous Prevalence of Asymptomatic and Sub-microscopic Malaria Infections on Islands in Lake Victoria , Kenya. *Nature Publishing Group*, (October), 1–13. https://doi.org/10.1038/srep36958

Igboeli, N U, Ukwe, C. V, & Aguwa, C. N. (2017). Effect of antimalarial prophylaxis with sulphadoxine-pyrimethamine on pregnancy outcomes in Nsukka, Nigeria. *Malaria World Journal*, *8*(3). Retrieved from https://malariaworld.org/sites/default/files/mwjournal/article/MWJ2017_8_3_0.pdf

Igboeli, Nneka U., Adibe, M. O., Ukwe, C. V., & Aguwa, C. N. (2018a). Comparison of the effectiveness of two-dose versus three-dose sulphadoxine-pyrimethamine in preventing adverse pregnancy outcomes in Nigeria. *Journal of Vector Borne Diseases*, *55*(3), 189–196. https://doi.org/10.4103/0972-9062.249128

Igboeli, Nneka U., Adibe, M. O., Ukwe, C. V., & Aguwa, N. C. (2018b). Prevalence of Low Birth Weight before and after Policy Change to IPTp-SP in Two Selected Hospitals in Southern Nigeria: Eleven-Year Retrospective Analyses. *BioMed Research International*, *2018*. https://doi.org/10.1155/2018/4658106

Influence of Antenatal Care on the Haematocrit Value of Pregnant Nigerian Igbo Women. (2002). *Tropical Journal of Obstetrics and Gynaecology*, Vol. 19, pp. 68-70–70.

Isah, D. A., Isah, A. Y., Thairu, Y., & Agida, E. T. (2017). Effectiveness of 3 doses of Intermittent Preventive Therapy with Sulphadoxine-Pyrimethamine in Pregnancy. *Annals of Medical and Health Sciences Research*, *7*(1), 52–57.

Ishaque, S., Yakoob, M. Y., Imdad, A., Goldenberg, R. L., Eisele, T. P., & Bhutta, Z. A. (2011). *Effectiveness of interventions to screen and manage infections during pregnancy on reducing stillbirths : a review*. *11*(Suppl 3). https://doi.org/10.1186/1471-2458-11-S3-S3

Iyoke, C., Lawani, L., Onoh, R., Okeke, E., & Onyebuchi, A. (2014). Adherence to intermittent preventive treatment for malaria with sulphadoxine-pyrimethamine and outcome of pregnancy among parturients in South East Nigeria. *Patient Preference and Adherence*, *8*, 447. https://doi.org/10.2147/PPA.S61448

Jäckle, M. J., Blumentrath, C. G., Zoleko, R. M., Akerey-Diop, D., Mackanga, J. R., Adegnika, A. A., … Ramharter, M. (2013). Malaria in pregnancy in rural Gabon: A cross-sectional survey on the impact of seasonality in high-risk groups. *Malaria Journal*, *12*(1), 1–6. https://doi.org/10.1186/1475-2875-12-412

Jones, A. (2019). *Investigating the Association between Socio-economic Position and Stillbirth in Brazil and the UK*. (January).

Kalilani, L., Mofolo, I., Chaponda, M., Rogerson, S. J., & Meshnick, S. R. (2010). The effect of timing and frequency of Plasmodium falciparum infection during pregnancy on the risk of low birth weight and maternal anemia. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *104*(6), 416–422. https://doi.org/10.1016/j.trstmh.2010.01.013

Kapisi, J., Kakuru, A., Jagannathan, P., Muhindo, M. K., Natureeba, P., Awori, P., … Gaw, S. L. (2017). Relationships between infection with Plasmodium falciparum during pregnancy, measures of placental malaria, and adverse birth outcomes NCT02163447 NCT. *Malaria Journal*, *16*(1), 1–11. https://doi.org/10.1186/s12936-017-2040-4

Kassa, G. M., Muche, A. A., Berhe, A. K., & Fekadu, G. A. (2017). *Prevalence and determinants of anemia among pregnant women in Ethiopia ; a systematic review and meta-analysis*. 1–9. https://doi.org/10.1186/s12878-017-0090-z

Kaur, P., Bhatia, A., Midha, K., & Debnath, M. (2017). Malaria: A Cause of Anemia and Its Effect on Pregnancy. *World Journal of Anemia*, *1*(2), 51–62. https://doi.org/10.5005/jp-journals-10065-0012

Kayentao, K., Garner, P., van Eijk, A. M., Naidoo, I., Roper, C., Mulokozi, A., … ter Kuile, F. O. (2013). 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: systematic review and meta-analysis. *Jama*, *309*(6), 594–604. https://doi.org/10.1001/jama.2012.216231

Kotepui, M., Piwkham, D., PhunPhuech, B., Phiwklam, N., Chupeerach, C., & Duangmano, S. (2015). Effects of malaria parasite density on blood cell parameters. *PLoS ONE*, *10*(3), 1–11. https://doi.org/10.1371/journal.pone.0121057

Kweku, M., Ofori, M., Takramah, W., Axame, W. K., Owusu, R., Adjuik, M., & Tarkang, E. (2017). *Prevalence of malaria and anaemia among pregnant women attending Antenatal Care Clinic in the Hohoe Municipality of Ghana*.

Lalani, M., Kaur, H., Mohammed, N., Mailk, N., van Wyk, A., Jan, S., … Leslie, T. (2015). Substandard antimalarials available in Afghanistan: a case for assessing the quality of drugs in resource poor settings. *The American Journal of Tropical Medicine and Hygiene*. https://doi.org/10.4269/ajtmh.14-0394

Larysa, A., Yao, T., Richard, G., Samuel, O., Damian, F., John, J., & Kweku, Q. I. (2017). *Journal of Pregnancy and Child Maternal Demographic and Placental Risk Factors in Term Low Birth Weight in*. *4*(3). https://doi.org/10.4172/2376-127X.1000325

Lawn, J. E., Blencowe, H., Waiswa, P., Amouzou, A., Mathers, C., Hogan, D., … Draper, E. S. (2016). Stillbirths: Rates, risk factors, and acceleration towards 2030. *The Lancet*, *387*(10018), 587–603. https://doi.org/10.1016/S0140-6736(15)00837-5

Leigh, J. P. (1983). Direct and indirect effects of education on health. *Social Science and Medicine*, *17*(4), 227–234. https://doi.org/10.1016/0277-9536(83)90120-X

Letamo, G., & Majelantle, R. G. (2001). *FACTORS INFLUENCING LOW BIRTH*. 391–403.

Liu, Y., Liu, J., Ye, R., Ren, A., Li, S., & Li, Z. (2008). Association of education and the occurrence of low birthweight in rural southern China during the early and late 1990s. *American Journal of Public Health*, *98*(4), 687–691. https://doi.org/10.2105/AJPH.2006.088716

Lufele, E., Umbers, A., Ordi, J., Ome-Kaius, M., Wangnapi, R., Unger, H., … Rogerson, S. (2017). Risk factors and pregnancy outcomes associated with placental malaria in a prospective cohort of Papua New Guinean women. *Malaria Journal*, *16*(1), 427. https://doi.org/10.1186/s12936-017-2077-4

Lugaajju, A., Reddy, S. B., Wahlgren, M., Kironde, F., & Persson, K. E. M. (2017). Development of Plasmodium falciparum specific naïve, atypical, memory and plasma B cells during infancy and in adults in an endemic area. *Malaria Journal*, *16*(1), 1–11. https://doi.org/10.1186/s12936-017-1697-z

Luxemburger, C., Mcgready, R., Kham, A., Morison, L., Cho, T., White, N. J., & Nosten, F. (2018). *Effects of Malaria during Pregnancy on Infant Mortality in an Area of Low Malaria Transmission*. *154*(5).

Mace, K. E., Chalwe, V., Katalenich, B. L., Nambozi, M., Mubikayi, L., Mulele, C. K., … Tan, K. R. (2015). Evaluation of sulphadoxine-pyrimethamine for intermittent preventive treatment of malaria in pregnancy: a retrospective birth outcomes study in Mansa, Zambia. *Malar J*, *14*(1), 69. https://doi.org/10.1186/s12936-015-0576-8

malaria. (2014).

Manirakiza, A., Serdouma, E., Ngbalé, R. N., Moussa, S., Gondjé, S., Degana, R. M., … Sepou, A. (2017). *A brief review on features of falciparum malaria during preg- nancy*. *8*, 27–29. https://doi.org/10.4081/jphia.2017

Manu, G., Boamah-Kaali, E. A., Febir, L. G., Ayipah, E., Owusu-Agyei, S., & Asante, K. P. (2017). Low Utilization of Insecticide-Treated Bed Net among Pregnant Women in the Middle Belt of Ghana. *Malaria Research and Treatment*, *2017*, 1–7. https://doi.org/10.1155/2017/7481210

Mayor, A., Dobaño, C., Nhabomba, A., Guinovart, C., Jiménez, A., Manaca, M. N., … Alonso, P. L. (2018). IgM and IgG against Plasmodium falciparum lysate as surrogates of malaria exposure and protection during pregnancy. *Malaria Journal*, *17*(1), 1–10.

https://doi.org/10.1186/s12936-018-2331-4

Mbu, R. E., Takang, W. A., Fouedjio, H. J., Fouelifack, F. Y., Tumasang, F. N., & Tonye, R. (2014a). *Clinical malaria among pregnant women on combined insecticide treated nets (ITNs) and intermittent preventive treatment (IPTp) with sulphadoxine-pyrimethamine in Yaounde , Cameroon*. *14*(1), 1–6. https://doi.org/10.1186/1472-6874-14-68

Mbu, R. E., Takang, W. A., Fouedjio, H. J., Fouelifack, F. Y., Tumasang, F. N., & Tonye, R. (2014b). Clinical malaria among pregnant women on combined insecticide treated nets (ITNs) and intermittent preventive treatment (IPTp) with sulphadoxine-pyrimethamine in Yaounde, Cameroon. *BMC Women's Health*, *14*(1), 68. https://doi.org/10.1186/1472-6874-14-68

Mbuagbaw, L., Medley, N., Aj, D., Richardson, M., & K, H. G. (2016). *Health system and community level interventions for improving antenatal care coverage and health outcomes (Review)*. (12). https://doi.org/10.1002/14651858.CD010994.pub2.www .cochranelibrary.com

McClure EM, Goldenberg RL, Dent AE, M. S. (2013). A systematic review of the impact of malaria prevention in pregnancy on low birth weight and maternal anemia. *Journal of Gynecology and Obstetrics*, *121*(2).

McGready, R., Lee, S. J., Wiladphaingern, J., Ashley, E. A., Rijken, M. J., Boel, M., … Nosten, F. H. (2012). Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: A population-based study. *The Lancet Infectious Diseases*, *12*(5), 388–396. https://doi.org/10.1016/S1473-3099(11)70339-5

McLEAN, A. R. D., ATAIDE, R., SIMPSON, J. A., BEESON, J. G., & FOWKES, F. J. I. (2015). Malaria and immunity during pregnancy and postpartum: a tale of two species. *Parasitology*, *142*(8), 999–1015. https://doi.org/10.1017/s0031182015000074

McLean, A. R. D., Stanisic, D., McGready, R., Chotivanich, K., Clapham, C., Baiwog, F., … Fowkes, F. J. I. (2017). P. falciparum infection and maternofetal antibody transfer in malaria-endemic settings of varying transmission. *PLoS ONE*, *12*(10), 1–18. https://doi.org/10.1371/journal.pone.0186577

Medina, A. C., Tobo, A., Posada, M., Campillo, A., Gonza, I. J., & Ding, X. (2018). *Performance of a highly sensitive rapid diagnostic test (HS-RDT) for detecting malaria in peripheral and placental blood samples from pregnant women in Colombia*. 1–14.

Meiriza, W. (2018). *The Correlation of Maternal Factors and The Quality of Antenatal Care Services With Low Birth Weight Babies In Health Facilities Level I*. *2*(1).

Mikomangwa, W. P., Oms, M., Aklillu, E., & Kamuhabwa, A. A. R. (2019). *Adverse birth outcomes among mothers who received intermittent preventive treatment with Sulphadoxine- Pyrimethamine in the low malaria transmission region*. *1*, 1–11.

Mohammed, K., Shaban, I., Al-akour, N., & Kassab, M. (2019). Low birth weight in Jordan : a hospital-based study. *The Journal of Maternal-Fetal & Neonatal Medicine*, *0*(0), 1–6. https://doi.org/10.1080/14767058.2019.1567707

Moise, K. K., Ndala, B., Blood, D., Mukendi, M., René, J., Paul, C. M., … Michel, K. N. (2017). *Risk Factors of Low Birth Weight in Mbujimayi City , Democratic Republic of Congo*. *4*. https://doi.org/10.4236/oalib.1103501

Moore, K. A., Fowkes, F. J. I., Wiladphaingern, J., Wai, N. S., Paw, M. K., Pimanpanarak, M., … Mcgready, R. (2017). *Mediation of the effect of malaria in pregnancy on stillbirth and neonatal death in an area of low transmission : observational data analysis*. 1–11. https://doi.org/10.1186/s12916-017-0863-z

Moore, K. A., Simpson, J. A., Paw, M. K., Pimanpanarak, M., Wiladphaingern, J., Rijken, M. J., & Jittamala, P. (2016). *Safety of artemisinins in fi rst trimester of prospectively followed pregnancies : an observational study*. *16*(May). https://doi.org/10.1016/S1473-3099(15)00547-2

Moore, K. A., Simpson, J. A., Scoullar, M. J. L., McGready, R., & Fowkes, F. J. I. (2017). Quantification of the association between malaria in pregnancy and stillbirth: a systematic review and meta-analysis. *The Lancet Global Health*, *5*(11), e1101–e1112. https://doi.org/10.1016/S2214-109X(17)30340-6

Moormann, A. M. (2009). How might infant and paediatric immune responses influence malaria vaccine efficacy? *Parasite Immunology*, *31*(9), 547–559. https://doi.org/10 .1111/ j.1365-3024.2009.01137.x

Mosha, D., Chilongola, J., Ndeserua, R., Mwingira, F., & Genton, B. (2014). Effectiveness of intermittent preventive treatment with sulfadoxine-pyrimethamine during pregnancy on placental malaria, maternal anaemia and birthweight in areas with high and low malaria transmission intensity in Tanzania. *Tropical Medicine and International Health*, *19*(9), 1048–1056. https://doi.org/10.1111/tmi.12349

Moya-Alvarez, V., Ouédraogo, S., Accrombessi, M., & Cot, M. (2018). High folate levels are not associated with increased malaria risk but with reduced anaemia rates in the context of high-dosed folate supplements and intermittent preventive treatment against malaria in pregnancy with sulphadoxine–pyrimethamine in Benin. *Tropical Medicine and International Health*, *23*(6), 582–588. https://doi.org/10.1111/tmi.13064

Mpogoro, F. J., Matovelo, D., Dosani, A., Ngallaba, S., Mugono, M., & Mazigo, H. D. (2014). Uptake of intermittent preventive treatment with sulphadoxine-pyrimethamine for malaria during pregnancy and pregnancy outcomes: a cross-sectional study in Geita district, North-Western Tanzania. *Malaria Journal*, *13*, 455. https://doi.org/10 .1186/1475-2875-13-455

Muanda, F. T., Chaabane, S., Boukhris, T., Santos, F., Sheehy, O., Perreault, S., … Bérard, A. (2015). Antimalarial drugs for preventing malaria during pregnancy and the risk of low birth weight: A systematic review and meta-analysis of randomized and quasi-randomized trials. *BMC Medicine*, *13*(1), 1–14. https://doi.org/10.1186/s12916-015-0429-x

National Malaria Control Programme. (2013). *Ghana Malaria Programme Review: Final Report*. (June), 198. Retrieved from http://www.ghanahealthservice.org/downloads /ghana_malaria_programme_review_final_report_june_2013.pdf

Ndam, N. T., Denoeud-ndam, L., Doritchamou, J., Viwami, F., Salanti, A., Nielsen, M. A., … Deloron, P. (2015). *Protective Antibodies against Placental Malaria and Poor Outcomes during Pregnancy , Benin*. *21*(5).

Ndeserua, R., Juma, A., Mosha, D., & Chilongola, J. (2015). Risk factors for placental malaria and associated adverse pregnancy outcomes in Rufiji, Tanzania: A hospital based cross sectional study. *African Health Sciences*, *15*(3), 810–818.

https://doi.org/10.4314/ahs.v15i3.15

Newman, R. D., Hailemariam, A., Jimma, D., Degifie, A., Kebede, D., Rietveld, A. E., … Parise, M. E. (2003). Burden of malaria during pregnancy in areas of stable and unstable transmission in Ethiopia during a nonepidemic year. *J Infect Dis*, *187*(11), 1765–1772. https://doi.org/10.1086/374878

Newton, P. N., Caillet, C., & Guerin, P. J. (2016). A link between poor quality antimalarials and malaria drug resistance? *Expert Review of Anti-Infective Therapy*. https://doi.org/10.1080/14787210.2016.1187560

Ngwira, A., & Stanley, C. C. (2015). *Determinants of Low Birth Weight in Malawi : Bayesian Geo-Additive Modelling*. 1–14. https://doi.org/10.1371/journal.pone.0130057

Nkoka, O., Chuang, T. W., & Chen, Y. H. (2018). Association between timing and number of antenatal care visits on uptake of intermittent preventive treatment for malaria during pregnancy among Malawian women. *Malaria Journal*, *17*(1), 1–11. https://doi.org/10.1186/s12936-018-2360-z

NMCP, 2015 Annual report. (2016). *2015 Annual Report National Malaria Control Centre for Health Information Management*. 1–70.

Nobile, C. G. A., Raffaele, G., Altomare, C., & Pavia, M. (2015). *Influence of maternal and social factors as predictors of low birth weight in Italy*. *9*, 1–9. https://doi.org/10.1186/1471-2458-7-192

Nsibu, C. N., Manianga, C., Kapanga, S., Mona, E., Pululu, P., & Aloni, M. N. (2016). *Determinants of Antenatal Care Attendance among Pregnant Women Living in Endemic Malaria Settings : Experience from the Democratic Republic of Congo*. *2016*.

Nwizu, E. N., Iliyasu, Z., Ibrahim, S. A., & Galadanci, H. S. (2011). Socio-demographic and maternal factors in anaemia in pregnancy at booking in Kano, northern Nigeria. *African Journal of Reproductive Health*, *15*(4), 33–41.

Odom, J. D., Westfall, A. O., Apinjoh, T. O., Kimbi, J. A., Achidi, E. A., & Tita, A. T. N. (2017). Predictors of the use of interventions to prevent malaria in pregnancy in Cameroon. *Malaria Journal*, 1–10. https://doi.org/10.1186/s12936-017-1786-z

Odongo, C. O., Odida, M., Wabinga, H., Obua, C., & Byamugisha, J. (2016). Burden of Placental Malaria among Pregnant Women Who Use or Do Not Use Intermittent Preventive Treatment at Mulago Hospital, Kampala. *Malaria Research and Treatment*, *2016*, 1–7. https://doi.org/10.1155/2016/1839795

Ofori, M. F., Lamptey, H., Dickson, E. K., Kyei-baafour, E., & Hviid, L. (2018). *Etiology of Placental Plasmodium falciparum Malaria in African Women*. *218*, 277–281. https://doi.org/10.1093/infdis/jiy168

Okube, O. T., Mirie, W., Odhiambo, E., Sabina, W., & Habtu, M. (2016). *Prevalence and Factors Associated with Anaemia among Pregnant Women Attending Antenatal Clinic in the Second and Third Trimesters at Pumwani Maternity Hospital , Kenya*. (January), 16–27.

Olatunbosun, O. A., Abasiattai, A. M., Bassey, E. A., James, R. S., Ibanga, G., & Morgan, A. (2014). Prevalence of anaemia among pregnant women at booking in the university of Uyo teaching hospital, Uyo, Nigeria. *BioMed Research International*, *2014*(June). https://doi.org/10.1155/2014/849080

Olubukola, A., Odunayo, A., & Adesina, O. (2011). Anemia in pregnancy at two levels of health care in Ibadan, south west Nigeria. *Annals of African Medicine*, *10*(4), 272–277. https://doi.org/10.4103/1596-3519.87042

Omer, S. A., Idress, H. E., Adam, I., Abdelrahim, M., Noureldein, A. N., Abdelrazig, A. M., … Sulaiman, S. M. (2017). Placental malaria and its effect on pregnancy outcomes in Sudanese women from Blue Nile State. *Malaria Journal*, 1–8. https://doi.org/10.1186/s12936-017-2028-0

Onyeneho, N. G., Idemili-aronu, N., Igwe, I., & Iremeka, F. U. (2015). Perception and attitudes towards preventives of malaria infection during pregnancy in Enugu State , Nigeria. *Journal of Health, Population and Nutrition*, 1–10. https://doi.org/10. 1186/s41043-015-0033-x

Orish, V. N., Ansong, J. Y., Anagi, I. B., Onyeabor, O. S., Sanyaolu, A. O., & Iriemenam, N. C. (2015). Malaria and associated co-morbidity in children admitted with fever manifestation in Western Ghana: A retrospective study. *The Journal of Infection in Developing Countries*, *9*(11), 7–13. https://doi.org/10.3855/jidc.6316

Orish, V. N., Onyeabor, O. S., Boampong, J. N., Afoakwah, R., Nwaefuna, E., Acquah, S., … Commission, A. E. (2015). *Prevalence of intermittent preventive treatment with sulphadoxine-pyrimethamine (IPTp-SP) use during pregnancy and other associated factors in*. *15*(4).

Orish, V. N., Onyeabor, O. S., Boampong, J. N., Afoakwah, R., Nwaefuna, E., Acquah, S., … Iriemenam, N. C. (2015). Prevalence of intermittent preventive treatment with sulphadoxine-pyrimethamine (IPTp-Sp) use during pregnancy and other associated factors in Sekondi-Takoradi, Ghana. *African Health Sciences*, *15*(4), 1087–1096. https://doi.org/10.4314/ahs.v15i4.6

Ouédraogo, S., Bodeau-Livinec, F., Briand, V., Huynh, B. T., Koura, G. K., Accrombessi, M. M., … Cot, M. (2012). Malaria and gravidity interact to modify maternal haemoglobin concentrations during pregnancy. *Malaria Journal*, *11*, 1–8. https://doi.org/10.1186/ 1475-2875-11-348

Owusu-Boateng, I., & Anto, F. (2017). Intermittent preventive treatment of malaria in pregnancy: a cross-sectional survey to assess uptake of the new sulfadoxine–pyrimethamine five dose policy in Ghana. *Malaria Journal*, *16*(1), 323. https://doi.org/10. 1186/s12936-017-1969-7

Parekh, F. K., Hernandez, J. N., Krogstad, D. J., Casapia, W. M., & Branch, O. H. (2007). *Prevalence and Risk of Plasmodium falciparum and P . vivax Malaria among Pregnant Women Living in the Hypoendemic Communities of the Peruvian Amazon*. *77*(3), 451–457.

Pereira, M. A., Clausen, T. M., Pehrson, C., & Mao, Y. (2016). *Placental Sequestration of Plasmodium falciparum Malaria Parasites Is Mediated by the Interaction Between VAR2CSA and Chondroitin Sulfate A on Syndecan-1*. 1–26. https://doi.org/10.1371 /journal.ppat.1005831

Plotkin, M., Said, K., Msellem, M. I., Chase, R. P., Hendler, N., Khamis, A. R., … Mcelroy, P. D. (2014). *Placental Malaria Is Rare Among Zanzibari Pregnant Women Who Did Not Receive Intermittent Preventive Treatment in Pregnancy*. *91*(2), 367–373. https://doi.org/10.4269/ajtmh.13-0586

Prah, J., Ameyaw, E. O., Afoakwah, R., & Kudom, A. (2016). *Factors affecting birth weight in Cape Coast , Ghana*. *5*(5), 1536–1539.

President ' S Malaria Initiative Ghana Malaria Operational Plan FY 2014. (2014).

Progress, C., & Report, T. (n.d.). *Every newborn action plan*.

Prudêncio, M., Rodriguez, A., Mota, M. M., Besteiro, S., Dubremetz, J. F., Lebrun, M., … Berendsen, H. J. C. (2012). Inhibition of myosin ATPase activity by halogenated pseudilins: A structure-activity study. *Proceedings of the National Academy of Sciences of the United States of America*, *59*(1), 19678–19682. https://doi.org/10.1073/pnas.0603873103

Rassi, C., Graham, K., Mufubenga, P., King, R., Meier, J., & Gudoi, S. S. (2016). Assessing supply - side barriers to uptake of intermittent preventive treatment for malaria in pregnancy : a qualitative study and document and record review in two regions of Uganda. *Malaria Journal*, 1–16. https://doi.org/10.1186/s12936-016-1405-4

Report, A. (2013). *2013 ANNUAL REPRODUCTIVE AND CHILD HEALTH REPORT*.

Report, M. W. (2017). *Malaria Surveillance — United States , 2014*. *66*(12).

Review, S., Garner, P., Macarthur, J. R., & Luntamo, M. (2013). *CLINICIAN ' S CORNER During Pregnancy Using 2 vs 3 or More Doses of Sulfadoxine-Pyrimethamine and Risk of Low Birth Weight in Africa*.

Rijken, M. J., De Livera, A. M., Lee, S. J., Boel, M. E., Rungwilailaekhiri, S., Wiladphaingern, J., … McGready, R. (2014). Quantifying low birth weight, preterm birth and small-for- Gestational-age effects of malaria in pregnancy: A population cohort study. *PLoS ONE*, *9*(7), 3–10. https://doi.org/10.1371/journal.pone.0100247

Rogerson, S. J., & Boeuf, P. (2007). New approaches to pathogenesis of malaria in pregnancy. *Parasitology*, *134*(13), 1883–1893. https://doi.org/10.1017/S0031182007000 11X

Rogerson, Stephen J., Mkundika, P., & Kanjalal, M. K. (2003). Diagnosis of Plasmodium falciparum malaria at delivery: Comparison of blood film preparation methods and of blood films with histology. *Journal of Clinical Microbiology*, *41*(4), 1370–1374. https://doi.org/10.1128/JCM.41.4.1370-1374.2003

Rogerson, Stephen J., Mwapasa, V., & Meshnick, S. R. (2007). Malaria in pregnancy: Linking immunity and pathogenesis to prevention. *American Journal of Tropical Medicine and Hygiene*, *77*(SUPPL. 6), 14–22. https://doi.org/77/6_Suppl/14 [pii]

Saba, N., Sultana, A., & Mahsud, I. (2008). *Outcome and Complications of*. *6*(2), 2–5.

Sappenfield, E., Jamieson, D. J., & Kourtis, A. P. (2013). *Pregnancy and Susceptibility to Infectious Diseases*. *2013*.

Saute, F., Menendez, C., Mayor, A., Aponte, J., Gomez-olive, X., Dgedge, M., & Alonso, P. (2002). *Malaria in pregnancy in rural Mozambique : the role of parity , submicroscopic and multiple Plasmodium falciparum infections*. *7*(1), 19–28.

Schuler, C., Edward, G., & Agbozo, F. (2019). Mothers ' Experiences with Neonatal Care for Low Birth Weight Infants at Home ; A Qualitative Study in the Hohoe Municipality , Ghana. *Journal of Pediatric Nursing*, *45*, e44–e52. https://doi.org/10.1016/j.pedn.2

018.12. 017

Scott, S., D'Alessandro, U., Kendall, L., Bradley, J., Bojang, K., Correa, S., … Pagnoni, F. (2019). Community-based malaria screening and treatment for pregnant women receiving standard intermittent preventive treatment with sulfadoxine-pyrimethamine: A multicenter (the gambia, burkina faso, and benin) cluster-randomized controlled trial. *Clinical Infectious Diseases*, *68*(4), 586–596. https://doi.org/10.1093/cid/ciy522

Sharma, L., & Shukla, G. (2017). *Placental Malaria : A new insight into the Pathophysiology*. *4*(July), 1–6. https://doi.org/10.3389/fmed.2017.00117

Shiferaw, C. B., Yallew, W. W., & Tiruneh, G. T. (2018). *Maternal Anthropometric Measurements Do Not Have Effect on Birth Weight of Term , Single , and Live Births in Addis Ababa City , Ethiopia*. *2018*. https://doi.org/10.1155/2018/1982134

Shulman, C. E., Dorman, E. K., & Bulmer, J. N. (2002, August). Malaria as a cause of severe anaemia in pregnancy. *Lancet (London, England)*, Vol. 360, p. 494. https://doi.org/10.1016/s0140-6736(02)09662-9

Silvestrin, S., Homrich, C., Naomi, V., Goldani, A. A. S., Silveira, P. P., & Goldani, M. Z. (2013). Maternal education level and low birth weight : a meta-analysis ☆. *Jornal de Pediatria (Versão Em Português)*, *89*(4), 339–345. https://doi.org/10.1016/j.jpedp.2013.01.004

Smith, E. R., Shankar, A. H., Wu, L. S. F., Aboud, S., Adu-Afarwuah, S., Ali, H., … Sudfeld, C. R. (2017). Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries. *The Lancet Global Health*, *5*(11), e1090–e1100. https://doi.org/10.1016/S2214-109X(17)30371-6

Sohail, M., Shakeel, S., Kumari, S., Bharti, A., Zahid, F., Anwar, S., … Raziuddin, M. (2015). *Prevalence of Malaria Infection and Risk Factors Associated with Anaemia among Pregnant Women in Semiurban Community of Hazaribag , Jharkhand , India*. *2015*. https://doi.org/10.1155/2015/740512

Sonko, S. T., Jaiteh, M., Jafali, J., Jarju, L. B. S., D'Alessandro, U., Camara, A., … Saho, A. (2014). Does socio-economic status explain the differentials in malaria parasite prevalence? Evidence from the Gambia. *Malaria Journal*, *13*(1), 1–12. https://doi.org/10.1186/1475-2875-13-449

Souza, R. M. De, Gonc, A., & Silva, M. (2018). *Malaria during pregnancy and newborn outcome in an unstable transmission area in Brazil : A population-based record linkage study*. 1–16.

Steketee, R. W., & Campbell, C. C. (2010). Impact of national malaria control scale-up programmes in Africa: magnitude and attribution of effects. *Malaria Journal*, *9*(1), 299. https://doi.org/10.1186/1475-2875-9-299

Stephens, J. K. oryo, Ofori, M. F., Quakyi, I. A. kyinbah, Wilson, M. L. ee, & Akanmori, B. D. icky. (2014). Prevalence of peripheral blood parasitaemia, anaemia and low birthweight among pregnant women in a suburban area in coastal Ghana. *The Pan African Medical Journal*. https://doi.org/10.11694/pamj.supp.2014.17.1.3541

Sumankuuro, J., Crockett, J., & Wang, S. (2016). *Antenatal care on the Agenda of the Post-Millennium Development Goals in northern Ghana*. *18*(2), 341–352.

Sutaa, F., Azongo, T. B., & Kubio, C. (2016). *Stillbirths at the West Gonja hospital in northern Ghana*. *5*, 1–7.

Tabernero, P., Fernández, F. M., Green, M., Guerin, P. J., & Newton, P. N. (2014). Mind the gaps - The epidemiology of poor-quality anti-malarials in the malarious world - Analysis of the WorldWide Antimalarial Resistance Network database. *Malaria Journal*. https://doi.org/10.1186/1475-2875-13-139

Tagbor, H., Cairns, M., Bojang, K., Coulibaly, S. O., Kayentao, K., Williams, J., … Greenwood, B. (2015). A non-inferiority, individually randomized trial of intermittent screening and treatment versus intermittent preventive treatment in the control of malaria in pregnancy. *PLoS ONE*, *10*(8). https://doi.org/10.1371/journal.pone.0132247

Taha, T. E. T., Gray, R. H., & Mohamedani, A. A. (1993). Malaria and Low Birth Weight in Central Sudan. *American Journal of Epidemiology*, *138*(5), 318–325. https://doi.org/10.1093/oxfordjournals.aje.a116861

Takem, E. N., & D'Alessandro, U. (2013). Malaria in pregnancy. *Mediterranean Journal of Hematology and Infectious Diseases*, *5*(1). https://doi.org/10.4084/MJHID.2013.010

Tako, E. a., Zhou, A., Lohoue, J., Leke, R., Taylor, D. W., & Leke, R. F. G. (2005). Risk factors for placental malaria and its effect on pregnancy outcome in Yaounde, Cameroon. *The American Journal of Tropical Medicine and Hygiene*, *72*(3), 236–242. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15772313

Tampah-naah, A. M., Anzagra, L., & Yendaw, E. (2016). *Factors Correlated with Low Birth Weight in Ghana*. *16*(4), 1–8. https://doi.org/10.9734/BJMMR/2016/24881

Tarkang, E., & Adjuik, M. (2017). *European of Biomedical AND Pharmaceutical sciences ASSESSMENT OF DELIVERY OUTCOMES AND FACTORS ASSOCIATED WITH LOW BIRTH WEIGHT FOLLOWING THE INTRODUCTION OF SP-IPTP AS PART OF FOCUSED ANTENATAL CARE IN THE HOHOE MUNICIPALITY , GHANA*. *4*(8), 83–92.

Taylor, R. B., Shakoor, O., Behrens, R. H., Everard, M., Low, A. S., Wangboonskul, J., … Kolawole, J. A. (2001). Pharmacopoeial quality of drugs supplied by Nigerian pharmacies. *Lancet*, *357*(9272), 1933–1936. https://doi.org/10.1016/S0140-6736(00)05065-0

Taylor, S. M., & Kuile, F. O. (2017). Comment Stillbirths : the hidden burden of malaria in pregnancy. *The Lancet Global Health*, *5*(11), e1052–e1053. https://doi.org/10.1016/S2214-109X(17)30378-9

Tesfaye, T., Mekonnen, H., & Negesa, L. (2017). *Journal of Women ' s Health Care Maternal Antenatal Care Service Satisfaction and Factors Associated with Rural Health Centers , Bursa District , Sidama Zone , Southern Ethiopia : A Cross- sectional Study*. *6*(2). https://doi.org/10.4172/2167-0420.1000363

Teye, J. K., & Awetoriyaro, J. (2013). Malaria control strategies in the Kassena-Nankana East and West Districts of Ghana. *Ghana Journal of Geography*, *5*(1), 102–120.

The_United_States_Pharmacopeia_USP_29. (n.d.).

Treatment, F. O. R. T. H. E., & Malaria, O. F. (n.d.). *For the treatment of malaria*.

Uppadhaya, S. K., Agrawal, N., Bhansali, S., Garg, K., Singh, M., Sk, U., … Mar, H. (2017).

Utilization of antenatal health care services and its impact on birth weight of newborn in rural area of Western Rajasthan , India. *4*(3), 680–685.

Vala, A., Rupe, M., Boene, H., Gonza, R., & Mene, C. (2014). *Perceptions of Malaria in Pregnancy and Acceptability of Preventive Interventions among Mozambican Pregnant Women : Implications for Effectiveness of Malaria Control in Pregnancy*. *9*(2). https://doi.org/10.1371/journal.pone.0086038

van Eijk, Anna M., Hill, J., Noor, A. M., Snow, R. W., & ter Kuile, F. O. (2015). Prevalence of malaria infection in pregnant women compared with children for tracking malaria transmission in sub-Saharan Africa: A systematic review and meta-analysis. *The Lancet Global Health*, *3*(10), e617–e628. https://doi.org/10.1016/S2214-109X(15)00049-2

Van Eijk, Anna Maria, Hill, J., Alegana, V. A., Kirui, V., Gething, P. W., ter Kuile, F. O., & Snow, R. W. (2011). Coverage of malaria protection in pregnant women in sub-Saharan Africa: A synthesis and analysis of national survey data. *The Lancet Infectious Diseases*, *11*(3), 190–207. https://doi.org/10.1016/S1473-3099(10)70295-4

Van Eijk, Anna Maria, Hill, J., Larsen, D. A., Webster, J., Steketee, R. W., Eisele, T. P., & ter Kuile, F. O. (2013). Coverage of intermittent preventive treatment and insecticide-treated nets for the control of malaria during pregnancy in sub-Saharan Africa: A synthesis and meta-analysis of national survey data, 2009-11. *The Lancet Infectious Diseases*, *13*(12). https://doi.org/10.1016/S1473-3099(13)70199-3

Verity, R., Hathaway, N. J., Waltmann, A., Doctor, S. M., Watson, O. J., Patel, J. C., … Meshnick, S. R. (2018). Plasmodium falciparum genetic variation of var2csa in the Democratic Republic of the Congo. *Malaria Journal*, *17*(1), 1–8. https://doi.org/ 10.1186/s12936-018-2193-9

Warland, J., & Mitchell, E. A. (2014). A triple risk model for unexplained late stillbirth. *BMC Pregnancy and Childbirth*, *14*(1), 1–6. https://doi.org/10.1186/1471-2393-14-142

WHO. (2016). *WHO recommendation on the method for diagnosing anaemia in pregnancy | RHL*. (March), 1–5. Retrieved from https://extranet.who.int/rhl/topics/preconception-pregnancy-childbirth-and-postpartum-care/antenatal-care/who-recommendation-method-diagnosing-anaemia-pregnancy

WHO. (2017). *World Malaria Report 2017*. https://doi.org/http://www.who.int/malaria/publications/world-malaria-report-2017/report/en/

WHO. (2018). WHO recommendation on daily oral iron and folic acid supplementation | RHL. *World Health Organisation*, (March), 1–8. Retrieved from https://extranet.who.int/rhl/topics/preconception-pregnancy-childbirth-and-postpartum-care/antenatal-care/who-recommendation-daily-oral-iron-and-folic-acid-supplementation

Williams, J. E., Cairns, M., Njie, F., Laryea Quaye, S., Awine, T., Oduro, A., … Greenwood, B. (2016). The performance of a rapid diagnostic test in detecting malaria infection in pregnant women and the impact of missed infections. *Clinical Infectious Diseases*, *62*(7), 837–844. https://doi.org/10.1093/cid/civ1198

Williams, J., Njie, F., Cairns, M., Bojang, K., Coulibaly, S. O., Kayentao, K., … Chandramohan, D. (2016). Non - falciparum malaria infections in pregnant women in West Africa. *Malaria Journal*, 1–8. https://doi.org/10.1186/s12936-016-1092-1

World Health Organization. (2010). WHO. Basic Malaria Microscopy, Part 1. *Geneva, Switzerland, Second edi*.

World Health Organization. (2013). *Summary of the World Malaria Report 2012*. 1–24. Retrieved from http://www.who.int/malaria/publications/world_malaria_report_2012/en/index.html

Yakob, B., Gage, A., Nigatu, T. G., Hurlburt, S., Hagos, S., Dinsa, G., … Tekle, E. (2019). *Low effective coverage of family planning and antenatal care services in Ethiopia*. 1–8. https://doi.org/10.1093/intqhc/mzy251

Yeboah, D. F., Afoakwah, R., Nwaefuna, E. K., Verner, O., & Boampong, J. N. (2016). Quality of sulfadoxine-pyrimethamine given as antimalarial prophylaxis in pregnant women in selected health facilities in central region of Ghana. *Journal of Parasitology Research, 2016*. https://doi.org/10.1155/2016/9231946

Zeidan, M. A. (2019). Maternal Risk Factors Associated with Low Birth Weight in Ibn al-Baladi Hospital in Baghdad Governorate. *Kufa Journal for Nursing Sciences. Vol . 9 No . 1 / 2019 . 9*(1), 1–9.

APPENDICES

Appendix 1: Consent form

(To be translated into Asante Twi, Hausa and Dagbani)

Study Woman's identification Number

Age: Address/house number:
Parity

Statement of person obtaining informed consent:
This research has been fully explained to me and has been given sufficient information about the study. It is explained that I am volunteering for a research on malaria in pregnancy. It was explained that I would receive the usual recommended care during delivery based on Ghana Health Service standard protocols.

During the study, I will have a number of examinations and laboratory tests similar to what is done at the ANC and would be required to answer some questions.

I understand that my participation is voluntary (not compulsory) and that I may freely stop being part of this study at any time without having to explain myself.

I have been reassured that all information obtained from me as a result of this study will be confidential and used for the purpose of this research only.

I know enough about the purpose, methods, risks and benefits of the research study to decide that I want to take part in it.

I have received a copy of this information leaflet and consent form to keep for myself.

NAME: _____

DATE: _____ **SIGNATURE/THUMB PRINT: _____**

Statement of person witnessing consent (Process for Non-Literate Participants):

I _____ (Name of Witness) certify that information given to

_____ (Name of Participant), in the local language, is a true reflection of what l have read from the study Participant Information Leaflet, attached.

WITNESS' SIGNATURE (maintain if participant is non-literate): _____

I have been reassured that all information obtained from me and my baby as a result of this study will be confidential and used for the purposes of this research only by Kwame Nkrumah University of Science and Technology, Ministry of Health and Ghana Health Service.

For further information you could contact;
Miss Yaa Nyarko Agyeman, School of Public Health, KNUST, Kumasi, mobile number +233 (0) 20 264 0796, email, ynyarko@uds.edu.gh, yaaadjeso2@gmail.com

Prof. Ellis Owusu-Dabo, School of Public Health, KNUST, Kumasi, mobile number, +233 (0) 20 196 4425, email, owusudabo@yahoo.com

Prof. Sam Newton, School of Public Health, KNUST, Kumasi, mobile number, +233 (0) 243 570 139, email, samkofinewton@yahoo.com

Appendix 2: Questionnaire

KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY, DEPARTMENT OF GLOBAL AND INTERNATIONAL HEALTH, SCHOOL OF PUBLIC HEALTH, KUMASI

MALARIA IN PREGNANCY; EVALUATING THE EFFECTIVENESS OF IPTp POLICY ON MATERNAL AND NEONATAL HEALTH

My name is ……., I am a Ph.D. student at KNUST. I am conducting a study on Malaria in Pregnancy; Evaluating the Effectiveness of new IPTp Policy on Maternal and Neonatal Health. The essence of the study is to find out whether the introduction of this new policy has made an impact on maternal and neonatal health.

You are assured of confidentiality of your responses. This study is purely for academic reasons; your name will not be identified. You are at will to stop the interview at any time without cost.

INTERVIEWER: INTRODUCTION AND CONSENT. May I begin the interview now?

NO	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
Name of Patient:		**Patient ID:**	
Hospital Name:		**Interviewer Name:**	
Date of Interview: |__|__| day |__|__| month |__|__||__|__| year			
Gravida:		**Parity…….**	
SOCIO-DEMOGRAPHIC CHARACTERISTICS I would like to start by asking you a few questions about yourself.			
Q1	Please tell me your date of birth or your age in years.	|__|__| day |__|__| month |__|__||__|__| year |__|__| age (completed years) Don't know 88	
Q2	Residence?	……	
Q3	What is your current marital status?	Married (civil, traditional, religious) ……1 Living together…… …..2 Divorced …….....…...3 Widowed…….....…...4 Single…….....…...5	
Q4	What is your highest school level?	No school…….....……0 Primary (include JSS) ……1 Secondary (include High school) …….....……..2 College/University……..…3 Graduate school…….…....4	
Q5	What is your main occupation?	Agricultural worker ……...……...1 Artisan……...……2 Salaried employment…….....……3 Petty trader/marketing…….....……4 Business.……5 Food vendor…….....…...6 Domestic activities.……..7 Student.……..8 Unemployed…….....…..9 Other (Specify)……10	
Q6	What is your religion?	Christian..... ……..1 Muslim..... ……..2 Traditional/Spiritualist ..... ……..3 Other ..... ……..4	
Q7	To what ethnic group do you belong?	Dagomba..... ……..1 Grussi..... ……..2 Kokomba..... ……..3 Frafra……..4 Akan..... ……..5 Ewe ..... ……..6 Other(specify) ..... ……..7	
Q8	Do you have	Yes ..... ……..1	

	ITN?	No…… ……..2	
Q9	If yes, do you sleep in ITN?	Yes ..... ……1 No ..... ……2	
Q10	How often do you sleep in it?	Every evening…… ….……..1 Once a while……..2	
REPRODUCTIVE HEALTH			
Q11	Have you ever been pregnant?	Yes ..... ……..1 No ..... ……..2	→ **Q20**
Q12	How many times have you been pregnant?	|__|__| number Don't know ..... ……88	
Q13	How many miscarriages have you had?	|__|__| number Don't know ..... ……88	
Q14	How many induced abortions have you had?	|__|__| number Don't know ..... ……88	
Q15	Have you ever given birth?	Yes ..... ……..1 No ..... ……..2	→ **Q20**
Q16	How many births do you have in total?	|__|__| number	
Q17	How many of these births are still alive?	|__|__| alive	
Q18	How many of these births are dead?	|__|__| dead	
Q19	How old is your last born?	|__|__| years |__|__| months Don't know……..88	
Q20	What is your height? (measure with stadiometer)	_____cm	
Q21	Are you currently pregnant?	Yes ..... ……1 No ..... ……2	
Q23	Did you plan to be pregnant for this current pregnancy?	Yes ..... ……1 No ..... ……2 Don't know ..... ……..88	
Q24	What (date) was your last menstrual period (LMP)?	|__|__| day |__|__| month |__|__||__|__| year	

Q25	At what gestation age did you start attending ANC for this current pregnancy?	|__|__|Weeks	
Q26	Any reason for reporting at that time?		
Q27	Do you currently experience any of the following symptoms of pregnancy? **(Please select all that apply)**	Abdominal pain …… ..1 Swollen breasts……2 Nausea……..3 Vomiting……..4 Headache……..5 Fever……6 Fatigue……7 Back ache……8 Baby movement……9	
PREGNANCY, MALARIA AND IPTp-SP			
29	Are you currently taking SP?	Yes ……1 No ……2	→ **Q30**
30	If no why?	G6PD defect ----------1 Was not given ----------2 Below 16 weeks ----------3 Client refused due to previous experience ----------4	
Q31	If yes, indicate the number of times and the weeks at which SP was given	1st Dose |__|__|Weeks 2nd Dose |__|__|Weeks 3rd Dose |__|__|Weeks 4th Dose |__|__|Weeks 5th Dose |__|__|Weeks Other (Specify) |__|__|Weeks	
Q32	When did you receive your last anti-malarial	|__|__|Weeks	
Q33	Have you ever experienced any adverse effect after taking SP?	Yes .....……..1 No .....……..2	→ **Q35**
Q34	If yes, indicate	Nausea ……1 Vomiting ……2 Skin rashes ……..3 Dizziness……..4 Itching……..5 Headache……..6 Difficulty in falling asleep at night……..7 Nightmares……..8 Constipation……9 Diarrhea……..10 Other(Specify)……11	

MEDICAL HISTORY			
Q35	Have you had fever in the last seven days?	Yes.....1 No.....2 Don't know.....88	→ **Q37** → **Q37**
Q36	If yes, have you been treated because of the fever?	Yes.....1 No.....2	→ **Q37**
Q37	What medicine were you given for the treatment?	Fansider.....1 Quinine.....2 Herbal drugs.....3 Other (Specify).....4	
Q38	Have you ever been told by a doctor or other health professional that you have hypertension/ high blood pressure?	Yes.....1 No.....2 Don't know.....88	→ **Q40** → **Q40**
Q39	Are you now taking a prescribed medicine for hypertension?	Yes.....1 No.....2 Don't know.....88	→ **Q40** → **Q40**
Q40	Have you ever been told by a doctor or other health professional that you have diabetes/ high blood sugar?	Yes.....1 No.....2 Don't know.....88	
Q41	Are you now taking a prescribed medicine for diabetes?	Yes.....1 No.....2	
Q42	How long have you been diabetic?	less than 1 year ago, ...1 1 -2 years ago,.....2 3-4 years .....3 5 years or more? .....4 Don't Know.....88	→ **END** → **END**
INTERVIEWER: THANK THE RESPONDENT FOR COMPLETING THIS FIRST PART OF THE INTERVIEW. TELL RESPONDENT THAT YOU WILL VISIT HER AGAIN DURING LABOUR AND DELIVERY.			

DELIVERY AND INDICATORS OF HEALTH OUTCOMES

NO	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
Name of Patient:		**Patient ID:**	
Hospital Name:		**Interviewer Name:**	
Date of Interview: |__|__| day |__|__| month |__|__||__|__| year		**Place of delivery:……**	
Date of delivery: |__|__| day |__|__| month |__|__||__|__| year		**Time of delivery:** |__|__||__|__|	
DELIVERY INFORMATION			
Q1	How many times have you taken the SP doses during this last pregnancy?	|__|__| number	
Q2	How many antenatal visits did you make before delivery?	|__|__| number	
Q3	In total, what was the gestation of this last pregnancy before delivery?	|__|__| number	
Q4	What was the mode of delivery?	SVD…….....…….1 CS…….2	
Q5	Complications during delivery?	Yes ..... …… 1 No..... ……2 Don't know ..... ……..88	 → **Q7** → **Q7**
Q6	If yes, indicate (**select all that apply**).	PPH……1 Seizures…….. ……2 Fever…….. ……3 Other (Specify)……. ……4	
Q7	Who attended to you during delivery?	Registered Midwife……1 Community Health Midwife……..2 Enrolled Nurse Midwife……3 Doctor……. ……..4 Other (Specify)…….. ……5	
Q8	What was your condition after delivery?	Very Good…….. 1 Good……2 Satisfactory…… 3 Fair……. 4 Poor…… 5	

		Other (Specify)……6	
Q9	What was the blood pressure of the mother after delivery?	ST|__|__||__|……..mm/Hg DT|__|__|__|……..mm/Hg	
Q10	What was the body temperature of the mother after delivery?	|__|__|	
Q11	Laboratory investigations	Haemoglobin level at booking…… Haemoglobin level at 36weeks……. Malaria parasites at booking……. Malaria parasites at 36 weeks……..	
Q12	Extract the weight of the mother the gestation at which the weight was taken from the ANC card at each visit	|__|__|kg----------|__|__|weeks |__|__|kg----------|__|__|weeks |__|__|kg----------|__|__|weeks |__|__|kg----------|__|__|weeks |__|__|kg----------|__|__|weeks |__|__|kg----------|__|__|weeks |__|__|kg----------|__|__|weeks |__|__|kg----------|__|__|weeks	
DELIVERY FINDINGS - NEWBORNS			
Q13	What is the sex of the baby?	Male……1 Female…… ……2	
Q14	Is the baby alive?	Yes ..... …… 1 No ..... …… 2	→ **Q17**
Q15	If no, was baby stillborn?	Yes ..... ……..1 No..... ……..2	→ **Q17**
Q16	If yes, was the baby……?	Fresh SB…… …….1 Macerated……2	
ANTHROPOMETRY OF THE BABY			
Q17	Birth weight of the new-born.	|__|__|kg	
Q18	Birth length.	|__|__|cm	
Q19	Head circumference.	|__|__|cm	
Q20	Chest circumference.	|__|__|cm	
GENERAL CONDITION OF THE BABY			

Q21	The baby has…….? (**Select all that apply**)	Fever……1 Not been able to suck……..2 Yellowish conjunctiva……3	
Q22	What was the baby's temperature at birth?	☐☐	

Appendix 3: Laboratory form

IDENTITY NO.

Age:……

Address:……..

Gravida ……

Date sample taken:

Laboratory no……

Name of the recorder:……

Malaria parasite seen at 36 weeks:

a. **Yes**
b. **No**

Appendix 4: Monitoring ANC Attendance

Name of Health Facility: Date…../...../.....

Month:

ID	Name of pregnant woman	Village	Date of attendance	DRUGS GIVEN			REFERED (Y/N)
				IPTp	ROUTINE	ANTIHELMINTHICS	

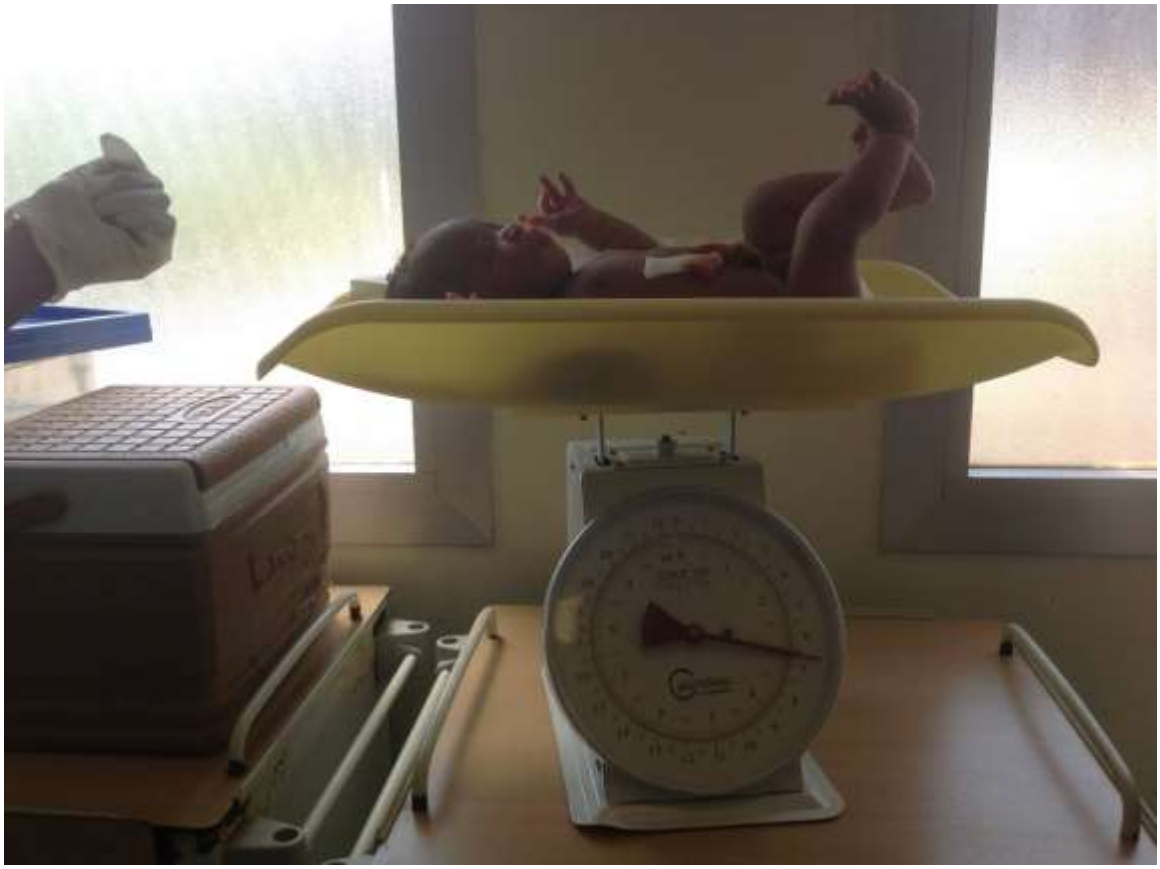
Appendix 5: Pictures on the data collection (birth weight)

A midwife weighing a baby at the West Hospital labour ward

Checking of the birth weight a newborn at the West hospital

Checking of the birth weight a newborn at the Central hospital

A Checking of the birth weight a newborn at the SDA hospital



Checking of the birth weight a newborn at the Tamale Teaching Hospital

Appendix 6: An interview session

Section of the women attending ANC at the SDA hospital

An interview session at the SDA hospital

Section of the women attending ANC at the West Hospital, Tamale

Pictures of a section of pregnant women attending ANC at the Tamale Teaching Hospital

Data collection session at the Tamale Teaching Hospital

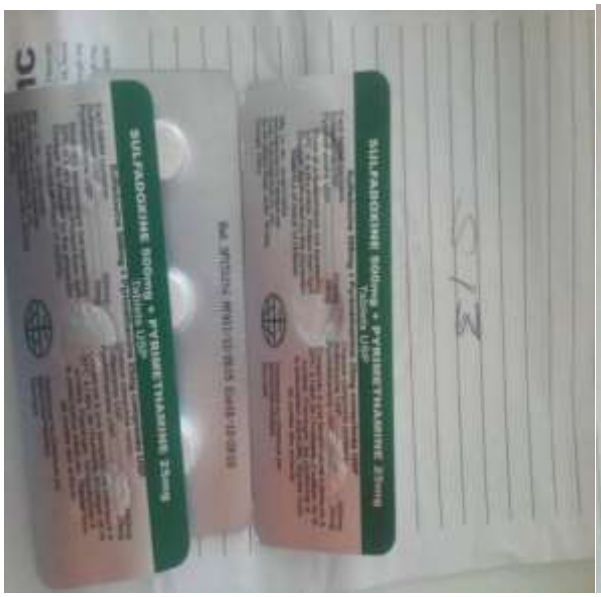
Appendix 7: A picture of the biomedical scientist performing the quality control

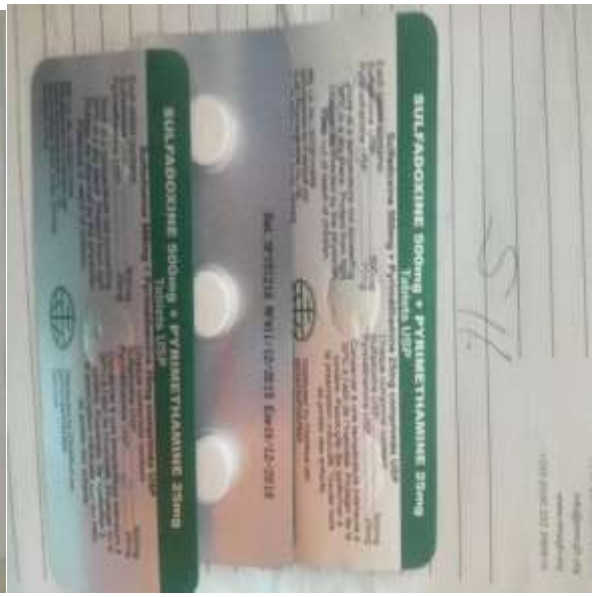
The Senior biomedical scientist performing the Quality Control on the Rapid Diagnostic Test Kits at the Tamale Teaching Hospital Laboratory

Appendix 8: The resident visualizing some slides for the malaria parasites

Appendix 9: The biomedical scientist visualizing the slides at the tamale teaching laboratory

Appendix 10: sample of SPs for analysis





KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY
COLLEGE OF HEALTH SCIENCES
SCHOOL OF MEDICAL SCIENCES / KOMFO ANOKYE TEACHING HOSPITAL
COMMITTEE ON HUMAN RESEARCH, PUBLICATION AND ETHICS

Our Ref: CHRPE/AP/375/16

15th August, 2016.

Miss Yaa Nyarko Agyeman
Tamale Nursing and Midwives
Training School
Post Office Box 565
TAMALE

Dear Madam,

LETTER OF APPROVAL

Protocol Title: ***"Malaria in Pregnancy; An Evaluation of the Effectiveness of IPTp Policy on Maternal Health Outcomes in the Tamale Metropolis in the Northern of Ghana."***

Proposed Sites: ***Tamale Teaching Hospital, Tamale Central Hospital, Tamale West Hospital, Tamale, Northern Region.***

Sponsor: **Principal Investigator.**

Your submission to the Committee on Human Research, Publications and Ethics on the above named protocol refers.

The Committee reviewed the following documents:

- A notification letter of 8th June, 2016 from the Metro Health Directorate, Tamale (study site) indicating approval for the conduct of the study in the Metropolis.
- A Completed CHRPE Application Form.
- Participant Information Leaflet and Consent form.
- Research Protocol.
- Interview Guide.

The Committee has considered the ethical merit of your submission and approved the protocol. The approval is for a fixed period of one year, beginning 15th August, 2016 to 14th August, 2017 renewable thereafter. The Committee may however, suspend or withdraw ethical approval at any time if your study is found to contravene the approved protocol.

Data gathered for the study should be used for the approved purposes only. Permission should be sought from the Committee if any amendment to the protocol or use, other than submitted, is made of your research data.

The Committee should be notified of the actual start date of the project and would expect a report on your study, annually or at the close of the project, whichever one comes first. It should also be informed of any publication arising from the study.

Thank you Madam, for your application.

Room 7 Block J, School of Medical Sciences, KNUST, University Post Office, Kumasi, Ghana
Phone: +233 3220 63248 Mobile: +233 20 5453785 Email: chrpe.knust.kath@gmail.com / chrpe@knust.edu.gh

Yours faithfully,

Rev. Prof. John Appiah-Poku.
Honorary Secretary
FOR: CHAIRMAN

KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY
COLLEGE OF HEALTH SCIENCES
SCHOOL OF MEDICAL SCIENCES / KOMFO ANOKYE TEACHING HOSPITAL
COMMITTEE ON HUMAN RESEARCH, PUBLICATION AND ETHICS

Our Ref: CHRPE/AP/404/18 12 July, 2018.

Miss Yaa Nyarko Agyeman
Tamale Nursing and Midwives
Training School
Post Office Box 565
TAMALE

Dear Madam,

LETTER OF APPROVAL - PROTOCOL AMENDMENT

Protocol Title: *"Malaria in Pregnancy; An Evaluation of the Effectiveness of IPTp Policy on Maternal Health Outcomes in the Tamale Metropolis in the Northern of Ghana."*

Original Study Sites: *"Tamale Teaching Hospital, Tamale Central Hospital, Tamale West Hospital, Tamale, Northern Region."*

Amended Study Sites: *"Tamale Teaching Hospital; Tamale Central Hospital; Tamale West Hospital and SDA Hospital;Tamale, Northern Region."*

The Committee has considered the ethical merit of your submission to amend the study sites as above and approved it.

Please note that any further amendment to this approved protocol should receive prior CHRPE approval before implementation.

Thank you, Madam, for your application.

Yours faithfully,

Osomfo Prof. Sir J. W. Achiampong MD; FWACP
Chairman

Room 7 Block J, School of Medical Sciences, KNUST, University Post Office, Kumasi, Ghana
Phone: +233 3220 63248 Mobile: +233 20 5453785 Email: chrpe.knust.kath@gmail.com / chrpe@knust.edu.gh

GHANA HEALTH SERVICE

Our core values:
1. People-centered
2. Professionalism
3. Team work
4. Innovation
5. Discipline
6. Integrity

METRO. HEALTH DIRECTORATE
GHANA HEALTH SERVICE
P.O. BOX TL. 1191,
TAMALE

Tel: 233 - 71: 23765
Fax: 233 - 71: 23765

8th JUNE, 2016

My Ref No: .....
Your Ref No: .....

The Medical Supts.
- Tamale Central Hospital
- Tamale West Hospital
- SDA Hospital

LETTER OF INTRODUCTION TO UNDERTAKE RESEARCH (MS. YAA NYARKO AGYEMAN)

I would be grateful if you could accept the above student from KNUST in your hospital to carry out her field work.

Find attached a self-explanatory letter from her head of department.

Thank you for your usual cooperation

DR. FRANCIS SOAH ALI
(METRO. DIRECTOR OF HEALTH SERVICES)

GHANA HEALTH SERVICE

OUR CORE VALUES:
1. People-Centered
2. Professionalism
3. Team work
4. Innovation
5. Discipline
6. Integrity

Regional Health Directorate
Ghana Health Service
P.O. BOX 99
Tamale

My Ref No: GHS/NR/18-0/72

Your Ref No: .....

Thursday, 01 September 2016

Tel: (233) (03720) 22912, 22710, 22146
Fax: (233) (03720) 22941
Email: rdhs.nr@ghsmail.org

PERMISSION TO COLLECT DATA FOR RESEARCH PURPOSE

I would be very grateful if Miss Yaa Nyarkoa Agyeman is granted permission to collect data from your facility to address her research topic " *Malaria in Pregnancy; an evaluation of the effectiveness of IPTp Policy on maternal health outcomes in the Tamale Metropolis in the Northern Region*"
The data so collected will be treated as confidential and it is only for research purpose.

She has been given Ethical Clearance from the Committee of Human Rights and Participants and Ethics, KNUST to enable her collect the needed data to address her research topic.

Thank you.

Mr.Imoro Mahama
Dep.Director – Administration
For: Reg.Director of Health Services
Northern Region

Distribution

The Med.Supts.
- *Tamale Central Hospital*
- *Tamale West Hospital*

Department of Research &Development
Tamale Teaching Hospital

TTH/R&D/SP/16/213
06/09/2016

TO WHOM IT MAY CONCERN

CERTIFICATE OF AUTHORIZATION TO CONDUCT RESEARCH IN TAMALE TEACHING HOSPITAL

I hereby introduce to you **Yaa Nyarko Agyemang,** a PhD student in the Department of the School of Public Health, KNUST. Who has been duly authorized to conduct a study on **"Malaria in Pregnancy: Evaluating the effectiveness of IPTP policy on maternal and neonatal Health".**

Please accord her the necessary assistance to be able to complete her study. If in doubt, kindly contact the Research Unit at the second floor of the administration block or on Telephone 0209281020. In addition, kindly report any misconduct of the Researcher to the Research Unit for necessary action, please.

Please note that this approval is given for a period of one Year, beginning from 6th of September, 2016 to 5th of September, 2017.

Thank You.

ALHASSAN MOHAMMED SHAMUDEEN
(HEAD, RESEARCH & DEVELOPMENT)